Isolation of Antithrombotic Phenolic Compounds from the Leaves of *Crataegus pinnatifida*

Shao-Jiang Song[1,2], Ling-Zhi Li[1,2], Pin-Yi Gao[3], Yan-Qiang Yuan[5], Ru-Ping Wang[1,2], Ke-Chun Liu[5], Ying Peng[4]

[1] School of Traditional Chinese Materia Medica, Shenyang Pharmaceutical University, Shenyang, PR China
[2] State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, PR China
[3] College of Chemical Engineering, Shenyang University of Chemical Technology, Shenyang, PR China
[4] School of Pharmacy, Shenyang Pharmaceutical University, Shenyang, PR China
[5] Biology Institute of Shandong Academy of Sciences, Jinan, PR China

Abstract

Four novel phenolic compounds (**1**–**4**) were isolated from the leaves of *Crataegus pinnatifida*, along with three known ones (**5**–**7**). Their structures were elucidated as: methyl 4-*O*-*β*-D-glucopyranosyl-3-[(2*E*,6*E*)-8-*O*-*β*-D-glucopyranosyl-3,7-dimethyl-2,6-octadienyl] benzoate (**1**), biphenyl-5-ol-3-*O*-*β*-D-glucoside (**2**), 3,4′-dimethoxy-biphenyl-5-ol-4-*O*-*β*-D-glucoside (**3**), (*E*)-6-(benzoyloxy)-1-hydroxyhex-3-en-2-*O*-*β*-D-glucoside (**4**), shanyenoside A (**5**), eriodectyol (**6**), and 2″-*O*-rhamnosyl vitexin (**7**), using a combination of mass spectroscopy, 1D and 2D NMR spectroscopy, and chemical analysis. The antithrombotic activity of the isolated compounds was investigated on the transgenic zebra fish system. Among them, eriodectyol (**6**) potently inhibited the production of thrombus.

Key words

Crataegus pinnatifida · Rosaceae · phenolic compounds · antithrombotic activity

Supporting information available online at http://www.thieme-connect.de/ejournals/toc/plantamedica

Hawthorn, well-known as both a medicine and food material, is the common name of the plants in the genus *Crataegus* of the Rosaceae family, which are distributed in the Northern Hemisphere, mostly in China, Japan, South Korea, Europe, and North America. More than 1000 species of the genus have been described [1,2]. Currently, hawthorn leaves, flowers, and both green (unripe) and red (ripe) berries are used to make herbal preparations to treat patients with severe heart diseases, such as congestive heart failure, high blood pressure, hypoxia, and hyperlipemia [3,4]. Aqueous alcohol extracts of hawthorn fruits and leaves are used as dietary supplements and herbal medicines in the United States and Europe for treating heart failure degrees I–III according to the classification of the New York Heart Association (NYHA) (11) [5]. Fruits and leaves of hawthorn are rich in phenolic compounds, which are considered the key bioactive compounds of this plant, offering antioxidative, free radical scavenging, anti-inflammatory, vasorelaxing, and hypolipidemic effects [6,7]. Previous investigations on the leaves of *Crataegus pinnatifida* Bge. by our group have resulted in the isolation and characterization of phenols, lignans, and terpenoids. In order to isolate the minor active constituents, we reinvestigated this plant and obtained four novel phenolic compounds (**1**–**4**) from the leaves of *C. pinnatifida*, along with three known ones (**5**–**7**) (**Fig. 1**).

