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Synthesis of andrographolide derivatives: A new family of α-glucosidase inhibitors

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Abstract—Andrographolide (**1**), the cytotoxic agent of the plant *Andrographis paniculata*, was subjected to semi-synthetic studies leading to a series of new derivatives, a novel family of glucosidase inhibitors. Nicotination of 3,19-hydroxyls in 15-alkylidene andrographolide derivatives (**9**) was favorable to α-glucosidase inhibition activity. Among them, 15-*p*-chlorobenzylidene-14-deoxy-11,12-didehydro-3,19-dinicotinateandrographolide (**11c**) was a very potent inhibitor against α-glucosidase with an IC_{50} value of 6 μM. However, all compounds concerned for β-glucosidase showed no inhibition. All compounds synthesized were characterized by the analysis of NMR, IR, HRMS spectra and the stereochemistry of **2** was confirmed by X-ray analysis.

1. Introduction

The intense interest of glucosidase inhibitors in chemistry, biochemistry and pharmacology has led to many types of natural and synthetic inhibitors, which are aiding in both unraveling the mechanism of glucosidase action and development of potential pharmaceuticals such as antitumor,[1–3] antiviral,[4,5] antidiabetic,[6–9] immunoregulatory agents,[10] and so forth. Various types of inhibitors have also been designed based on the structures that resemble the glycosyl cations in a transition state of hydrolysis by glucosidase.[11]

The plant, *Andrographis paniculata*,[12,13] is extensively used in the traditional Chinese medicine.[14,15] Extracts of the plant and their constituents are reported to exhibit a wide spectrum of biological activities including antibacterial,[16,17] antiinflammatory,[18,19] antimalarial,[20,21] immunological,[22,23] hepatoprotective,[24] and antitumor[25] properties. In recent years, the antidiabetic activity of the plant has also attracted some researchers' attention.[26–30] In the course of our study on searching for glucosidase inhibitors, some andrographolide derivatives have been proven to be potent and specific α-glucosidase inhibitor.[31]

Some glucosidase inhibitors show antitumor metastasis[32] and anti-HIV activities,[33] and are also clinically useful for treatment of diabetes[34], which prompted us to study andrographolide to synthesize new stronger glucosidase inhibitors.

In this study, a series of andrographolide derivatives were synthesized by a facile route. And the α-glucosidase inhibition activity of the derivatives was appraised, which would be aiding in designing and synthesizing novel stronger α-glucosidase inhibitors and exploring the mechanisms of *A. paniculata* as drugs, especially as antidiabetic agents.

2. Results and discussion

The structure of andrographolide contains: (1) an α-alkylidene-γ-butyrolactone moiety. (2) two double bonds $\Delta^{8(17)}$ and $\Delta^{12(13)}$. (3) three hydroxyls at C-3, C-19, and C-14. Of the three hydroxyls, that one at C-14 is allylic, the others at C-3 and C-19 are secondary and primary, respectively. Andrographolide derivatives were synthesized by modification of the above structural features.

Keywords: Synthesis; Glucosidase inhibitor; Andrographolide derivative.
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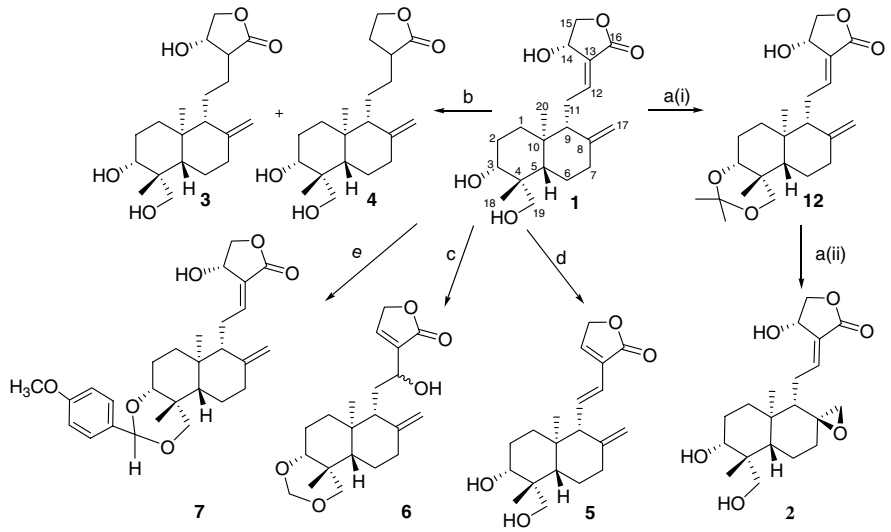


