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Enantiomeric lignans with anti-β-amyloid aggregation activity from the twigs and leaves of *Pithecellobium clypearia* Benth

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ABSTRACT

To develop potential agents for slowing the progression of Alzheimer's disease, two pairs of new enantiomeric lignans, including a couple of rarely 8′,9′-dinor-3′,7-epoxy-8,4′-oxyneolignanes named (7*S*, 8*S*)- and (7*R*, 8*R*)-pithecellobiumin A (**1a**/**1b**) and a pair of 2′,9′-epoxy-arylnaphthalenes named (7*R*, 8*R*, 8′*R*)- and (7*S*, 8*S*, 8′*S*)-pithecellobiumin B (**2a**/**2b**) were separated by chiral high performance liquid chromatography (HPLC). Their planar structures were elucidated by spectroscopic data analyses. The absolute configurations were determined by comparing of experimental and calculated electronic circular dichroism (ECD). The inhibitory activity on Aβ aggregation of all optical pure compounds was tested by ThT assay. Interestingly, enantiomeric inhibitors **1a** (62.1%) and **1b** (81.6%) exhibited different degrees of anti-Aβ aggregation activity. However, **2a** (65.4%) and **2b** (68.4%) showed similar inhibition rate. The different inhibition profiles were explained by molecular dynamics and docking simulation studies.

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the progressive loss of cognitive functions [1]. For the observation of amyloid-β (Aβ) in senile plaques is one of the typical pathological hallmarks of AD [2], Aβ oligomers were targeted as an attractive drug development strategy [3]. It is reported that Aβ is sensitive to chiral environment due to the chirality composition of α-helical structure and l-amino acids [4,5]. Among them, $A\beta_{42}$ is initially believed to be the more harmful disease culprit compared with the most abundant form of its 40 amino acid long analogue [6]. The interaction between $A\beta_{42}$ and chiral inhibitors is significant and exhibits a specific orientation for AD treatment [4].

Pithecellobium clypearia Benth, a member of Fabaceae family, is widely distributed in many provinces of the southern China [7]. Previous phytochemical investigations revealed the isolation of abundant lignans and flavonoids [8–10]. They exhibited several pharmacological effects such as anti-β-amyloid aggregation [11], antiviral [7] and anti-inflammatory activity [12]. Numerous evidences indicated that quite a large percentage of enantiomers exist in natural products [13–15]. Considering different spatial configurations may lead the enantiomers to have diverse activity, safety and toxicity [16,17], optically pure compounds were required for the detailed investigation. During our further study on *P. clypearia*, two pairs of new enantiomeric lignans, including a couple of rarely 8′,9′-dinor-3′,7-epoxy-8,4′-oxyneolignanes named (7*S*, 8*S*)- and (7*R*, 8*R*)-pithecellobiumin A (**1a**/**1b**) and another pair of 2′,9′-epoxy-arylnaphthalenes named (7*R*, 8*R*, 8′*R*)- and (7*S*, 8*S*, 8′*S*)-pithecellobiumin B (**2a**/**2b**) were separated by a chiral chromatographic column. The inhibitory activity on Aβ aggregation was tested by ThT assay. Compared with the different inhibitory degrees of **1a** (62.1%) and **1b** (81.6%), **2a** (65.4%) and **2b** (68.4%) showed similar inhibition rate. The interesting observations were rationalized by molecular dynamics and docking simulation studies.

2. Experimental section

2.1. General experimental procedures

Optical rotations were measured on a JASCO DIP-370 digital polarimeter. UV spectra were recorded on a Shimadzu

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double-beam 210A spectrometer. ECD spectra were measured on a Bio-Logic MOS450 spectrophotometer, and IR spectra were obtained on a Bruker IFS 55 spectrometer. NMR experiments were performed on Bruker ARX-400 and AV-600 spectrometers. HR-ESIMS experiments were performed on a Bruker micro Q-TOF mass spectrometer. Column chromatography (CC) was performed on silica gel (200–300 mesh, Qingdao Marine Chemical Factory, Qingdao, People's Republic of China), octadecyl silica gel (50 μm, Japan), and HP20 colunm (75–150 μm Tokyo, Japan). Semi-preparative RP-HPLC isolation was achieved with an Agilent 1100 instrument using YMC C18 column (10 mm × 250 mm, 5 μm). Peak detection was made with a refractive index detector (RID). A chiral column Daicel IC (4.6 mm × 250 mm, 5 μm) was used for chiral HPLC separation on a Shimadzu LC-10AD liquid chromatograph instrument equipped with a Shimadzu SPD-M10A UV–vis detector. Thioflavin T and curcumin were purchased from Sigma-Aldrich (St. Louis, MO). Aβ_{42} was purchased from Aladdin (Qigang Rd, Fengxian, Shanghai). The OD value was performed on Varioskan Flash Multimode Reader (Thermo scientific). All reagents were HPLC or analytical grade and were purchased from Tianjin Damao Chemical Company (Tianjin, People's Republic of China). TLC was carried out on silica gel 60 F254 on glass plates (Qingdao Marine Chemical, Inc.) using various solvent systems, and spots were visualized by heating the silica gel plates sprayed with anisaldehyde–H_2SO_4 reagent.

