Acylated Iridoids with Cytotoxicity from *Valeriana jatamansi*

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Thirteen new acylated iridoids, jatamanvaltrates A−M (**1**−**13**), together with nine known valepotriates (**14**−**22**), were isolated from the whole plants of *Valeriana jatamansi* (syn. *Valeriana wallichii*). The structures of these new compounds were assigned by detailed interpretation of spectroscopic data. Jatamanvaltrates D (**4**) and H (**9**) are the first examples of naturally occurring valepotriates containing an *o*-hydroxybenzoyloxy moiety at C-10. All isolated compounds were tested for their cytotoxicity against lung adenocarcinoma (A549), metastatic prostate cancer (PC-3M), colon cancer (HCT-8), and hepatoma (Bel7402) cell lines.

The genus *Valeriana* (Valerianaceae), containing about 200 species, is distributed throughout the world. The root preparation of *Valeriana officinalis* L., popularly known as valerian, has been employed as a mild sedative for centuries.[1−3] *Valeriana jatamansi* Jones (syn. *Valeriana wallichii* DC.),[4] native to mainland China and India, is known as a multipurpose medicinal plant. 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 trouble, and skin diseases.[4−6] Besides sesquiterpenoids,[6] essentials oils,[6,7] and flavone glycosides,[8,9] members of a small group of acylated iridoids, the valepotriates,[10−14] have been reported previously from this plant or its tissue cultures. The valepotriates have shown sedative, cytotoxic, antitumor, and antifugal activities.[15,16] The current study was begun to search for novel bioactive secondary metabolites from this plant and has led to the isolation of 13 new acylated iridoids, jatamanvaltrates A−M (**1**−**13**), and nine known valepotriates (**14**−**22**). Jatamanvaltrates D (**4**) and H (**9**) are the first examples of naturally occurring valepotriates containing an *o*-hydroxybenzoyloxy moiety at C-10. This paper deals with the isolation, structure elucidations, and cytotoxic activities of these valepotriates.

Results and Discussion

An ethanolic extract of the whole plants of *V. jatamansi* was partitioned between H_2O and EtOAc. The EtOAc phase was subjected to column chromatography on silica gel and Sephadex LH-20, preparative TLC, and reversed-phase preparative HPLC, to yield compounds **1**−**22**.

Jatamanvaltrate A (**1**) was isolated as a colorless oil that analyzed for the molecular formula $C_{34}H_{52}O_{15}$ by HRESIMS at *m/z* 699.3242 $[M - H]^-$. The IR spectrum showed absorption bands due to hydroxy (3502 cm^{-1}) and ester carbonyl (1733 cm^{-1}) groups. Analysis of the ^1H and ^{13}C NMR spectroscopic data (Tables 1 and 2) indicated signals for a trisubstituted olefinic bond [δ_H 6.63 (s, H-3); δ_C 145.1 (C-3) and 112.4 (C-4)], a hemiketal methine [δ_H 6.60 (d, J = 1.8 Hz, H-1); δ_C 89.3 (C-1)], and an oxymethylene [δ_H 4.24 and 4.13 (each 1H, J = 12.0, H_2-10); δ_C 67.4 (C-10)]. These data, and the presence of one oxygenated quaternary carbon at δ 69.5 (C-5) and six ester carbonyls at δ_C 170.6, 171.2, 169.8, 170.7, 169.9, and 173.2, led to the conclusion that compound **1** is a 5-hydroxy-5,6-dihydrovaltrate hydrin-type iridoid with acyloxy substituents.[11,12] In addition, four acyloxy substituents were readily assigned by comparison with the ^1H and ^{13}C NMR data from the reported valepotriates as an isovaleroxy, an acetoxy, a β-(acetoxy)-isovaleroxy, and an α-(isovaleroxy)isovaleroxy group, respectively.[10,11,14,17−24] Analysis of the HSQC and $^1H-^1H$ COSY spectra of **1** provided unambiguous assignments of proton and carbon signals in the NMR spectra. The connectivities of the acyloxy substituents to the iridoid nucleus were fully assigned by a HMBC experiment. The linkage of the isovaleroxy group to C-1 was established by the HMBC correlation from H-1 to the carbonyl carbon at δ_C 170.6. The subsequent connection of the acetoxy group to C-7 was proposed on the basis of the HMBC correlation from H-7 to the carbonyl carbon at δ_C 171.6. Further, HMBC correlations between H_2-10 and the carbonyl carbon at δ_C 169.8 led to the assignment of a β-(acetoxy)isovaleroxy group to C-10, leaving the α-(isovaleroxy)isovaleroxy residue to be located at C-11. HMBC correlations were also observed between H_2-11 and the carbonyl carbon at δ_C 169.9, in full support of this assignment.

The relative configuration of **1** was elucidated by ROESY NMR experiments. Since all the naturally occurring valepotriates exhibit an α-orientation for H-1 and β-orientation for H-9,[25,26] NOE correlations of H-9 with H_2-10, and OH-8 with H-7, indicated that H_2-10 has a β-orientation and that H-7 and OH-8 were α-oriented. Additionally, OH-5 was determined to be β-oriented by comparison of NMR data of **1** with those reported for other valepotriates.[10,11,17,18,20] From the above observations and on biogenetic grounds, the absolute configurations at C-1, C-7, C-8, and C-9 of **1** were proposed to be identical to those of the co-occurring didrovaltrate (**20**), for which absolute configuration has been proved by chemical correlation with asperuloside.[27] On the basis of these data, the structure of jatamanvaltrate A (**1**) was defined as (1*S*,5*R*,7*S*,8*R*,9*S*)-7-acetoxy-10-[β-(acetoxy)isovaleroxy]-5-hydroxy-1-isovaleroxy-11-[α-(isovaleroxy)isovaleroxy]-5,6-dihydrovaltrate hydrin.