Scheme 1. Synthesis of compounds **2**–**7**. Reagents and conditions: (a) i—acetone, *p*-TsOH, 2,2-dimethoxy propane, reflux, 10 h. ii—$CHCl_3$, *m*CPBA, rt, 2h; (b) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, methanol, −5 to 5 °C, 10–30 min; (c) i—THF, H_2SO_4, paraform, reflux, 1 h; ii—CH_2Cl_2, PDC, rt, 3 h; (d) xylene, pyridine, Al_2O_3, reflux, 6–10 h; (e) THF, H_2SO_4, anisaldehyde, reflux, 1.5 h.

In order to find a lead compound, **2**–**7** were designed and synthesized (Scheme 1). Compound **2** was obtained by the selective epoxidation of the exocyclic double bond ($\Delta^{8(17)}$) of andrographolide (**1**) with *m*-CPBA. Initially, the efforts to epoxidate the double bond ($\Delta^{8(17)}$) of **1**–**2** did not give satisfactory results. It is probably the reason that **1** is insoluble in the reaction solution. Thus, the hydroxyls, at C-3, C-9 of **1** were protected as an isopropylidene to **12** which was oxidated to **2**. The structure of **2** was elucidated by the spectral analysis and finally confirmed by single crystal X-ray diffraction analysis (Crystallographic data for **2** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number 631560.). The perspective view of the molecule is shown in Figure 1. Both the six-membered rings adopt the chair conformation, whereas the five-membered is an envelope conformation. The absolute stereochemistry at C-3, C-4, C-5, C-9, and C-10 was assumed to be the same as that observed in **1**. Based on this information, the conformations at C-8 and C-14 have been confirmed to be **S**.

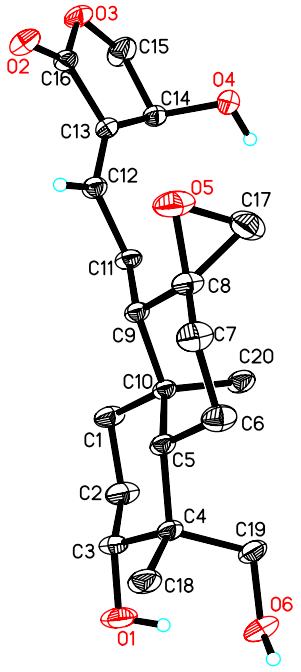


Figure 1. Structure of **2**.

Compound **3** was prepared by selective reduction of the conjugated double bond. To further study the role of allylic hydroxyl at C-14 and the conjugated double bond, **5** and **6** were prepared, in which the exocyclic double bond ($\Delta^{12(13)}$) isomerized to the endocyclic double bond ($\Delta^{13(14)}$), with the simultaneous removal of C-14 hydroxyl. Compound **5** was obtained by refluxing **1** in the mixture of xylene and pyridine in the presence of Al_2O_3. Compound **6** was synthesized by the oxidation of 3,19-methene-*O*-andrographolide with PDC. Compound **7** was also obtained by heating **1** and anisaldehyde in THF in the presence of H_2SO_4. According to the NMR spectra, 7 should be a single isomer. However, its stereochemistry could be confirmed based on the present data.