2.2. Plant material

P. clypearia were purchased from Guangxi Province, People's Republic of China, in May 2015 and were identified by Professor Jincai Lu, Department of Pharmaceutical Botany, School of Traditional Chinese Materia Medica, Shenyang Pharmaceutical University. A voucher specimen (DG-20150529) has been deposited in the herbarium of the Department of Natural Products Chemistry, Shenyang Pharmaceutical University.

2.3. Extraction and isolation

The dried leaves and twigs of *P. Clypearia* (40 kg) were extracted with 70% EtOH for three times (50 L, 2 h for each time) under reflux. The organic extract was concentrated to dryness, suspended in water, and partitioned successively with *n*-BuOH (15.0 L × 4) to give 700 g of crude extract. The sample was chromatographed on a silica gel column (200–300 mesh) with a step gradient of CH_2Cl_2-MeOH (from 50:1 to 2:1) to yield three fractions (A–C). Fraction B was further fractionated by a polyamide gel CC (200–300) mesh with a gradient of increasing polarity of a solvent system consisting of EtOH to H_2O (0:100, 20:80, 40:60, 60:40, 80:20 and 90:10 v/v) to give two fractions (D and E). The first fraction was then passed over MCI-gel CHP 20P eluted with mixtures of EtOH-H_2O (40:60, 60:40, 80:20, and 1:0 v/v) to yield fractions F and G. Separations of F and G were subjected sequentially to reversed-phase C18 silica gel and silica gel column chromatography. Purification of the obtained fractions by semi-preparative reversed-phase C18 HPLC afforded compounds **1** (4.3 mg) and **2** (9.6 mg). Subsequently, the separation of optical pure compounds by chiral HPLC using a Daicel IC column eluted with *n*-hexane and 2-propanol (1:1) afforded **1a**, **1b** (t_R 31, 59 min, 1.3, 1.7 mg) and **2a**, **2b** (t_R 34, 41 min, 4.1, 4.3 mg).

(7*S*, 8*S*)- and (7*R*, 8*R*)-Pithecellobiumin A (**1**): Pale yellow solid; $[\alpha]_D^{20}$ − 1 (c 0.10, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 210 (6.21), 276 (3.34) nm; IR (KBr) ν_{max} 3409, 2937, 1630, 1275 cm^{-1}; ^1H and ^{13}C NMR data see Table 1; HRESIMS *m*/*z* 415.0991 $[M+Na]^+$ (calcd for $C_{19}H_{20}O_9Na$, 415.1000). (7*S*, 8*S*)-pithecellobiumin A_1 (**1a**): Pale yellow solid; $[\alpha]_D^{20}$ + 22 (c 0.10, MeOH); ECD (MeOH) λ ($\Delta\varepsilon$): 207 (−0.48), λ ($\Delta\varepsilon$) 224 (−0.37), 260 (+0.75), 279 (+1.47), 306 (−0.22) nm; (7*R*, 8*R*)-pithecellobiumin A (**1b**): Pale yellow solid; $[\alpha]_D^{20}$ − 15 (c 0.10, MeOH); ECD (MeOH) λ ($\Delta\varepsilon$): 208 (+1.25), 229 (+0.45), 264 (−0.89), 279 (−1.43), 305 (+0.31) nm.

Table 1
^1H and ^{13}C NMR spectral data for compounds **1** and **2** (in DMSO d_6).

Position	**1**		**2**	
	δ_H (multi, *J* in Hz)	δ_C	δ_H (multi, *J* in Hz)	δ_C
1	–	126.2	–	124.2
2	6.72, s	105.3	–	151.8
3	–	147.9	–	145.7
4	–	135.9	–	135.1
5	–	147.9	–	146.4
6	6.72, s	105.3	6.14, s	101.2
7	4.89, d (7.83)	76.0	4.43, brs	43.4
8	4.22, m	78.1	1.99, m	28.8
9	3.40, dd (12.3, 5.0)	60.1	4.30, dd (11.9, 2.8)	79.7
	3.53, dd (12.3, 2.6)		3.65, d (11.9)	
1′	–	121.2	–	125.8
2′	6.98, d (2.0)	108.9	–	122.7
3′	–	144.0	–	146.0
4′	–	136.5	–	136.6
5′	–	146.2	–	146.8
6′	7.07, d (2.0)	109.2	6.39, s	106.2
7′	–	165.9	2.93, dd (17.3, 7.2)	33.3
			2.72, d (17.3)	
8′	–	–	2.14, m	29.5
9′	–	–	3.39, m	63.1
3-OCH_3	3.76, s	56.1	3.29, s	58.9
4-OH	9.65, s	–	8.02, s	–
5-OCH_3	3.76, s	56.1	3.63, s	55.6
3′-OCH_3	–	–	3.77, s	60.6
4′-OH	–	–	8.12, s	–
5′-OCH_3	–	–	3.71, s	55.6
5′-OH	8.53, s	–	–	–
7′-OCH_3	3.77	51.9	–	–

The coupling constants (*J*) were in parentheses and reported in Hz; chemical shifts were given in ppm; 1H NMR spectra were recorded at 400 MHz and 13C NMR spectra were recorded at 100 MHz.

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