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Cytotoxic quinazoline alkaloids from the seeds of *Peganum harmala*

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ABSTRACT

Seventeen quinazoline alkaloids and derivatives, containing two pairs of new epimers, named as (*S*)- and (*R*)-1-(2-aminobenzyl)-3-hydroxypyrrolidin-2-one *β*-D-glucopyranosyl-(1 → 6)-*β*-D-glucopyranoside (**1**, **2**), (*S*)- and (*R*)-vasicinone *β*-D-glucopyranosyl-(1 → 6)-*β*-D-glucopyranoside (**3**, **4**), and a new enantiomer (**12b**), together with six known ones (**5**–**8**, **10**, and **12a**), and three pairs of known enantiomers (**9**, **11**, and **13**), were isolated from the ethanol extracts of the seeds of *Peganum harmala* L.. Their structures including the absolute configuration were elucidated by using 1D and 2D NMR, and ECD calculation approaches. The cytotoxic activities of all isolated compounds were evaluated. **11** showed moderate cytotoxicity against PC-3 cells with an IC_{50} value of 15.41 μM.

Peganum harmala L. (Zygophyllaceae) is a perennial plant growing widely in Mediterranean Sea, North Africa, Middle East and Central Asian.[1–3] In China, *P. harmala* is mainly located in Inner Mongolia and Xinjiang Province, used as a traditionally folk herb for the treatment of hemiplegia, amnesia, asthma, malaria, and rheumatism.[1,4] The preparation consisted of total alkaloids from the seeds of *P. harmala* was used for the treatment of alimentary tract cancers in northwest China. The previous research has revealed that quinazolines and *β*-carboline alkaloids in *P. harmala* play an crucial role in pharmacology and therapeutic effects, such as monoamine oxidase inhibitory,[2,3] cholinesterase inhibitory,[4] anti-inflammatory,[5] antimicrobial,[5–7] vasorelaxant,[8] and antitumor activities.[1,9–11] The seeds of *P. harmala* are rich in quinazoline alkaloids. The main compounds in the seeds were vasicine and its glycoside with two glucose units.[3] Due to their unusual structures and fascinating bioactivities, many synthetic and natural products chemists have been making effort to improve their activity by the molecular modeling and structural modification.[12–16] Therefore, phytochemical investigation on the alkaloids of *P. harmala* was performed to find novel antitumor lead compounds.[11,17–20] After obtaining a series of *β*-carboline alkaloids from *P. harmala*, further research resulted in the isolation of 17 quinazoline alkaloids and derivatives (Fig. 1) including two pairs of new alkaloid glycoside epimers (**1**–**4**), and a new enantiomer (**12b**). Herein the structure elucidation of all new compounds was presented and all the isolates were evaluated for *in vitro* cytotoxicity on cancer cells (see Supplementary data for the details of experimental section).

Compound **1** was obtained as a yellow solid. The assigned molecular formula $C_{23}H_{34}N_2O_{12}$ was established by HRESIMS (*m*/*z* 531.2185 $[M+H]^+$, calcd 531.2185), corresponding to eight degrees of unsaturation. The ^1H NMR (Table 1) spectrum indicated the presence of 1,2-disubstituted benzene ring [δ_H 6.99 (1H, td, *J* = 7.5, 1.0 Hz), 6.96 (1H, dd, *J* = 7.5, 1.0 Hz), 6.63 (1H, dd, *J* = 7.5, 1.0 Hz), 6.51 (1H, td, *J* = 7.5, 1.0 Hz)], an amino group [δ_H 5.09 (2H, br.s)], an oxygenated methine [δ_H 4.48 (1H, t, *J* = 7.8 Hz)], a magnetic nonequivalent methylene [δ_H 4.23 (1H, d, *J* = 14.8 Hz), 4.19 (1H, d, *J* = 14.8 Hz)], and two methylenes [δ_H 3.22 (1H, td, *J* = 9.6, 2.6 Hz), 3.10 (1H, overlapped), 2.38 (1H, m), 1.83 (1H, m)]. The ^{13}C NMR and HSQC data (Table 1) displayed 23 carbon signals assigned to a carbonyl, a disubstituted benzene ring, three methylenes and one oxygenated methine, as well as two sets of glucosyl moiety. The anomeric protons of two glucosyls at δ_H 4.58 (1H, d, *J* = 7.8 Hz), and 4.22 (1H, d, *J* = 7.8 Hz) suggested two *β*-configuration sugar units in **1**. When **1** was hydrolyzed with 10% HCl, only D-glucose was detected in the hydrolysate by the HPLC-ORD (see Supplementary data for the details of acid hydrolysis). Comparison of ^1H and ^{13}C NMR data with those of **13**[21] indicated the aglycone of **1** as 1-(2-aminobenzyl)-3-hydroxypyrrolidin-2-one. Furthermore, the HMBC spectrum (Fig. 2) confirmed the above deduction. The observed HMBC correlations from δ_H 4.48 (H-3) to δ_C 102.7 (C-1′), from δ_H 4.58 (H-1′) to δ_C 74.9 (C-3), and from δ_H 4.22 (H-1″) to δ_C 68.7 (C-6′) indicated that the sugar chain was located at C-3 of the aglycone, and the terminal glucose