Jatamanvaltrate B (**2**) gave a molecular formula of $C_{32}H_{50}O_{13}$ as indicated by HRESIMS. The ^1H and ^{13}C NMR spectra of **2** closely resembled those of jatamanvaltrate A (**1**). However, there was a notable absence of two carbon resonances at δ_C 170.7 and 22.3, assigned for the terminal acetoxy unit of the β-(acetoxy)isovaleroxy residue in **1** (Tables 1 and 2), and this appeared to explain the 58 Da mass reduction found between the two compounds. These observations, coupled with analysis of the 2D gHSQC and gHMBC NMR spectra of **2**, revealed that

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Table 1. ^{1}H NMR Data (δ) for Compounds **1**−**13** and **16** in $CDCl_3$[a]

	position	1	2	3	4	5	6	7
	1	6.60 d (1.8)	6.61 d (1.2)	6.62 d (1.8)	6.71 d (1.2)	6.58 d (1.2)	6.27 d (4.2)	6.36 d (2.4)
	3	6.63 s	6.63 s	6.64 s	6.69 s	6.56 s	6.45 s	6.34 s
	5						2.92 m	2.95 m
	6	2.61 dd (13.2, 6.0)	2.61 dd (13.2, 6.0)	2.61 dd (13.2, 6.0)	2.66 dd (13.2, 6.0)	2.54 dd (13.2, 6.0)	2.15 m	2.06 m
		2.09 dd (13.2, 9.6)	2.10 dd (13.2, 9.6)	2.08 dd (13.2, 9.6)	2.10 dd (13.2, 9.6)	2.08 dd (13.2, 7.2)	2.08 m	2.00 m
	7	4.94 dd (9.6, 6.0)	4.95 dd (9.6, 6.0)	4.95 dd (9.6, 6.0)	5.04 dd (9.6, 6.0)	4.91 dd (7.2, 6.0)	5.03 dd (4.8, 4.2)	3.94 dd (6.0, 5.4)
	9	2.63 d (1.8)	2.64 d (1.2)	2.63 d (1.8)	2.76 d 1.2)	2.61 d (1.2)	2.44 dd (9.6, 4.2)	2.64 dd (9.6, 2.4)
	10	4.24 d (12.0)	4.25 d (11.4)	4.26 d (11.4)	4.48 d (12.0)	3.51 d (9.6)	4.26 d (11.4)	4.29 d (12.6)
		4.13 d (12.0)	4.11 d (11.4)	4.11 d (11.4)	4.37 d (12.0)	3.45 d (9.6)	4.22 d (11.4)	4.19 d (12.6)
	11	4.91 d (12.6)	4.93 d (12.6)	4.93 d (12.6)	4.97 d (12.6)	4.85 d (12.6)	4.62 d (12.6)	4.60 d (12.6)
		4.69 d (12.6)	4.68 d (12.6)	4.68 d (12.6)	4.69 d (12.6)	4.72 d (12.6)	4.43 d (12.6)	4.39 d (12.6)
R_1	2	2.23 m[d]	2.23 m[d]	2.22 m[d]	2.25 m[d]	2.22 m[d]	2.23 m[d]	2.21 m[d]
	3	2.10 m[e]	2.11 m[e]	2.11 m[e]	2.10 m[e]	2.10 m[e]	2.10 m[e]	2.10 m[e]
	4	0.96 d (6.6)	0.96 d (6.6)	0.96 d (6.6)	0.96 d (6.6)	0.96 d (6.6)	0.97 d (6.6)	0.96 d (6.6)
	5	0.96 d (6.6)	0.96 d (6.6)	0.96 d (6.6)	0.96 d (6.6)	0.96 d (6.6)	0.97 d (6.6)	0.96 d (6.6)
R_7	2	2.08 s	2.08 s	2.08 s	2.07 s	2.08 s	2.07 s	
R_{10}	2	2.96 d (15.0)	2.25 m[d]	2.13 s		3.41 s	2.94 d (15.0)	2.12 s
		2.92 d (15.0)					2.92 d (15.0)	
	3		2.10 m[e]		7.00 d (8.4)			
	4	1.55 s[f]	0.96 d (6.6)		7.49 ddd (8.4, 7.8, 1.8)		1.53 s	
	5	1.54 s[f]	0.96 d (6.6)		6.92 t (7.8)		1.53 s	
	7	2.00 s			7.85 dd (7.8, 1.8)		2.00 s	
R_{11}	2	4.80 d (4.8)	4.80 d (4.8)	4.80 d (4.8)	4.80 d (4.8)	4.80 d (4.8)	2.20 m[d]	2.20 m[d]
	3	2.21 m[d]	2.20 m[d]	2.20 m[d]	2.21 m[d]	2.20 m[d]	2.11 m[e]	2.11 m[e]
	4	1.01 d (7.2)	1.01 d (7.2)	1.01 d (7.2)	1.01 d (7.2)	1.01 d (7.2)	0.97 d (6.6)	0.96 d (6.6)
	5	1.01 d (7.2)	1.01 d (7.2)	1.01 d (7.2)	1.01 d (7.2)	1.01 d (7.2)	0.97 d (6.6)	0.96 d (6.6)
	7	2.26 m[d]	2.26 m[d]	2.26 m[d]	2.26 m[d]	2.26 m[d]		
	8	2.12 m[e]	2.11 m[e]	2.10 m[e]	2.11 m[e]	2.11 m[e]		
	9	0.96 d (6.6)	0.96 d (6.6)	0.96 d (6.6)	0.96 d (6.6)	0.96 d (6.6)		
	10	0.96 d (6.6)	0.96 d (6.6)	0.96 d (6.6)	0.96 d (6.6)	0.96 d (6.6)		