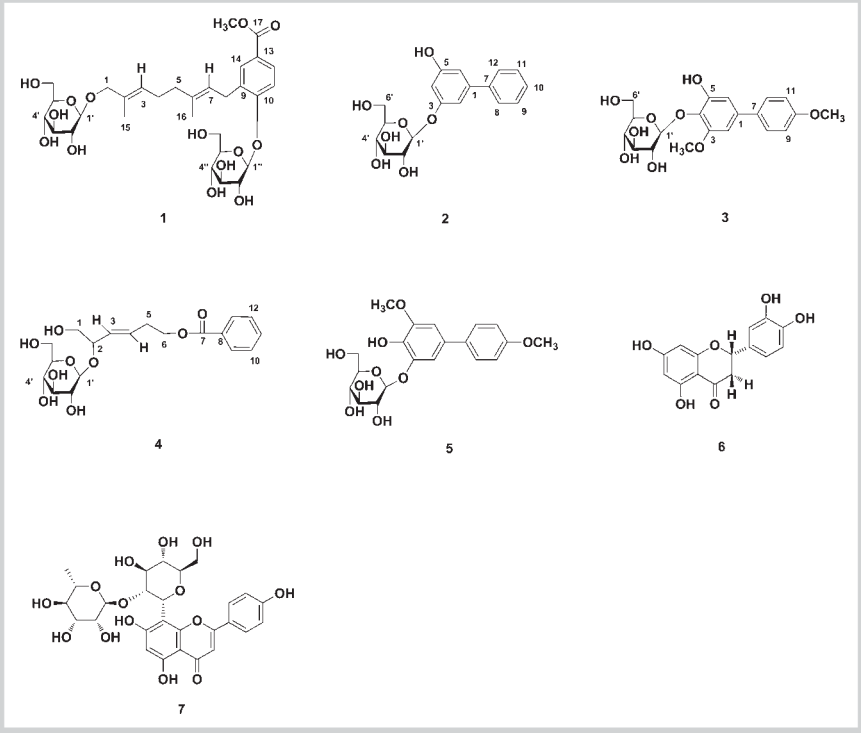

Fig. 1 Structures of compounds **1**–**7** from the leaves of *C. pinnatifida*.

Table 1 ^{1}H NMR and ^{13}C NMR spectroscopic data for compounds **1**–**4**.

Positions	1		2		3		4	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	3.87 d (11.7); 4.08 d (11.7)	74.4		142.8		137.3	4.50 m (2H)	66.6
2		132.5	6.75 br.s	106.4	6.68 br.s	107.9	3.32 m	74.0
3	5.40 m	127.8		159.7		153.8	5.47 m (17.4)	132.8
4	2.11 m (2H)	26.7	6.46 br.s	103.6		134.0	5.54 m (17.4)	127.5
5	2.04 m (2H)	40.1		159.3		151.4	2.55 m (2H)	27.5
6		136.9	6.68 br.s	108.3	6.69 br.s	103.3	4.29 t (6.6) (2H)	64.5
7	5.33 m	122.4		140.9		133.2		166.2
8	3.35 m (2H)	28.3	7.58 d (8.4)	127.3	7.54 d (8.4)	128.4		130.2
9		130.8	7.42 t (8.4)	129.6	6.98 d (8.4)	114.9	7.97 dd (8.4, 1.2)	129.6
10		159.6	7.33 t (8.4)	128.3		159.5	7.52 t (8.4)	129.2
11	7.16 d (8.4)	114.7	7.42 t (8.4)	129.6	6.98 d (8.4)	114.9	7.65 t (8.4)	133.7
12	7.76 d (8.4)	129.4	7.58 d (8.4)	127.3	7.54 d (8.4)	128.4	7.52 t (8.4)	129.2
13		123.3					7.97 t (8.4)	129.6
14	7.71 br.s	130.8						
15	1.60 s	14.6						
16	1.68 s	16.6						
17		166.8						
OMe	3.80 s	52.6			3.78 s	55.8		
OMe					3.81 s	56.3		
1′	4.08 d (7.8)	100.9	4.86 d (7.2)	101.2	4.60 d (7.2)	105.9	4.15 d (7.8)	104.1
2′	3.33 m	74.0	3.21 m	74.0	3.27 m	74.6	2.95 m	74.0
3′	2.94 m	77.8	3.28 m	77.8	3.16 m	77.9	3.08 m	77.3
4′	3.09 m	70.3	3.20 m	70.5	3.24 m	70.3	3.04 m	70.4
5′	3.44 m	77.3	3.14 m	77.6	3.27 m	76.9	3.14 m	76.8
6′	3.63 m; 4.08 m	61.3	3.68 m; 3.49 m	61.3	3.64 d (10.8); 3.51 dd (10.8, 4.8)	61.2	3.42 m; 3.63 m	61.4
1′′	4.94 d (7.8)	102.3						
2′′	3.31 m	74.4						
3′′	3.10 m	77.8						
4′′	3.16 m	70.8						
5′′	3.41 m	77.3						
6′′	3.87 d (11.7); 4.09 m	61.7						