In vitro activity screening of the above derivatives showed that **3**, **5**, **6**, and **7** demonstrated α-glucosidase inhibition activity, while **1**, **2**, and **4** showed no activity at 100 μM (Table 1). It is possible for **3** and **5** to be the lead compound.

However, **4** was a major byproduct and yielded easily during the course of preparation of **3**, which led to the low yield of **3**. On the other hand, it is difficult to selectively modify the hydroxyls present in **3**. Though **3** showed the highest inhibition activity, it was not taken as the lead compound. On the contrary, **5** could be prepared in excellent yield, possessing butenolide moiety

Table 1. α-Glucosidase inhibition activity of andrographolide analogues

α-Glucosidase inhibition activity[b] (IC_{50} μM)			
Compound	α-Glucosidase	Compound	α-Glucosidase
1	Ni[a]	**9f**	16.7%
2	Ni	**9g**	60.6% (70)
3	34%	**9h**	100% (16)
4	Ni	**9i**	59.3% (82)
5	16.5%	**9j**	49.6% (100)
6	6.9%	**10**	—
7	13.2%	**11a**	68.9% (28)
8	17.1%	**11b**	100% (16)
9a	Ni	**11c**	100% (6)
9b	84.3% (58)	**11d**	100% (14)
9c	Ni	**11e**	74.8% (25)
9d	57.8% (84)	**11f**	95.9% (36)
9e	Ni	**11g**	100% (11)

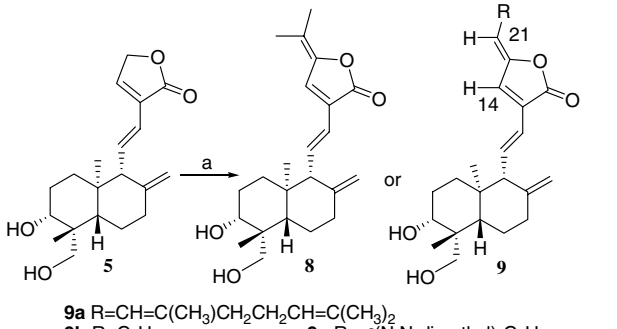
Acarbose was taken as positive control. The inhibition percentage of 1 m acarbose was 56.5%.

[a] No inhibition at 100 μM.

[b] % Inhibition determined at 100 μM concentration of compound.

and most of the foundational groups of **1**. It is also one active constituent isolated from *A. paniculata*. At the same time, 15-alkylidene derivatives showed best inhibition activity among the published work.[31] Our attention has been drawn to the 15-alkylidene andrographolide analogues. So 5 was taken as a lead structure for further modification. 15-Alkylidene andrographolide derivatives were synthesized as shown in Schemes 2 and 3.

In order to prepare more alkylidene andrographolide derivatives, the reaction condition was optimized. At first, we investigated the effect of base and solvent on the reaction of **5** to acetone and benzaldehyde, respectively, at room temperature. Na_2CO_3 proved to be more effective in promoting the reaction. The catalyst diaminoethane could also promote the reaction. The solvents such as methanol and ethanol proved to be effective in promoting the reaction. Under the above optimized conditions, 15-alkylidene derivatives **8** and **9** (Scheme 1) were synthesized by heating **5** with acetone or various



9a R=CH=C(CH$_3$)CH$_2$CH$_2$CH=C(CH$_3$)$_2$
9b R=C$_6$H$_5$
9c R=p-F-C$_6$H$_4$
9d R=2,4,5-triMeO-C$_6$H$_4$
9e R=p-Cl-C$_6$H$_4$
9f R=m-Br-C$_6$H$_4$
9g R=p-(N,N-dimethyl)-C$_6$H$_4$
9h R=p-MeO-C$_6$H$_4$
9i R=benzo[1,3]dioxole-5-methanyl
9j R=furoyl

Scheme 2. Synthesis of **8** and **9**. Reagents and conditions: (a) acetone or aldehydes, Na_2CO_3, methanol, refluxing, 3–5 h.

aldehydes. Without functional protection, the reaction can be carried out smoothly. Following the reaction, most of the desired products could precipitate from the reaction solution with good yield and stereoselectivity in most cases.