	position	8	9	10	10[b]	11[c]	12	13	16
	1	6.37 d (2.4)	6.29 d (10.2)	6.17 d (10.2)	6.09 d (10.8)	6.20 d (10.2)	6.06 d (2.4)	6.03 d (2.4)	6.29 d (4.2)
	3	6.36 s	6.72 s	6.67 s	6.77 s	6.70 s	6.65 s	6.47 s	6.46 s
	5	2.97 m							2.92 m
	6	2.15 m	5.82 dd (3.0, 2.4)	5.51 brs	5.78 dd (3.0, 2.4)	5.50 dd (1.8, 1.8)	2.51 dd (12.6, 6.0)	2.82 dd (12.6, 6.6)	2.16 m
		2.08 m					2.10 dd (12.6, 8.4)	2.08 dd (12.6, 10.2)	2.09 m
	7	5.12 dd (6.0, 5.4)	5.64 d (2.4)	4.83 brs	4.40 brs	5.75 d (0.6)	3.95 dd (8.4, 6.0)	4.83 dd (10.2, 6.6)	5.05 dd (4.8, 4.8)
	9	2.64 dd (9.6, 2.4)	3.07 dd (10.2, 3.0)	2.69 d (10.2)	3.15 dd (10.8, 2.4)	2.67 dd (10.2, 1.8)	2.83 d (2.4)	2.88 d (2.4)	2.45 dd (9.6, 4.2)
	10	3.81 d (12.0)	4.68 d (12.0)	4.39 d (11.4)	4.18 d (11.4)	3.78 s	3.23 d (4.8)	4.28 d (12.6)	4.24 d (12.0)
		3.59 d (12.0)	4.58 d (12.0)	4.14 d (11.4)	3.96 d (11.4)		2.77 d (4.8)	3.97 d (12.6)	4.21 d (12.0)
	11	4.60 d (12.6)	4.74 d (12.0)	4.73 d (12.6)	4.71 d (12.6)	4.75 d (12.0)	4.82 d (12.0)	4.93 d (12.6)	4.63 d (12.0)
		4.39 d (12.6)	4.68 d (12.0)	4.64 d (12.6)	4.65 d (12.6)	4.63 d (12.0)	4.80 d (12.0)	4.68 d (12.6)	4.43 d (12.0)
R_1	2	2.21 m[d]	2.35 m	2.23 m[d]	2.35 m	2.29 m	2.21 m[d]	2.23 m	2.21 m[d]
	3	2.10 m[e]	2.19 m	2.10 m[e]	2.03 m	2.15 m	2.10 m[e]	2.10 m	2.10 m[e]
	4	0.96 d (6.6)	1.03 d (6.6)	0.97 d (6.6)	0.97 d (6.6)	1.01 d (6.6)	0.96 d (6.6)	0.96 d (6.6)	0.96 d (6.6)[f]
	5	0.96 d (6.6)	1.03 d (6.6)	0.97 d (6.6)	0.97 d (6.6)	1.01 d (6.6)	0.96 d (6.6)	0.96 d (6.6)	0.96 d (6.6)[f]
R_7		2.13 s	2.06 s					2.07 s	2.08 s
R_{10}	2			2.26 m[d]	2.19 m				2.12 s
	3		7.00 d (8.4)	2.11 m[e]	2.18 m				
	4		7.50 ddd (8.4, 7.8, 1.8)	0.97 d (6.6)	1.01 d (6.6)				
	5		6.91 t (7.8)	0.97 d (6.6)	1.01 d (6.6)				
	6		7.78 dd (7.8, 1.8)						
R_{11}	2	2.20 m[d]	2.13 m	2.07 s	2.01 s	2.09 s	4.80 d (4.8)	3.56 q (7.2)	2.20 m[d]
	3	2.11 m[e]	2.00 m				2.20 m[d]	1.24 t (7.2)	2.11 m[e]
	4	0.96 d (6.6)	0.88 d (6.6)[d]				1.01 d (7.2)		0.97 d (6.6)[f]
	5	0.96 d (6.6)	0.87 d (6.6)[d]				1.01 d (7.2)		0.97 d (6.6)[f]
	7						2.26 m[d]		
	8						2.11 m[e]		
	9						0.96 d (6.6)		
	10						0.96 d (6.6)		

[a] ^{1}H NMR data (δ) were measured on a 600 MHz NMR instrument. Proton coupling constants (J) in Hz are given in parentheses. The assignments are based on DEPT, ^{1}H−^{1}H COSY, NOESY, HSQC, and HMBC experiments. [b] ^{1}H NMR data (δ) were measured in Me_2CO-d_6. [c] Data of the isovaleroxy group at C-7 of **11**: δ 2.29 (2H, m, H_{R7-2}), 2.15 (1H, m, H_{R7-3}), 1.01 (3H, d, J = 6.6 Hz, H_{R7-4}), 1.01 (3H, d, J = 6.6 Hz, H_{R7-5}). [d−f] Assignments bearing the same superscript may be interchanged in each column.

jatamanvaltrate B contains an isovaleroxy group rather than the β-(acetoxy)isovaleroxy residue found in jatamanvaltrate A. The remaining structural features were identical between the two metabolites, as determined by detailed NMR analysis. Thus, the structure of jatamanvaltrate B (**2**) was assigned as (1*S*,5*R*,7*S*,8*R*,9*S*)-7-acetoxy-5-hydroxy-1,10-diisovaleroxy-11-[α-(isovaleroxy)isovaleroxy]-5,6-dihydrovaltrate hydrin.

Jatamanvaltrate C (**3**) gave a molecular formula of $C_{29}H_{44}O_{13}$, as deduced by HRESIMS. The overall NMR data for this compound were almost identical to those of jatamanvaltrate B (**2**). The only difference that could be discerned was the presence of a new acetoxy moiety and lack of an isovaleroxy moiety in **3** (Tables 1 and 2), suggesting that compound **3** contains an acetoxy moiety rather than an isovaleroxy moiety at C-10. Further interpretation of 2D NMR data led to this assignment being made. Hence, the structure of jatamanvaltrate C (**3**) was characterized as (1*S*,5*R*,7*S*,8*R*,9*S*)-7,10-diacetoxy-5-hydroxy-1-isovaleroxy-11-[α-(isovaleroxy)isovaleroxy]-5,6-dihydrovaltrate hydrin.

Jatamanvaltrate D (**4**) gave a molecular formula of $C_{34}H_{46}O_{14}$ on the basis of its HRESIMS. The 1D and 2D NMR data of **4**