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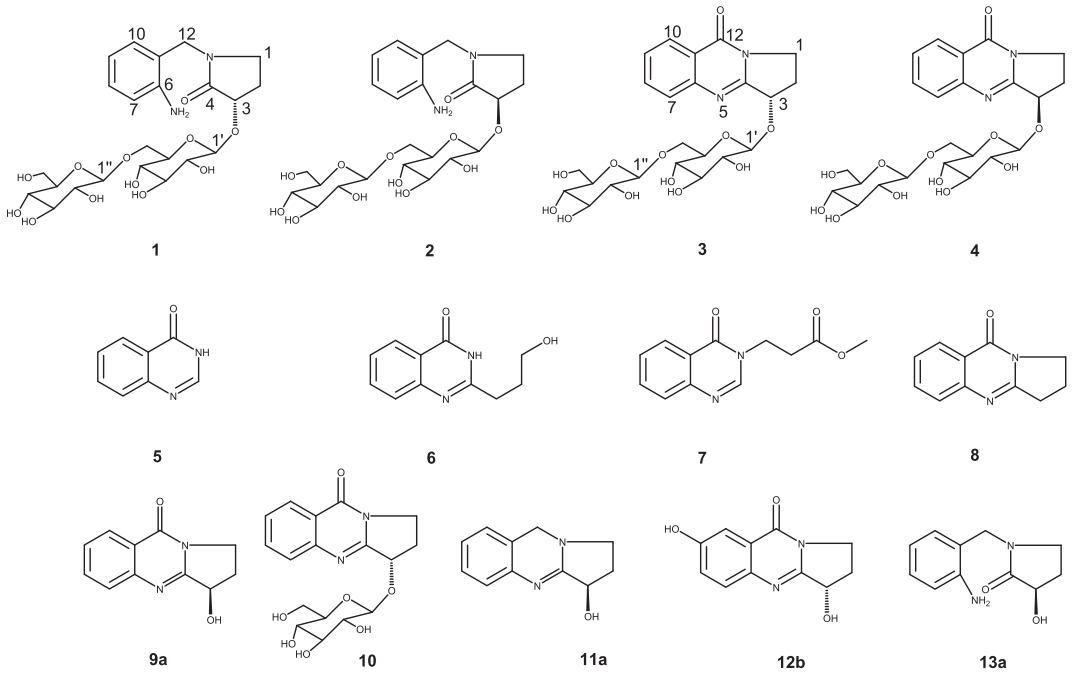

Fig. 1. Structures of compounds **1**–**13**.

Table 1
^{1}H (600 Hz) and ^{13}C (150 Hz) NMR data of compounds **1**–**4** (δ in ppm, J in Hz, DMSO d_6).