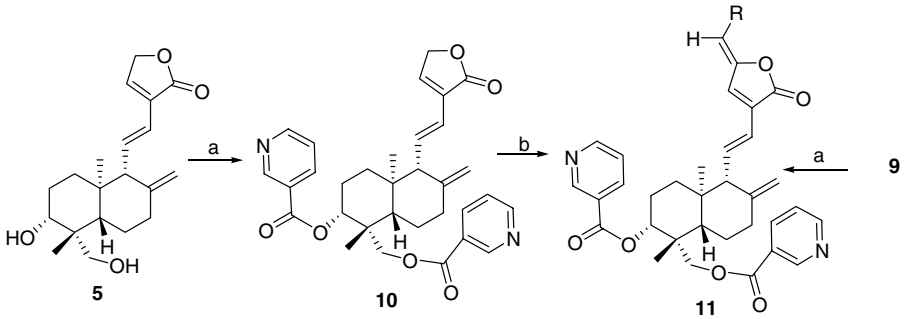
The structures of **8** and **9** were elucidated by the analysis of NMR, IR, and, HRMS spectra. In ^{1}H NMR spectrum of **5**, the conjugated olefinic protons were detected at δ 6.8 (H-11), 6.1 (H-12), and 7.2 (H-14). Based on the coupling constant $J_{H\text{-}11,H\text{-}12}$ (15.6 Hz), the conformation of double bond $\Delta^{11(12)}$ was assumed to be *E*. The structure of **8** could be confirmed by the analysis of HRMS ([M+Na]$^+$ 395.2197) and NMR with the methyl signals (δ 2.0 and 1.9) and the disappearation of H-15 signal (δ 4.8). In the NOE spectrum of **9**, the correlation between signals of H-14 (δ 7.1) and H-21 (δ 5.9) showed the geometry of double bond ($\Delta^{15\ (21)}$) in **9** was *Z* conformation, which was corresponding to those of the natural products.[35,36]

The previous result indicated[31] that (a) the γ-alkylidene butenolide moiety of andrographolide derivatives and (b) the aromatic group at 3,19-hydroxyls are favorable to the activity, (c) the epoxidation of double bond ($\Delta^{8(17)}$) is bad to the activity. Thus, it was interesting to concurrently modify γ-butenolide and 3,19-hydroxyls, and keep the free double bond ($\Delta^{8(17)}$).

Thus, Combination of nicotinate to 3,19-hydroxyls in **9** become significant. First the aromatic group was introduced to the C-3 and C-19 by ester. Second, the nicotinate could increase the hydrophilicity and could be prepared to be hydrochlorate. It could be observed that three aromatic groups are around the mother structure.

In order to alleviate workload to prepare **11**, **10** was synthesized by the reaction of **5** and nicotinic chloride in chloroform in the presence of Et_3N, and was treated with aldehydes in the presence of Na_2CO_3 to give **11**(Scheme 3). Unfortunately, some hydrolysis products **9** were obtained as the reaction progressed in the presence of base. To improve the yield, **11a**–**g** were also prepared by nicotination of corresponding 15-alkylidene derivatives (**9**).

The biological activity results showed that arylidene derivatives (**9**) are selective α-glucosidase inhibitor. The substitution at C-15 could enhance the inhibition activity to α-glucosidase. But different arylidene derivatives gave inconsistent bioactivity results. 4-Fluoro and 4-chlorobenzylidene derivatives (**9c** and **9e**) made the activity lost, while the activity of 3-bromobenzylidene derivative (**9f**) was retained. The activity of 4-methoxylphenylidene derivative (**9h**) was much stronger than that of **5**. Its IC_{50} value is 16 μM (Table 1). The bioactivity of **11a**–**g** (IC_{50}, 28, 16, 6, 14, 25, 36, and 11 μM, respectively) was better than that of their corresponding compounds **9a**, **9b**, **9e**, **9f**, **9g**, **9j**, and **9h**. However, the nicotinate derivative **11c** (IC_{50}, 6 μM) of **9e** (no inhibition) showed best bioactives among all compounds concerned instead of the corresponding derivatives **11g** (IC_{50}, 11 μM) of **9h**(IC_{50}, 16 μM) which is more effective