Table 2. ^{13}C NMR Data (δ) for Compounds **1**−**13** and **16** in $CDCl_3$[a]

	position	1	2	3	4	5	6	7	8	9	10	10[b]	11[c]	12	13	16
	1	89.3	89.2	89.3	89.0	89.7	89.2	88.3	88.2	92.6	92.1	92.8	91.8	89.0	88.4	89.2
	3	145.1	145.1	145.2	145.6	144.1	140.9	139.9	140.2	148.2	147.4	147.3	147.8	145.5	141.7	140.9
	4	112.4	112.4	112.3	112.1	113.2	112.9	113.1	113.0	108.7	108.3	109.5	108.1	112.7	112.3	112.9
	5	69.5	69.4	69.4	69.0	70.3	31.4	28.1	28.1	139.1	134.0	137.2	135.4	70.6	69.9	31.4
	6	40.4	40.3	40.3	40.0	41.2	34.8	34.3	34.3	117.5	120.7	121.1	117.4	43.1	41.0	34.7
	7	80.0	80.0	80.0	80.2	79.6	80.4	73.6	76.1	83.3	78.8	77.0	80.2	71.8	73.2	80.3
	8	79.2	79.1	79.1	78.8	80.2	80.8	79.2	80.3	80.1	79.4	78.3	82.1	64.2	62.1	80.9
	9	53.4	53.4	53.4	53.3	53.6	44.6	47.9	47.5	48.6	47.6	52.0	47.3	48.9	47.1	44.7
	10	67.4	67.3	67.7	67.9	75.3	66.5	66.6	64.6	66.2	67.8	65.1	67.0	49.1	49.1	66.9
	11	61.8	61.8	61.8	61.7	62.3	63.3	63.1	63.1	60.9	61.0	60.6	60.8	62.2	68.8	63.3
R_1	1	170.6	170.7	170.7	170.6	171.0	171.1	171.4	171.3	170.9	171.0	171.0	170.9	170.7	171.5	171.2
	2	43.1[d]	43.1[d]	43.0[d]	43.0	43.0[d]	43.4[d]	43.4[d]	43.4[d]	43.2[d]	43.2	43.0	43.2	42.8[d]	43.2	43.4[d]
	3	25.7[e]	25.7[e]	25.7[e]	25.7[d]	25.7[e]	25.7[e]	25.7[e]	25.7[e]	25.7[e]	25.7[d]	25.7	25.6	25.7[e]	25.5	25.7[e]
	4	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.2[f]	22.3	22.1[d]	22.2[d]	22.3	22.3	22.3[f]
	5	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3[f]	22.3	22.1[d]	22.3[d]	22.3	22.3	22.3[f]
R_7	1	171.2	171.2	171.2	171.5	170.8	170.2		170.8	171.9					169.9	170.4
	2	20.8	20.8	20.8	20.8	20.9	21.0		20.8	20.9					20.9	21.0
R_{10}	1	169.8	172.9	170.8	111.8	59.6	169.9	171.6		111.6	173.1	172.1				170.9
	2	44.1	43.2[d]	20.8	161.8		44.1	20.8		161.8	43.2	43.0				20.8
	3	79.0	25.7[e]		117.7		79.2			117.8	25.6[d]	25.7				
	4	26.7[g]	22.3		136.2		26.7[f]			136.4	22.3	22.1[d]				
	5	26.6[g]	22.3		119.5		26.6[f]			119.5	22.3	22.0[d]				
	6	170.7			129.8		170.6			129.8						
	7	22.3			169.8		22.4			169.9						
R_{11}	1	169.9	169.9	169.9	170.0	169.8	172.9	172.9	172.9	170.9	171.0	170.4	171.0	169.9	65.9	172.9
	2	77.0	77.0	77.0	77.0	77.0	43.3[d]	43.2[d]	43.2[d]	43.3[d]	21.0	20.3	21.0	77.0	15.1	43.3[d]
	3	29.9	29.9	29.9	29.9	30.0	25.6[e]	25.6[e]	25.6[e]	25.6[e]				30.1		25.6[e]
	4	18.7[f]	18.7[f]	18.7[f]	18.6[e]	18.7[f]	22.3	22.3	22.3	22.4[f]				18.9[f]		22.4[f]
	5	17.4[f]	17.4[f]	17.4[f]	17.4[e]	17.3[f]	22.3	22.3	22.3	22.4[f]				17.3[f]		22.4[f]
	6	173.2	173.3	173.3	173.4	173.0								173.6		
	7	43.0[d]	43.0[d]	43.1[d]	43.0	43.1[d]								43.1[d]		
	8	25.6[e]	25.6[e]	25.6[e]	25.6[d]	25.6[e]								25.6[e]		
	9	22.3	22.3	22.3	22.3	22.3								22.3		
	10	22.3	22.3	22.3	22.3	22.3								22.3		

[a] ^{13}C NMR data (δ) were measured in $CDCl_3$ for **1**−**13** and **16** at 150 MHz. The assignments were based on DEPT, $^1H-^1H$ COSY, HSQC, and HMBC experiments. [b] ^{13}C NMR data (δ) were measured in Me_2CO-d_6. [c] Data of the isovaleroxy group at C-7 of **11**: δ 173.8 (C_{R7-1}), 43.4 (C_{R7-2}), 25.8 (C_{R7-3}), 22.4 (C_{R7-4}), 22.3 (C_{R7-5}). [d−g] Assignments bearing the same superscript may be interchanged in each column.

disclosed that it is another 5-hydroxy-5,6-dihydrovaltrate hydrin-type iridoid with isovaleroxy, acetoxy, and α-(isovaleroxy)isovaleroxy substituents at C-1, C-7, and C-11, respectively. Additionally, in the ^1H NMR spectrum, signals at δ_H 7.85 (1H, dd, J = 7.8, 1.8 Hz), 7.49 (1H, ddd, J = 8.4, 7.8, 1.8 Hz), 7.00 (1H, d, J = 8.4 Hz), and 6.92 (1H, t, J = 7.8 Hz) and at δ_H 10.61 (a phenolic hydroxy proton) suggested the presence of an *o*-hydroxybenzoyloxy moiety in **4**. In a consistent manner, the ^{13}C NMR data showed six aromatic carbon signals at δ_C 111.8, 161.8, 117.7, 136.2, 119.5, and 129.8 and a carbonyl carbon signal at δ_C 169.8. Finally, HMBC correlations from H_2-10 to the ester carbonyl carbon at δ_C 169.8 provided convincing evidence that the *o*-hydroxybenzoyloxy moiety was positioned at C-10. Thus, the structure of jatamanvaltrate D (**4**) was determined as (1*S*,5*R*,7*S*,8*R*,9*S*)-7-acetoxy-5-hydroxy-10-(*o*-hydroxybenzoyloxy)-1-isovaleroxy-11-[α-(isovaleroxy)isovaleroxy]-5,6-dihydrovaltrate hydrin.