NMR spectroscopic data were recorded in DMSO-d_6 at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR)

Compound **1** was obtained as colourless needles, and its molecular formula was determined as $C_{30}H_{44}O_{14}$ by HRESIMS at *m/z* 651.2624 $[M + Na]^+$ (calcd. 651.2623). The ^{1}H NMR spectrum (**Table 1**) showed the presence of two methyl groups attached to the quaternary carbon at δ 1.60 (3H, s), 1.68 (3H, s), a methoxyl group attached to the carbonyl group at δ 3.80 (3H, s), a 1,3,4-trisubstituted benzene indicated by the signals at δ 7.16 (1H, d, J = 8.4 Hz), 7.76 (1H, br.d, J = 8.4 Hz), 7.71 (1H, br.s, J = 8.4 Hz), two olefinic groups at δ 5.33 (1H, m), 5.40 (1H, m), and two anomeric proton signals at δ 4.08 (1H, d, J = 7.8 Hz) and 4.94 (1H, d, J = 7.8 Hz). The ^{13}C NMR spectrum exhibited two methyls at δ 14.6, 16.6, one methoxyl at δ 52.6, two olefinic groups at δ 132.5, 127.8, 136.9, 122.4, six aromatic carbons at δ 159.6, 114.7, 129.4, 123.3, 130.8 × 2, and one carbonyl carbon at δ 166.8, in addition to the sugar part. Further analysis of 2D NMR spectra of **1** established the novel skeleton as in **Fig. 1**. The ^{13}C NMR chemical shifts and spin-spin coupling constants (7.8, 7.8 Hz) of two anomeric protons allowed the identification of two β-glucopyranosyl moieties [8]. The absolute configuration of the sugar part in **1** was determined by acid hydrolysis. The glucose isolated from the acid hydrolysis of **1** gave a positive specific rotation $[\alpha]_D^{20}$ = +15.0 (c = 0.80, H_2O), indicating that it was D-glucose [9]. This fact was further confirmed by comparing its R_f value with the authentic sample. Both the glucose isolated and authentic sample exhibited the same R_f value (0.45) in the same condition. The glycosidic sites were established unambiguously by an HMBC experiment in which long-range correlations between H-1′ (δ_H 4.08) and C-1 (δ_C 74.4), H-1″ (δ_H 4.94) and C-10 (δ_C 159.6) were observed (**Fig. 2**). In addition, the geometry of the 2,3- and 6,7-double bonds were both assigned to be *E* on the basis of high-field olefinic methyl resonances at δ_C 14.6 (C-15) and 16.6 (C-16) [10]. Consequently, the structure of compound **1** was established as methyl 4-*O*-β-D-glucopyranosyl-3-[(2*E*,6*E*)-8-*O*-β-D-glucopyranosyl-3,7-dimethyl-2,6-octadienyl]benzoate, and given the trivial name shanyenoside E.

Compound **2** was obtained as amorphous powder. The molecular formula was established as $C_{18}H_{20}O_7$ by HRESIMS, which showed a quasimolecular ion peak $[M + Na]^+$ at *m/z* 371.1104 (calcd. 371.1101). The ^{1}H NMR spectrum (**Table 1**) showed three proton signals of a phenyl ring (1,3,5-substitution pattern) at δ 6.75 (1H, br.s), 6.46 (1H, br.s), and 6.68 (1H, br.s), five aromatic protons of a single phenyl ring (single substitution pattern) at δ 7.58 (1H, d, J = 8.4 Hz), 7.42 (2H, t, J = 8.4 Hz), 7.33 (2H, t, J = 8.4 Hz) and one anomeric proton signal at δ 4.86 (1H, d, J = 7.2 Hz). The ^{13}C NMR spectrum exhibited twelve aromatic carbons of two phenyl rings at δ 142.8, 106.4, 159.7, 103.6, 159.3, 108.3, 140.9, 127.3 × 2,