Position	**1**		**2**		**3**		**4**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1a	3.22 (td, 9.6, 2.6)	42.9	3.25 (td, 9.3, 2.6)	42.8	4.09 (m)	43.8	4.15 (ddd, 12.6, 8.2, 5.3)	43.5
1b	3.10 (overlapped)		3.12 (overlapped)		3.99 (ddd, 12.0, 7.9, 5.0)		3.97 (m)	
2a	2.38 (m)	26.9	2.35 (m)	25.6	2.56 (m)	28.4	2.54 (m)	26.8
2b	1.83 (m)		1.80 (m)		2.21 (m)		2.20 (m)	
3	4.48 (t, 7.8)	74.9	4.58 (t, 7.6)	72.9	5.22 (dd, 6.8, 4.8)	77.1	5.34 (t, 5.9)	76.0
4		172.1		171.4		158.1		157.8
6		146.5		146.5		148.6		148.7
7	6.63 (dd, 7.5, 1.0)	114.8	6.62 (dd, 7.8, 1.0)	114.8	7.72 (d, 8.0)	127.3	7.72 (dd, 8.0, 1.0)	127.2
8	6.99 (td, 7.5, 1.0)	128.6	6.99 (td, 7.8, 1.0)	128.6	7.83 (td, 8.0, 1.0)	134.3	7.84 (td, 8.0, 1.0)	134.3
9	6.51 (td, 7.5, 1.0)	115.8	6.51 (td, 7.8, 1.0)	115.8	7.55 (td, 8.0, 1.0)	126.8	7.55 (td, 8.0, 1.0)	126.8
10	6.96 (dd, 7.5, 1.0)	129.9	6.96 (dd, 7.8, 1.0)	130.0	8.16 (d, 8.0)	125.8	8.16 (dd, 8.0, 1.0)	125.8
11		118.5		118.5		120.8		120.6
12a	4.23 (d, 14.8)	43.1	4.29 (d, 14.8)	43.2		159.8		159.7
12b	4.19 (d, 14.8)		4.15 (d, 14.8)					
1′	4.58 (d, 7.8)	102.7	4.27 (d, 7.7)	100.7	4.72 (d, 7.8)	101.9	4.42 (d, 7.9)	100.3
2′	2.96 (m)	73.6	3.01 (m)	73.6	3.00 (m)	73.6	3.04 (m)	72.9
3′	3.15 (m)	76.7	3.16 (m)	76.5	3.16 (m)	76.8	3.20 (m)	76.4
4′	3.04 (m)	70.1	3.05 (m)	69.8	3.04 (m)	70.2	3.11 (m)	69.8
5′	3.32 (m)	75.8	3.31 (m)	76.0	3.42 (m)	75.9	3.40 (m)	75.8
6′a	4.01 (d, 11.5)	68.7	3.98 (d, 11.6)	68.3	4.06 (d, 11.4)	68.8	3.98 (d, 11.1)	68.3
6′b	3.51 (dd, 11.5, 7.5)		3.51 (dd, 11.6, 6.7)		3.58 (dd, 11.4, 7.2)		3.62 (dd, 11.1, 6.5)	
1″	4.22 (d, 7.8)	103.5	4.22 (d, 7.8)	103.4	4.29 (d, 7.8)	103.5	4.30 (d, 7.9)	103.5
2″	2.96 (m)	73.5	2.96 (m)	73.5	3.00 (m)	73.5	2.97 (m)	73.5
3″	3.10 (m)	76.7	3.12 (m)	76.7	3.16 (m)	76.6	3.16 (m)	76.6
4″	3.04 (m)	70.0	3.05 (m)	70.0	3.10 (m)	70.1	3.10 (m)	70.0
5″	3.04 (m)	76.9	3.05 (m)	76.8	3.08 (m)	76.9	3.08 (m)	76.9
6″a	3.66 (dd, 11.5, 5.6)	61.0	3.66 (dd, 11.4, 5.6)	61.0	3.69 (dd, 11.2, 4.2)	61.1	3.68 (dd, 11.2, 3.4)	61.1
6″b	3.42 (m)		3.43 (m)		3.46 (m)		3.45 (m)	
6-NH_2	5.09 (br.s)		5.11 (br.s)					
2′-OH	5.13 (d, 4.5)		5.21 (d, 3.7)		5.14 (d, 3.9)		5.34 (br.s)	
3′,4′-OH	5.07 (d, 5.2)		5.08 (br.s)		5.10 (d, 3.5)		5.12 (br.s)	
2″,3″-OH	4.97 (d, 3.8)		4.96 (overlapped)		5.00 (overlapped)		4.96 (br.s)	
4″-OH	4.93 (br.s)		4.95 (overlapped)		4.94 (d, 3.7)		4.92 (br.s)	
6″-OH	4.51 (t, 5.6)		4.50 (t, 5.4)		4.54 (t, 5.6)		4.51 (t, 5.6)	

unit was linked at C-6′ of the inner glucose unit. To determine the absolute configuration of C-3 in **1**, electronic circular dichroism (ECD) spectrum of (3*S*)-**1** (Fig. 3) were calculated by using the Gaussian09 program. The experimental ECD curve matched the simulated one of (3*S*)-**1** assigning the absolute configuration of C-3 as 3*S*. Consequently, the structure of **1** was defined as shown,