The molecular formula of jatamanvaltrate E (**5**) was inferred as $C_{28}H_{44}O_{12}$ by HRESIMS. The ^1H NMR spectrum of **5** was similar to that of jatamanvaltrate D (**4**) except that H_2-10 (δ_H 3.51 and 3.45, each 1H) were distinctly shielded and an *O*-methyl group (δ_H 3.41) rather than an *o*-hydroxybenzoyloxy group was present (Table 1). These spectroscopic differences suggested that the C-10 *o*-hydroxybenzoyloxy substituent in **4** was replaced in **5** by an *O*-methyl group. The ^{13}C and 2D NMR data closely matched those observed for **5** and confirmed the position of the *O*-methyl group at C-10. Consequently, the structure of jatamanvaltrate E (**5**) was elucidated as (1*S*,5*R*,7*S*,8*R*,9*S*)-7-acetoxy-5-hydroxy-1-isovaleroxy-11-[α-(isovaleroxy)isovaleroxy]-10-methoxy-5,6-dihydrovaltrate hydrin.

Jatamanvaltrate F (**6**) gave a molecular formula of $C_{29}H_{44}O_{12}$, as established by HRESIMS. Analysis of the ^1H and ^{13}C NMR data (Tables 1 and 2) revealed that compound **6** is an analogue of didrovaltrate acetoxy hydrin (**16**), with the only difference being the C-10 acyloxy ester group, which was defined as a β-(acetoxy)-isovaleroxy unit by the ^1H and ^{13}C NMR data (Tables 1 and 2). This was confirmed from the HMBC spectrum, in which H_2-10 correlated with the carbonyl carbon at δ_C 169.9. The relative configuration of **6** was identical with that of **20** on the basis of the NOE correlation of H-5/H-9/H_2-10 and the coupling constant (9.6 Hz) between H-9 and H-5.[28,29] Therefore, the structure of jatamanvaltrate E (**6**) was determined as (1*S*,5*S*,7*S*,8*R*,9*S*)-7-acetoxy-10-[β-(acetoxy)isovaleroxy]-1,11-diisovaleroxy-5,6-dihydrovaltrate hydrin.

Jatamanvaltrates G (**7**) and H (**8**) were shown to possess the same molecular formula and exhibited similar NMR spectroscopic features to those of **16**. Since the NMR spectra of **7** and **8** both showed the absence of one acetyl signal, it was clear that compounds **7** and **8** are the deacetyl analogues of **16** (Tables 1 and 2). As expected, H-7 of **7** and H_2-10 of **8** were shifted upfield due to the deacylation effect when compared with the ^1H NMR spectrum of **16** (Table 1), indicating that compounds **7** and **8** are the 7- and 10-deacetyl derivative of **16**, respectively. This was confirmed by interpretation of the 2D NMR data of **7** and **8**. The structures of jatamanvaltrates G (**7**) and H (**8**) were thereby assigned as (1*S*,5*S*,7*S*,8*R*,9*S*)-10-acetoxy-7-hydroxy-1,11-diisovaleroxy-5,6-dihydrovaltrate hydrin and (1*S*,5*S*,7*S*,8*R*,9*S*)-7-acetoxy-10-hydroxy-1,11-diisovaleroxy-5,6-dihydrovaltrate hydrin, respectively.

The molecular formula of jatamanvaltrate I (**9**) was inferred as $C_{29}H_{36}O_{11}$ by HRESIMS. The ^1H NMR spectrum displayed characteristics of a valtrate hydrin nucleus,[23] exhibiting signals for two olefinic methines [δ_H 6.72 (s, H-3) and 5.82 (dd, J = 3.0, 2.4 Hz, H-6)] and an oxymethylene [δ_H 4.68 and 4.58 (each 1H, J = 12.0 Hz, H_2-10)]. Detailed analysis of the ^{13}C and 2D NMR spectroscopic data showed that compound **9** contains two isov-

aleroxy groups at C-1 and C-11, respectively, an acetoxy group at C-7, and an *o*-hydroxybenzoyloxy moiety at C-10. In the NOESY spectrum, the observed NOE correlations between H-9 and H_2-10 and between H-7 and OH-8 indicated that **9** has the same configuration as **20** at C-1, C-7, C-8, and C-9. Thus, jatamanvaltrate I (**9**) was defined as (1*S*,7*S*,8*R*,9*S*)-7-acetoxy-10-(*o*-hydroxybenzoyloxy)-1,11-diisovaleroxyvaltrate hydrin.

Spectroscopic analysis of jatamanvaltrates J (**10**) and K (**11**) revealed that they have almost identical structures in possessing the same molecular formula and exhibiting similar NMR spectroscopic features. On the basis of analysis of NMR data, the two compounds were assigned as a valtrate hydrin-type iridoid with one acetoxy group and two isovaleroxy groups. By interpretation of the 2D NMR spectra, two isovaleroxy groups were located at C-1 and C-10 of **10**, and compound **11** was assigned with 1,7-diisovaleroxy substitution. Also, compounds **10** and **11** had a common C-11 acetoxy substituent. Accordingly, the structures of jatamanvaltrates J (**10**) and K (**11**) were elucidated as (1*S*,7*S*,8*R*,9*S*)-11-acetoxy-7-hydroxy-1,10-diisovaleroxyvaltrate hydrin and (1*S*,7*S*,8*R*,9*S*)-11-acetoxy-10-hydroxy-1,7-diisovaleroxyvaltrate hydrin, respectively.

Jatamanvaltrate L (**12**) was formulated as $C_{25}H_{38}O_{10}$ from the HRESIMS. Analysis of the ^{1}H and ^{13}C NMR data (Tables 1 and 2) showed signals similar to those of IVHD-valtrate (**18**),[17,20] but H-7 was significantly shielded (δ_H 3.95) and an acetyl group was absent. These spectroscopic differences suggested that compound **12** is a 7-deacetyl derivative of **18**. The 2D NMR data were also consistent with those observed for **12**. Hence, the structure of jatamanvaltrate L (**12**) was confirmed as (1*S*,5*R*,7*S*,8*R*,9*S*)-5,7-dihydroxy-1-isovaleroxy-11-[α-(isovaleroxy)isovaleroxy]-5,6-dihydrovaltrate.