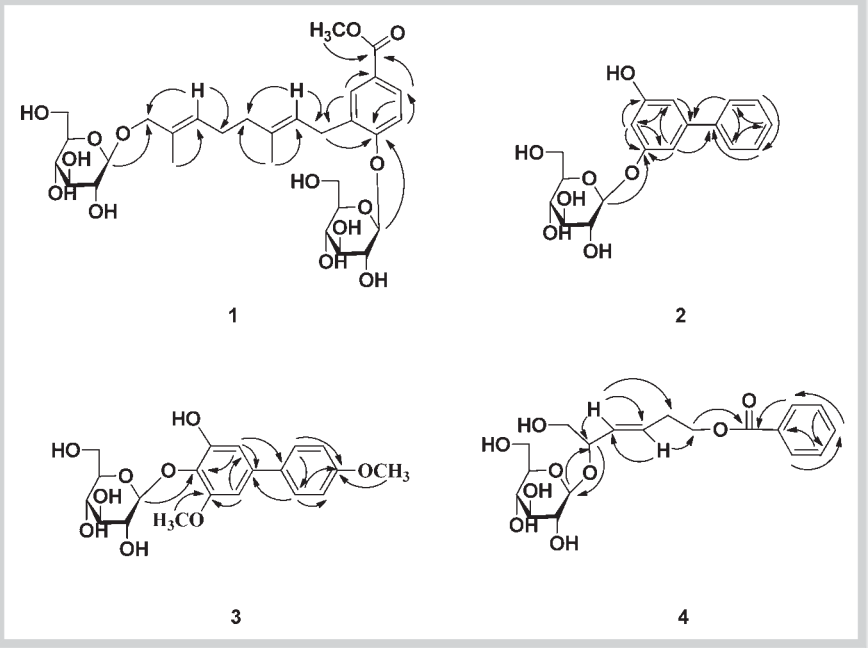

Fig. 2 Observed key HMBC correlations of compounds **1**–**4**.

128.3, 129.6 × 2, and a glucopyranosyl group at δ 101.2, 74.0, 77.8, 70.5, 77.6, 61.3, which revealed that **2** had a skeleton of biphenyl. Further demonstration of the planar skeleton structure of **2** was obtained from the HMBC experiment (**Fig. 2**). The correlation between the signal at δ 159.7 (C-3) and δ 4.86 (H-1′) indicated that the glucopyranosyl group was located at C-3. β-Stereochemistry of anomeric carbon was determined by the coupling constant (*J* = 7.2 Hz) of the anomeric proton [8, 11]. The absolute configuration of glucose was determined by acid hydrolysis and comparison with an authentic sample [9]. Therefore, the structure of **2** was identified as biphenyl-5-ol-3-*O*-β-D-glucoside and given the trivial name shanyenoside F.

Compound **3** was obtained as colourless needles. According to the HRESIMS, ^{1}H, and ^{13}C NMR spectroscopic data, the molecular formula of **3** was determined to be $C_{20}H_{24}O_9$, $[M + Na]^+$ at *m/z* 431.1314 (calcd. 431.1313). The ^{1}H NMR spectrum (**Table 1**) showed proton signals of two methoxyl groups at δ 3.78 (3H, s), 3.81 (3H, s), two aromatic proton signals of a phenyl ring (1,3,4,5-substitution pattern) at δ 6.68 (1H, br.s) and 6.69 (1H, br.s), four aromatic protons of a phenyl ring (1,4 substitution pattern) at δ 7.54 (2H, d, *J* = 8.4 Hz), 6.98 (2H, d, *J* = 8.4 Hz), and one anomeric proton signal at δ 4.60 (1H, d, *J* = 7.2 Hz). The ^{13}C NMR spectrum exhibited twelve aromatic carbons of two phenyl rings at δ 137.9, 107.9, 153.8, 134.0, 151.4, 103.3, 133.2, 128.4 × 2, 159.5, 114.9 × 2, and a glucopyranosyl group at δ 105.9, 74.6, 77.9, 70.3, 76.9, 61.2, which suggested that **3** had the same skeleton as **2**. Further demonstration of the planar skeleton structure of **3** was obtained from the HMBC experiment (**Fig. 2**). The correlation between the signal at δ 134.0 (C-4) and δ 4.60 (H-1′) indicated that the glucopyranosyl group was located at C-4. β-Stereochemistry of anomeric carbon was determined by the coupling constant (*J* = 7.2 Hz) of the anomeric proton [8, 11]. Furthermore, the absolute configuration of glucose was determined by acid hydrolysis and comparison with an authentic sample [9]. Therefore, the structure of **3** was identified as 3,4′-dimethoxy-biphenyl-5-ol-4-*O*-β-D-glucoside and given the trivial name shanyenoside G.