11a R = CH=C(CH$_3$)CH$_2$CH$_2$CH=C(CH$_3$)$_2$ **11b** R = C$_6$H$_5$ **11c** R = *p*-Cl-C$_6$H$_4$
11d R = *m*-Br-C$_6$H$_4$ **11e** R = *p*-(N,N-dimethyl)-C$_6$H$_4$ **11f** R = furoyl,
11g R = *p*-MeO-C$_6$H$_4$

Scheme 3. Synthesis of **10** and **11**. Reagents and conditions: (a) $CHCl_3$, nicotinic chloride, Et_3N, refluxing, 3 h; (b) aldehyde, Na_2CO_3, Methanol, refluxing, 3–6 h.

than any other **9**. The above results suggested that the nicotinate of hydroxyls at C-3 and C-19 is favorable to the activity. But the increase in bioactivity is not linear.

In the α-glucosidase inhibition activity testing, acarbose was taken as positive control. The inhibition percentage of 1 mM acarbose was 56.5%. Most of 15-alkylidene andrographolide derivatives (**9** and **11**) showed better activity than acarbose which is useful in reducing peak postprandial blood glucose (PPBG) concentrations.

The compounds concerned for β-glucosidase showed no inhibition activity.

It is reported that ethanolic extract of *A. paniculata* or andrographolide can lower plasma glucose.[37–39] **5** and **8** may play an important role in the antidiabetic activity of the plant extracts, because **5** is one of the andrographolide metabolites isolated from rat urine[40] and **8** is one constituent of the plant.[41] It can be deduced that α-glucosidase inhibition activity of **5** and **8** may be one of the reasons for the antidiabetic activity of the constituents of *A. paniculata*. The plant extract or andrographolide could promote the glucose metabolism via treating diabetic rat.[38,39] So, it can be assumed that extracts of *A. paniculata* and andrographolide lower plasma glucose by inhibiting the disaccharide metabolism and/or promoting the glucose metabolism.

In summary, a novel family of α-glucosidase inhibitors were synthesized. Their structures were identified by the analysis of IR, NMR, HRMS spectra. Most of the products exhibit good α-glucosidase inhibition activity. And **11c**, **11d**, and **11g** would be useful for development of New Drugs such as antidiabetes, antitumor, and anti-inflammatory.

3. Experimental

3.1. General methods

Melting points were determined on a Beijing Keyi XT5 apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Thermo Nicolet (IR200) Spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Brüker DPX-400 spectrometer at 400 and 100 MHz with TMS as internal standard. Mass spectra were taken by Waters Q-Tof micro mass spectrometer. X-ray analysis was taken on a Rigaku RAXIS-IV. The absorbance at 405 nm was measured by a PowerWaveX Microplate Scanning Spectrophotometer (Bio-Tek Instruments, Inc).

3.2. General procedure for α-glucosidase inhibition assay

Inhibition rate was determined at 37 °C in 0.067 M K_2HPO_4/KH_2PO_4 buffer (pH 6.8). The reaction mixture contained 40 μL of enzyme solution, 40 μL of inhibitor, and 20 μL of substrate. *p*-Nitrophenyl-α-D-glucopyranoside, the substrate, and α-glucosidase (Baker's yeast) were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Acarbose (1 mM) (extracted from Glucobay tablet, Bayer Pharmaceuticals Corporation) was tested as a positive control. Both inhibitor and substrate were first dissolved in dimethylsulfoxide (DMSO), and then diluted with 0.067 M K_2HPO_4/KH_2PO_4 buffer to make the final concentration of DMSO 10%. The enzymatic reaction was started after incubation of the enzyme (0.04 U/ml) for 30 min in the presence of the inhibitor (0.1 mM) by the addition of substrate (0.5 mM). The mixture was incubated at 37 °C for 5 min, and the reaction was quenched by the addition of 0.1 M Na_2CO_3 (pH 9.8). The absorption at 405 nm was measured immediately and taken as the relative rate for the hydrolysis of substrate. All the experiment was carried out in triplicate.