The molecular formula of jatamanvaltrate M (**13**) was determined as $C_{19}H_{28}O_8$ by HRESIMS. The ^{1}H and ^{13}C NMR data of this compound closely resembled those of **18** except for the presence of an *O*-ethyl unit [δ_H 3.56 (2H, q, J = 7.2 Hz), 1.24 (3H, t, J = 7.2 Hz); δ_C 65.9, 15.1] instead of an α-(isovaleroxy)isovaleroxy group at C-11 in **13**, which was further confirmed by the downfield shift of C-11 from δ_C 61.9 in **18** to δ_C 68.8 in **13**,[20] as well as by 2D NMR data of **13**. Thus, the structure of jatamanvaltrate M (**13**) was identified as (1*S*,5*R*,7*S*,8*R*,9*S*)-7-acetoxy-11-ethoxy-5-hydroxy-1-isovaleroxy-5,6-dihydrovaltrate. Since the extraction was carried out in 95% EtOH, jatamanvaltrate M (**13**) could be an artifact. For this reason, LC-MS was run on a methanol extract from the same plant material to look for **13**. None could be detected, suggesting that compound **13** is indeed an extraction artifact.

By comparing their physical and spectroscopic data with those reported in the literature or analyzing their 2D NMR data, the known valepotriates were identified as valeriotetrate A (**14**),[12] valeriotriate B (**15**),[11] didrovaltrate acetoxy hydrin (**16**),[30] 10-acetoxyvaltrathydrin (**17**),[19,31] IVHD-valtrate (**18**),[17,20] 5-hydroxydidrovaltrate (**19**),[13] didrovaltrate (**20**),[17,20,32] valtrate (**21**),[25,33] and acevaltrate (**22**).[17,20,33]

Compounds **1**−**22** were examined for their cytotoxic properties on lung adenocarcinoma (A549), metastatic prostate cancer (PC-3M), colon cancer (HCT-8), and hepatoma (Bel7402) cell lines, using the MTT method.[34,35] Paclitaxel was used as a positive control, and the data obtained are shown in Table S1, Supportiong Information. Compounds **16**, **18**, **19**, **21**, and **22** showed activity against all tested cell lines, with IC_{50} values ranging from 1.0 to 7.4 μM. The most active compound was acevaltrate (**22**), which exhibited values of 2.9, 1.4, 1.0, and 1.7 μM against the A549, PC-3M, HCT-8, and Bel7402 cell lines, respectively. Except for compounds **3**, **5**, and **17**, the remaining compounds displayed cytotoxicity against the PC-3 M cell line, in the IC_{50} value range of 1.4−6.3 μM.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. IR and UV spectra were recorded on Bruker Vector-22 and Shimadzu UV-2550 UV−visible spectrophotometers, respectively. NMR spectra were obtained on a Bruker Avance 600 MHz or Avance 300 MHz NMR spectrometer in $CDCl_3$ or Me_2CO-d_6 with TMS as an internal standard. ESIMS and HRESIMS were acquired on an Agilent LC/MSD Trap XCT and a Q-TOF micro mass spectrometer (Waters, Milford, MA), respectively. Column chromatography was performed using silica gel (100−200 mesh and 10−40 μm; Huiyou Silica Gel Development Co. Ltd., Yantai, People's Republic of China) and Sephadex LH-20 (40−70 μm; Amersham Pharmacia Biotech AB, Uppsala, Sweden). Semipreparative HPLC was conducted on an ODS column (Kromasil, 5 μm, 300 × 10 mm) using a PDA UV detector at 208 nm. Preparative TLC (0.4−0.5 mm) was carried out on precoated silica gel GF_{254} plates (Yantai). Zones were visualized under UV light (254 nm) or by spraying with 10% H_2SO_4 followed by heating.

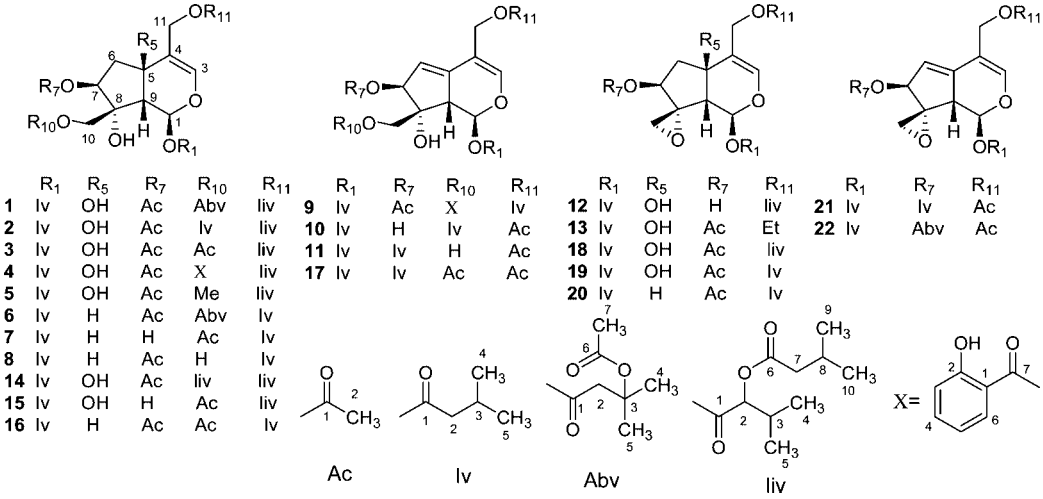
Plant Material. The whole plants of *V. jatamansi* were collected in Gaopo, Guizhou Province, People's Republic of China, in July 2007, and identified by Prof. Shun-zhi He, of Guiyang University of Traditional Chinese Medicine. A herbarium specimen was deposited in the School of Pharmacy, Second Military Medical University, People's Republic of China (herbarium no. 2007-08-16).