Compound **4** was isolated as amorphous powder, and its molecular formula was determined to be $C_{19}H_{26}O_9$, based on HRESIMS (experimental *m/z* $[M + Na]^+$ at *m/z* 421.1467, calcd. 421.1469). The ^{1}H NMR spectrum (**Table 1**) showed the presence of five aromatic protons of a single phenyl ring (single substitution pattern) at δ 7.97 (2H, dd, *J* = 8.4, 1.2 Hz), 7.52 (2H, t, *J* = 8.4 Hz), 7.65 (1H, t, *J* = 8.4 Hz), and one trans olefin group at δ 5.47 (2H, m, *J* = 17.4 Hz), 5.54 (1H, m, *J* = 17.4 Hz). In the sugar part, one anomeric proton signal at δ 4.15 (1H, *J* = 7.8 Hz) and the ^{13}C NMR signals of sugar showed the existence of a glucopyranosyl moiety (**Table 1**). This assignment was confirmed by detailed analysis of the HSQC and HMBC spectra. The HMBC correlation between the signal at δ 74.0 (C-2) and δ 4.15 (H-1′) indicated that the glucopyranosyl group was located at C-2. The β-form of glucose was indicated by the coupling constant of the anomeric proton signal at δ_H 4.15 (1H, d, *J* = 7.8 Hz) in the ^{1}H NMR data [10]. The absolute configuration of glucose was further determined by acid hydrolysis and comparison with an authentic sample [9]. Thus, the structure of compound **4** was established as (*E*)-6-(benzoyloxy)-1-hydroxyhex-3-en-2-*O*-β-D-glucoside and given the trivial name shanyenoside H.

By comparing physical and spectroscopic data with those from the literature, the three known constituents were identified as shanyenoside A (**5**) [12], eriodectyol (**6**) [13], and 2″-*O*-rhamnosyl vitexin (**7**) [14].

The small size (3–4 cm long), ease of care (easily kept and bred in the laboratory), and rapid generation time (produce 200 eggs per spawning and reach sexual maturity within 2–3 months) are but a few of the aspects making zebrafish a particularly useful model organism [15–20]. All isolated compounds were tested *in vivo* for their antithrombotic activity on transgenic zebra fish system. Among them, compound **6** showed significant antithrombotic activity. Compared with the control group, the forming thrombosis time of the tested zebra fish was obviously prolonged, which indicated that compound **6** (eriodectyol) potently inhibited the production of thrombus (* $p < 0.05$) (**Fig. 3**).

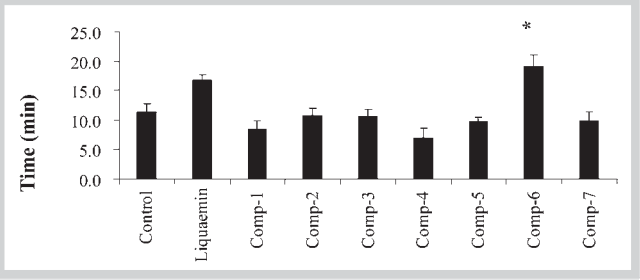

Fig. 3 Antithrombotic activity of compounds **1**–**7** on the transgenic zebra fish system. Differences statistically significant from control: * $p < 0.05$.

Materials and Methods

The leaves of *C. pinnatifida* were collected from Liaoning province, China, in June 2007, and authenticated by Prof. Qi-Shi Sun, Department of Pharmacognosy, Shenyang Pharmaceutical University. A voucher specimen (No. CPLN0706) is kept in the Nature Products Laboratory of the Shenyang Pharmaceutical University, Shenyang, China.