3.3. General procedure for β-glucosidase inhibition assay

Inhibition rate was determined at 37 °C in 0.08 M citric acid/Na_2HPO_4 buffer (pH 4.2). The enzymatic reaction was started after incubation of the enzyme (0.02 U/ml) for 30 min in the presence of the inhibitor (0.1 mM) by the addition of substrate (5 mM). The mixture was incubated at 37 °C for 5 min, and the reaction was quenched by the addition of 0.25 M borate buffer (pH 9.8). The absorption at 405 nm was

measured immediately and taken as the relative rate for the hydrolysis of substrate.

3.3.1. 8,17-Epoxyandrographolide (2). Andrographolide (1.0 g, 2.8 mmol) and 2,2-dimethoxyl propane (6 mL, 49 mmol) in acetone (20 mL) were refluxed for 10 h in the presence of *p*TsOH. The solvent was evaporated under reduced pressure to afford a crude product which was crystallized from methanol as colorless crystal. The colorless crystal (500 mg, 1.3 mmol) and *m*CPBA (260 mg, 1.5 mmol) in $CHCl_3$(15 mL) were stirred for 2 h. After completion of the reaction, the mixture was washed with aq Na_2CO_3, brine, and water successively. The $CHCl_3$ phase was dried over Na_2SO_4, filtered, and concentrated to yield **2** (460 mg, 1.3 mmol, 95%). IR 3392, 2979, 2934, 2854, 1723, 1672, 1458, 1368, 1221, 1080, 1035, 983, 894 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 6.83 (1H, dd, $J = 4.4$, 10.8 Hz), 5.01 (1H, d, $J = 6.0$ Hz), 4.42 (1H, dd, $J = 6.0$, 10.4 Hz), 4.30 (1H, dd, $J = 1.6$, 10.4 Hz), 4.20 (1H, d, $J = 11.2$ Hz), 3.53 (1H, m), 3.36 (1H, d, $J = 10.8$ Hz), 2.90 (1H, d, $J = 2.0$ Hz), 2.70 (1H, d, $J = 3.6$ Hz), 2.07 (1H, m), 1.94–1.77 (8H, om), 1.48 (2H, m), 1.46 (1H, m), 1.31–1.26 (2H, m), 1.29 (3H, s), 1.23 (1H, m), 0.85 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.3, 146.0, 129.1, 80.0, 73.3, 65.1, 63.8, 60.2, 54.5, 53.3, 50.9, 42.6, 39.7, 36.7, 35.8, 27.3, 22.8, 22.7, 21.2, 15.1. HRMS *m*/*z*: $[M+Na]^+$ 389.1944 (calcd 389.1940).

A colorless prismatic crystal of **2** with approximate dimensions of 0.20 mm × 0.18 mm × 0.17 mm was selected for the data collection on a Rigaku RAXIS-IV imaging plate area detector equipped with a graphite-monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å). A total of 2938 reflections together with 2815 independent ones ($R_{int} = 0.0312$) were collected in the range of $2.29 < \theta < 25.00°$ by using ''Osillation frames'' scan techniques at 291(2) K, of which 2452 were observed with $I > 2\sigma(I)$ and used in the succeeding refinements. The intensities were corrected for *Lp* factors and empirical absorption (DIFABS).