Extraction and Isolation. The air-dried whole plants of *V. jatamansi* (8.5 kg) were powdered and extracted with 11.0 L of 95% EtOH at room temperature for 3 × 48 h. The combined extracts were evaporated under reduced pressure to yield a residue. The residue was suspended in H_2O (1500 mL) and then partitioned with EtOAc (5 × 1000 mL). The EtOAc fraction (420 g) was chromatographed over silica gel (1500 g), eluting with increasing amounts of Me_2CO (0−100%) in petroleum ether, to afford 10 fractions (F_1−F_{10}) based on TLC analysis. Fraction F_2 (32.0 g) was subjected to chromatography on Sephadex LH-20 eluting with petroleum ether−$CHCl_3$−MeOH (5:5:1) to give three subfractions, and the third subfraction was further purified by preparative TLC developed with $CHCl_3$−MeOH (20:1) to afford **21** (R_f 0.51, 182 mg) and **22** (R_f 0.62, 159 mg). Fraction F_3 (27.0 g) was fractioned by column chromatography over Sephadex LH-20 using petroleum ether−$CHCl_3$−MeOH (5:5:1) as eluent to yield five corresponding subfractions. Compound **18** (317 mg) was crystallized from a Me_2CO solution of the first subfraction. The second subfraction was further purified by preparative TLC developed with $CHCl_3$−MeOH (20:1) to give **10** (R_f 0.52,17 mg) and **11** (R_f 0.41, 8 mg). The third subfraction was purified by reversed-phase preparative HPLC (RP_{18}, 5 μm, 300 × 10 mm, 208 nm, MeCN−H_2O, 60:40) to give **1** (t_R 56.7 min, 56 mg), **3** (t_R 31.1 min, 21 mg), **5** (t_R 34.2 min, 18 mg), and **6** (t_R 51.5 min, 11 mg). Using the same HPLC system, the last two subfractions afforded **15** (t_R 15.2 min, 27 mg), **16** (t_R 30.5 min, 12 mg), and **17** (t_R 33.5 min, 8 mg). Fraction F_4 (18.2 g) was chromatographed over Sephadex LH-20 eluting with petroleum ether−CH_3Cl−MeOH (5:5:1) and then further separated by reversed-phase preparative HPLC (RP_{18}, 5 μm, 300 × 10 mm, 208 nm, MeOH−H_2O, 77:23) to afford **2** (t_R 45.1 min, 7 mg), **4** (t_R 48.5 min, 8 mg), **9** (t_R 72.9 min, 5 mg), and **14** (t_R 98.5 min, 20 mg). Fraction F_5 (28.8 g) was subjected to Sephadex LH-20 column chromatography eluting with petroleum ether−$CHCl_3$−MeOH (5:5:1) to give two subfractions. The first subfraction was further purified by preparative TLC developed with $CHCl_3$−Me_2CO (5:1) to give **7** (R_f 0.54, 67 mg) and **8** (R_f 0.45, 6 mg). The second subfraction was purified by reversed-phase preparative HPLC (RP_{18}, 5 μm, 300 × 10 mm, 208 nm, MeCN−H_2O, 45:55) to obtain **13** (t_R 15.1 min, 21 mg) and **19** (t_R 18.2 min, 15 mg). Separation of fraction F_6 (10.8 g) by repeated chromatography over Sephadex LH-20 eluting with petroleum ether−$CHCl_3$−MeOH (5:5:1) and reversed-phase preparative HPLC (RP_{18}, 5 μm, 300 × 10 mm, 208 nm, MeCN−H_2O, 50:50) yielded **12** (t_R 15.6 min, 13 mg) and **20** (t_R 22.7 min, 9 mg).

Jatamanvaltrate A (1): colorless oil; $[\alpha]^{20}_D$ −51.0 (*c* 0.42, MeOH); UV (MeOH) λ_{max} (log ϵ) 212 (3.87) nm; IR (KBr) ν_{max} 3502, 2962, 2875, 1733, 1667, 1540, 1467, 1245, 1111, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz) data, see Tables 1 and 2; ESIMS *m*/*z* 723 $[M + Na]^+$ and 699 $[M - H]^-$; HRESIMS *m*/*z* 699.3242 $[M - H]^-$ (calcd for $C_{34}H_{51}O_{15}$, 699.3228).

Jatamanvaltrate B (2): colorless oil; $[\alpha]^{20}_D$ −48.5 (*c* 0.36, MeOH); UV (MeOH) λ_{max} (log ϵ) 210 (3.92) nm; IR (KBr) ν_{max} 3503, 2962, 2874, 1740, 1668, 1541, 1466, 1294, 1242, 1096, 1027 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz) data, see Tables 1 and 2; ESIMS *m*/*z* 665 $[M + Na]^+$ and 641 $[M - H]^-$; HRESIMS *m*/*z* 677.2975 $[M + Cl]^-$ (calcd for $C_{32}H_{50}ClO_{13}$, 677.2940).

Chart 1



	R_1	R_5	R_7	R_{10}	R_{11}
1	Iv	OH	Ac	Abv	Iiv
2	Iv	OH	Ac	Iv	Iiv
3	Iv	OH	Ac	Ac	Iiv
4	Iv	OH	Ac	X	Iiv
5	Iv	OH	Ac	Me	Iiv
6	Iv	H	Ac	Abv	Iv
7	Iv	H	H	Ac	Iv
8	Iv	H	Ac	H	Iv
14	Iv	OH	Ac	Iiv	Iiv
15	Iv	OH	H	Ac	Iiv
16	Iv	H	Ac	Ac	Iv

	R_1	R_7	R_{10}	R_{11}
9	Iv	Ac	X	Iv
10	Iv	H	Iv	Ac
11	Iv	Iv	H	Ac
17	Iv	Iv	Ac	Ac

	R_1	R_5	R_7	R_{11}
12	Iv	OH	H	Iiv
13	Iv	OH	Ac	Et
18	Iv	OH	Ac	Iiv
19	Iv	OH	Ac	Iv
20	Iv	H	Ac	Iv

	R_1	R_7	R_{11}
21	Iv	Iv	Ac
22	Iv	Abv	Ac

Jatamanvaltrate C (3): colorless oil; $[\alpha]^{20}_D$ −52.0 (*c* 0.13, MeOH); UV (MeOH) λ_{max} (log ϵ) 212 (3.88) nm; IR (KBr) ν_{max} 2970, 2874, 1739, 1684, 1541, 1456, 1365, 1229, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz) data, see Tables 1 and 2; ESIMS *m/z* 623 $[M + Na]^+$ and 599 $[M - H]^-$; HRESIMS *m/z* 599.2720 $[M - H]^-$ (calcd for $C_{29}H_{43}O_{13}$, 599.2704).

Jatamanvaltrate D (4): colorless oil; $[\alpha]^{20}_D$ −25.0 (*c* 0.14, MeOH); UV (MeOH) λ_{max} (log ϵ) 209 (3.86), 245 (4.01) nm; IR (KBr) ν_{max} 2969, 2874, 1739, 1684, 1635, 1540, 1521, 1457, 1371, 1230, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz) data, see Tables 1 and 2; ESIMS *m/z* 701 $[M + Na]^+$ and 677 $[M - H]^-$; HRESIMS *m/z* 713.2601 $[M + Cl]^-$ (calcd for $C_{34}H_{46}ClO_{14}$, 713.2576).

