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Anti-diabetes Agents---I: Tetralone Derivative from *Juglans regia*

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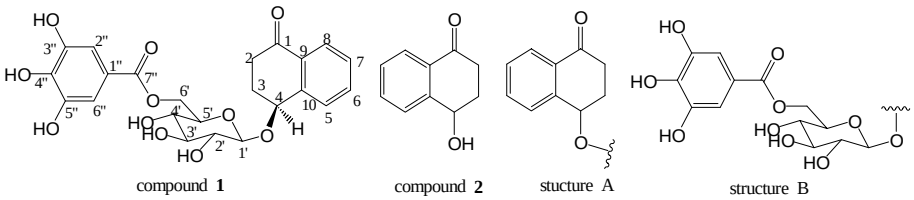
Abstract: A new compound, 4-hydroxy-α-tetralone-4-O-β-D-[6′-O-(3″,4″,5″-trihydroxybenzoyl) glucopyranoside (**1**), together with a known compound, 4-hydroxy-α-tetralone (**2**), has been isolated from the roots of *Juglans regia*. **2** showed moderate bioactivity against protein tyrosine phosphatase 1B (PTP1B).

Keyword: *Juglans regia*, Juglandaceae, tetralone, PTP1B inhibitor.

Many cellular and biochemical studies have shown that protein tyrosine phosphatase 1B (PTP1B) plays a major role in the dephosphorylation of the insulin receptor[1]. Thus potent and orally active PTP1B inhibitors could be potential pharmacological agents for the treatment of Type-2 diabetes and obesity.

In our research work for natural PTP1B inhibitor from our extract bank, we found that the ethanol extract of the roots of *Juglans regia* Linn. (Juglandaceae), designated PL00269, showed strong inhibitory bioactivity against PTP1B enzyme. Using the PTP1B enzyme bioassay as a guide, chromatography of the fraction afforded a new tetralone derivative, 4-hydroxy-α-tetralone-4-O-β-D-[6′-O-(3″,4″,5″-trihydroxybenzoyl)] glucopyranoside (**1**), together with a known compound, 4-hydroxy-α-tetralone (**2**)[2], which showed moderate bioactivity against PTP1B, IC_{50}= 66.7 μmol/L.

Figure 1 Structures of compound **1** and **2**



Compound **1**, an optically active colorless oil, $[\alpha]_D^{25}$-43 (*c* 0.67, CH_3OH), with the following spectral characteristics: IR (film) ν: 3384, 1674, 1610 cm^{-1}; UV (MeOH) λ_{max}

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(log ε): 261 (3.91), 214 (4.01) nm; positive FABMS *m/z* $[M^+ + 1]$ 477 (corresponding to $C_{23}H_{24}O_{11}$); NMR data see **Table 1**.

Comparing the NMR data of compound **1** (see **Table 1**) with those of **2** showed the presence of 4-hydroxy-α-tetralone skeleton in **1** (structure A in **Figure 1**), together with a 3,4,5-trihydroxyphenyl unit [δ_C: 120.8, 109.3 (x 2), 145.5 (x 2), 138.5], an unsaturated carbonyl (δ_C: 166.5), and a glycopyranosyl unit (δ_C: 102.8, 77.2, 74.3, 71.0, 75.0, 64.1). The later three units formed the structure B (**Figure 1**), which was revealed by comparing the NMR data of **1** with those of the similar compound, 1,4,8-trihydroxy-1-O-β-D-[6′-O-(3″,4″,5″-trihydroxybenzoyl)] glucopyranoside, isolated from *J. mandshurica*[3]. Combining structure A and B formed compound **1**. The equatorial orientation of H-4 was deduced from its coupling constant with the two protons at C-3 ($J_{H\text{-}4,\ H\text{-}3}$ = 6.6, 3.3 Hz). Therefore, the structure of compound **1** was determined as 4-hydroxy-α-tetralone-4-O-β-D-[6′-O-(3″,4″,5″-trihydroxybenzoyl)] glucopyranoside.

Table 1 ^{13}C NMR (CD_3COCD_3, 75 Hz) and ^1H NMR (CD_3COCD_3, 300 Hz) spectral data of **1**

No.	H (δppm, *J* Hz)	C (δppm)	No.	H (δppm, *J* Hz)	C (δppm)
1		197.5 s	3′	3.44, m	74.3 d
2	2.83, m; 2.45, m	34.6 t	4′	3.35 (t, 8.1)	71.0 d
3	2.39, m; 2.23, m	30.6 t	5′	3.58, m	75.0 d
4	4.99 (dd, 6.6, 3.3)	74.1 d	6′	4.64 (dd, 11.7, 2.1)	64.1 t
5	7.70 (d, 7.5)	128.6 d		4.41 (dd, 11.7, 7.2)	
6	7.57 (td, 7.5, 1.5)	133.7 d	1‴		120.8 s
7	7.43 (td, 7.5, 1.5)	126.7 d	2‴	7.18, s	109.3 d
8	7.89 (dd, 7.5, 1.5)	128.9 d	3‴		145.5 s
9		131.8 s	4‴		138.5 s
10		143.1 s	5‴		145.5 s
1′	4.53 (d, 7.5)	102.8 d	6‴	7.18, s	109.3 d
2′	3.46, m	77.2 d	7‴		166.5 s

Bioassay: PTP1B catalytic activities were routinely measured as in literature[4]. Na_3VO_4 acts as positive control (IC_{50} = 2μmol/L).

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