The structure was solved by direct methods and expended using difference Fourier map techniques, and refinement on F^2 was performed by full-matrix least-squares method with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms of the hydroxyl were found by difference Fourier map techniques with SHELXS-97 program and refined isotropically in the riding mode with fixed thermal factors, and the other hydrogen atoms were found by theoretical method. The refinement converged to the final $R = 0.0427$ and $wR = 0.0990$ $(w = 1/[\sigma^2(F_o^2)+(0.0723P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3)$, $(\Delta/\sigma)_{max} = 0.000$, $S = 1.014$, $(\Delta\rho)_{max} = 0.186$, and $(\Delta\rho)_{min} = -0.146$ e/Å^3. The molecular graphics was drawn with SHELXL-97 crystallographic software package. The crystal is of Monoclinic system ($C_{20}H_{30}O_6$, $M_r = 366.44$), space group *P*2(1), with $a = 6.6273$ (13), $b = 8.0802(16)$, $c = 17.882(4)$ Å, $V = 951.6$ (3) Å^3, $Z = 2$, $D_c = 1.279$ g/cm^3, $F(000) = 396$, and $\mu = 0.093$ mm^{-1}.

3.4. 12,13-Dihydroandrographolide (3) and 14-deoxy-12,13-dihydroandrographolide (4)[42]

3.4.1. 14-Deoxy-11,12-didehydroandrographolide (5)[43]

3.4.1.1. 13,14-Didehydro-12-hydroxy-3,19-methene-*O*-andrographolide (6). Andrographolide (500 mg, 1.4 mmol) and paraform (85 mg, 2.8 mmol) in THF (20 mL) were refluxed for 1 h in the presence of H_2SO_4. The solvent was evaporated under reduced pressure to afford white powder. The white powder and PDC (100 mg, 0.26 mmol) were stirred in $CHCl_3$ for 3 h at room temperature. The reaction mixture was filtered with Celite and silicon gel. The filter cake was washed with $CHCl_3$. The combined $CHCl_3$ phase was extracted with brine and water, and dried with Na_2SO_4. The solvent was evaporated to afford oil **6** (507 mg, 1.4 mmol, 98%). ^1H NMR (400 MHz, $CDCl_3$): 7.28 (1H, s), 4.93 (2H, s), 4.84 (2H, s), 4.80 (1H, d, $J = 6.4$ Hz), 4.75 (1H, s), 4.53 (1H, t, $J = 4.4$ Hz), 3.97 (1H, d, $J = 11.2$ Hz), 3.45 (1H, dd, $J = 4.8$, 12.8 Hz), 3.40 (1H, d, $J = 11.2$ Hz), 2.43 (1H, br), 2.25 (1H, m), 2.04 (1H, br), 1.90–1.87 (3H, br), 1.66 (1H, m), 1.60 (1H, d, $J = 10.0$ Hz), 1.42 (1H, m), 1.38 (3H, s), 1.25 (1H, m), 1.20 (1H, m), 1.09 (1H, m), 0.80 (1H, m), 0.76 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 172.9, 147.9, 145.3, 136.0, 108.1, 87.6, 79.3, 70.4, 69.0, 67.4, 55.1, 52.9, 39.1, 38.0, 37.6, 35.6, 30.2, 25.9, 22.8, 20.9, 15.3. HRMS *m*/*z*: $[M+Na]^+$ 385.1987 (calcd 385.1991).