Jatamanvaltrate E (5): colorless oil; $[\alpha]^{20}_D$ −53.7 (*c* 0.69, MeOH); UV (MeOH) λ_{max} (log ϵ) 213 (3.92) nm; IR (KBr) ν_{max} 2962, 2875, 1739, 1684, 1466, 1390, 1244, 1170, 1109 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz) data, see Tables 1 and 2; ESIMS *m/z* 595 $[M + Na]^+$ and 571 $[M - H]^-$; HRESIMS *m/z* 607.2558 $[M + Cl]^-$ (calcd for $C_{28}H_{44}ClO_{12}$, 607.2521).

Jatamanvaltrate F (6): colorless oil; $[\alpha]^{20}_D$ −11.0 (*c* 0.07, MeOH); UV (MeOH) λ_{max} (log ϵ) 210 (3.91) nm; IR (KBr) ν_{max} 2960, 2873, 1735, 1683, 1472, 1395, 1231, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz) data, see Tables 1 and 2; ESIMS *m/z* 607 $[M + Na]^+$ and 583 $[M - H]^-$; HRESIMS *m/z* 619.2546 $[M + Cl]^-$ (calcd for $C_{29}H_{44}ClO_{12}$, 619.2521).

Jatamanvaltrate G (7): colorless oil; $[\alpha]^{20}_D$ −78.0 (*c* 1.28, MeOH); UV (MeOH) λ_{max} (log ϵ) 212 (3.96) nm; IR (KBr) ν_{max} 3468, 2960, 2873, 1740, 1673, 1466, 1371, 1245, 1153, 1095 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz) data, see Tables 1 and 2; ESIMS *m/z* 465 $[M + Na]^+$; HRESIMS *m/z* 477.1926 $[M + Cl]^-$ (calcd for $C_{22}H_{34}ClO_9$, 477.1891).

Jatamanvaltrate H (8): colorless oil; $[\alpha]^{20}_D$ −68.0 (*c* 0.38, MeOH); UV (MeOH) λ_{max} (log ϵ) 212 (3.92) nm; IR (KBr) ν_{max} 3467, 2962, 2873, 1741, 1673, 1467, 1370, 1246, 1153, 1095 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz) data, see Tables 1 and 2; ESIMS *m/z* 465 $[M + Na]^+$; HRESIMS *m/z* 477.1925 $[M + Cl]^-$ (calcd for $C_{22}H_{34}ClO_9$, 477.1891).

Jatamanvaltrate I (9): colorless oil; $[\alpha]^{20}_D$ +79.0 (*c* 0.14, MeOH); UV (MeOH) λ_{max} (log ϵ) 212 (3.93), 248 (4.06) nm; IR (KBr) ν_{max} 2961, 2873, 1734,1717, 1699, 1636, 1540, 1457, 1418, 1362, 1249, 1159, 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz) data, see Tables 1 and 2; ESIMS *m/z* 559 $[M - H]^-$; HRESIMS *m/z* 583.2157 $[M + Na]^+$ (calcd for $C_{29}H_{36}O_{11}Na$, 583.2179).

Jatamanvaltrate J (10): colorless oil; $[\alpha]^{20}_D$ +40.0 (*c* 0.16, MeOH); UV (MeOH) λ_{max} (log ϵ) 223 (4.09), 254 (3.98) nm; IR (KBr) ν_{max} 2970, 2873, 1738, 1684, 1456, 1366, 1229, 1093 cm^{-1}; ^1H NMR ($CDCl_3$ and Me_2CO-d_6, 600 MHz) and ^{13}C NMR ($CDCl_3$ and Me_2CO-d_6, 150 MHz) data, see Tables 1 and 2; ESIMS *m/z* 463 $[M + Na]^+$ and 475 $[M + Cl]^-$; HRESIMS *m/z* 475.1767 $[M + Cl]^-$ (calcd for $C_{22}H_{32}O_9Cl$, 475.1735).

Jatamanvaltrate K (11): colorless oil; $[\alpha]^{20}_D$ +35.0 (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ϵ) 220 (4.13), 254 (4.01) nm; IR (KBr) ν_{max} 2969, 2873, 1736, 1684, 1540, 1456, 1365, 1229, 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz) data, see Tables 1 and 2; ESIMS *m/z* 463 $[M + Na]^+$ and 475 $[M + Cl]^-$; HRESIMS *m/z* 475.1714 $[M + Cl]^-$ (calcd for $C_{22}H_{32}O_9Cl$, 475.1735).

Jatamanvaltrate L (12): colorless oil; $[\alpha]^{20}_D$ −18.0 (*c* 0.13, MeOH); UV (MeOH) λ_{max} (log ϵ) 212 (3.93) nm; IR (KBr) ν_{max} 2962, 2874, 1736, 1684, 1636, 1540, 1457, 1390, 1230, 1096 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz) data, see Tables 1 and 2; ESIMS *m/z* 521 $[M + Na]^+$ and 497 $[M - H]^-$; HRESIMS *m/z* 521.2392 $[M + Na]^+$ (calcd for $C_{25}H_{38}O_{10}Na$, 521.2363).

Jatamanvaltrate M (13): colorless oil; $[\alpha]^{20}_D$ −78.2 (*c* 0.43, MeOH); UV (MeOH) λ_{max} (log ϵ) 213 (3.89) nm; IR (KBr) ν_{max} 2962, 2872, 1741, 1684, 1540, 1457, 1395 1234, 1155, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz) data, see Tables 1 and 2; ESIMS *m/z* 407 $[M + Na]^+$; HRESIMS *m/z* 407.1669 $[M + Na]^+$ (calcd for $C_{19}H_{28}O_8Na$, 407.1682).

Cytotoxicity Assays. The cytotoxic activity was determined against four human cancer cell lines, A549, PC-3M, HCT-8, and Bel7402, obtained from the American Type Culture Collection (ATCC, Rockville, MD). 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**−**22**. 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).[34,35] IC_{50} values were calculated using Microsoft Excel software.

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Supporting Information Available: Table of cytotoxicity data for **1**−**22**; 1D and 2D NMR spectra of compounds **1**−**13** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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