Air-dried leaves (5.0 kg) of *C. pinnatifida* were extracted with 70% ethanol (30 L) by reflux (95 °C, 2 h) three times. The ethanol extract was concentrated *in vacuo* to yield a brownish-dark crude extract (492 g) which was subjected to macroporous resin (0.25–0.84 mm, 10 kg) column chromatography (17 × 150 cm) eluted with EtOH/H_2O (v/v = 0 : 100, 30 : 70, 50 : 50, 95 : 5) to yield 4 main fractions: Frs. A–D, according to chemical monitoring by TLC. Fr. B (120 g) was further separated by column chromatography (10 × 80 cm) on Diaion HP-20 eluted with MeOH/H_2O (v/v = 60 : 40, 70 : 30, 80 : 20, 100 : 0) to provide subfractions B1–B4, among which Fr. B1 (15 g) was purified by silica gel (200–300 mesh, 80 g) column chromatography (5 × 50 cm) eluting with a CH_2Cl_2-MeOH gradient system (v/v = 30 : 1, 20 : 1, 10 : 1, 5 : 1, and 0 : 1) to yield compounds **1** (12 mg) and **7** (500 mg) which were further purified over Sephadex LH-20 column chromatography (2.5 × 70 cm) eluting with MeOH : H_2O (2 : 3). Subfraction B2 (20 g) was applied to MCI gel column chromatography (4 × 40 cm) eluting with MeOH : H_2O (v/v = 0 : 100 → 100 : 0) and further purified over Sephadex LH-20 column chromatography (2.5 × 100 cm) eluting with MeOH : H_2O (1 : 1), followed by preparative HPLC (65% MeOH) to yield compounds **2** (t_R 31.6 min, 11 mg), **3** (t_R 38.5 min, 28 mg), and **5** (t_R 40.2 min, 58 mg). Fr. B3 (10 g) was then combined on the basis of TLC analysis and finally purified by reversed-phase C18 silica gel (70 µm, 50 g) column chromatography (4 × 40 cm) using MeOH/H_2O with a gradient solvent system of (v/v = 30 : 70 → 90 : 10) and HPLC (75% MeOH) to obtain compounds **4** (t_R 20.2 min, 10 mg) and **6** (t_R 23.2 min, 12 mg). The purities of all isolates (> 95.0%) were analysed by HPLC.

Shanyenoside E (**1**) was obtained as colourless needles. HRESIMS *m/z* 651.2624 $[M + Na]^+$ (calcd. for $C_{30}H_{44}O_{14}Na$, 651.2623). For ^1H and ^{13}C NMR spectroscopic data, see **Table 1**.

Shanyenoside F (**2**) was obtained as amorphous powder. HRESIMS *m/z* 371.1104 $[M + Na]^+$ (calcd. for $C_{18}H_{20}O_7Na$ 371.1101). For ^1H and ^{13}C NMR spectroscopic data, see **Table 1**.

Shanyenoside G (**3**) was obtained as colourless needles. HRESIMS *m/z* 431.1314 $[M + Na]^+$ (calcd. for $C_{20}H_{24}O_9Na$ 431.1313). For ^1H and ^{13}C NMR spectroscopic data, see **Table 1**.

Shanyenoside H (**4**) was isolated as amorphous powder. HRESIMS *m/z* 421.1467 $[M + Na]^+$ (calcd. for $C_{19}H_{26}O_9Na$, 421.1469). For ^1H and ^{13}C NMR spectroscopic data, see **Table 1**.

Supporting information

General experimental procedures, detailed extraction/isolation of compounds, NMR and HRESIMS spectra of novel compounds, as well as protocols for the *in vivo* antithrombotic assay on the transgenic zebra fish system are available as Supporting Information.

Acknowledgements

This research was supported by the China National Fundamental Fund of Personnel Training (No. J1103606) and the China State Key Laboratory Open Project of Bioactive Substance and Function of Natural Medicines. The authors wish to thank Professor Qi-Shi Sun (Shenyang Pharmaceutical University, Shenyang, People's Republic of China) for identification of the plant material.

Conflict of Interest

All authors declare that there are no conflicts of interest.

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received April 19, 2012
revised August 27, 2012
accepted September 29, 2012

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DOI http://dx.doi.org/10.1055/s-0032-1327877
Published online October 31, 2012
Planta Med 2012; 78: 1967–1971

ISSN 0032-0943

Correspondence
Prof. Dr. Ying Peng
School of Pharmacy
Shenyang Pharmaceutical University
103 Wenhua Road
Shenyang Liaoning 110016
PR China
Phone: + 86 24 23 98 63 61
Fax: + 86 24 23 98 63 61
yingpeng99@yahoo.com.cn