3.4.1.2. 3,19-(*p*-methanoxylphenylmethene-*O*-)-andrographolide (7). Andrographolide (500 mg, 1.4 mmol) and anisaldehyde (250 mg, 1.8 mmol) in THF (20 mL) were refluxed for 1.5 h in the presence of H_2SO_4. The reaction mixture was concentrated under reduced pressure and diluted with $CHCl_3$ (20 mL). The $CHCl_3$ phase was washed with aq Na_2CO_3, brine, and water successively. The solvent was removed to afford **7** (632 mg, 1.3 mmol 95%). Mp: 200.1–202.5 °C. ^1H NMR (400 MHz, $CDCl_3$): 7.42 (2H, d, $J = 8.8$ Hz), 6.97 (1H, t, $J = 6.9$ Hz), 6.89 (2H, d, $J = 8.4$ Hz), 5.72 (1H, s), 5.04 (1H, t, $J = 6.0$ Hz), 4.92 (1H, s), 4.63 (1H, s), 4.46 (1H, dd, $J = 6.0$, 10.8 Hz), 4.25 (2H, m), 3.90 (3H, s), 3.65 (1H, m), 3.58 (1H, d, $J = 11.2$ Hz), 2.59 (2H, m), 2.43 (2H, m), 2.0 (1H, m), 1.91–1.80 (4H, br), 1.49 (3H, s), 1.31–1.23 (4H, m), 0.87 (3H, s). HRMS *m*/*z*: $[M+Na]^+$ 491.2397, (calcd 491.2410).

3.5. General procedure for synthesis of 14-deoxy-11,12-didehydro-15-isopropylideneandrographolide analogues (8 and 9)

Compound **5** (100 mg, 0.3 mmol) and various aldehydes or ketones (0.45–0.9 mmol) in dry methanol were refluxed in the presence of Na_2CO_3 (10 mg, 0.09 mmol). After completion of the reaction, the mixture was diluted with $CHCl_3$ and washed with water. The organic phase was evaporated in vacuo to afford corresponding product by flash chromatography or crystallization from methanol.

3.5.1. 14-Deoxy-11,12-didehydro-15-isopropylideneandrographolide (8). Yield 85%; mp 179.1–181.4 °C; IR 3337, 3080, 2928, 2855, 1746, 1642, 1445, 1375, 1073,

1034, 896 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.26 (1H, d, J = 3.67 Hz), 6.83 (1H, dd, J = 10.0, 15.8 Hz), 6.15 (1H, d, 15.8 Hz), 4.78 (1H, d, J = 1.5 Hz), 4.54 (1H, d, 1.48 Hz), 4.22 (1H, d, J = 13.1 Hz), 3.50 (1H, dd, J = 13.4, 4.7 Hz), 3.35 (1H, d, J = 13.0 Hz), 2.47 (1H, m), 2.33 (1H, d, J = 9.8 Hz), 2.05 (1H, m), 2.01 (3H, s), 1.93 (3H, s), 1.82 (1H, m), 1.78 (2H, m), 1.53 (1H, m), 1.34 (1H, m), 1.26 (3H, s), 1.25 (1H, m), 1.20 (1H, m), 0.82 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 148.1, 144.8, 136.3, 130.6, 126.9, 122.0, 121.8, 109.2, 80.9, 64.2, 61.9, 54.7, 43.0, 38.7, 38.3, 36.6, 29.7, 28.1, 23.0, 22.6, 18.7, 15.9; HRMS m/z: $[M+Na]^+$ 395.2197, (calcd 395.2198).

3.5.2. 14-Deoxy-11,12-didehydro-15-(2,8-dimethanyl-2,7-octanedieneylidene)-andrographolide (9a). A mixture of Z and E isomers (3: 1), yield 60%; IR 3388, 2966, 2928, 2852, 1747, 1642, 1623, 1449, 1374, 1316, 1034, 940, 896 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.01 (1H, s), 6.85 (1H, dd, J = 10.2, 15.6 Hz), 6.44 (1H, d, J = 11.8 Hz), 6.16 (1H, d, J = 15.8 Hz), 5.98 (0.75H, d, J = 11.8 Hz), 5.95 (0.25H, d, J = 11.8 Hz), 5.09 (1H, t, J = 4.6 Hz), 4.78 (1H, s), 4.54 (1H, s), 4.23 (1H, d, J = 8.1 Hz), 3.50 (1H, d, J = 8.8 Hz), 3.36 (1H, d, J = 9.8 Hz), 2.46 (1H, d, J = 13.6 Hz), 2.33 (1H, d, J = 10.0 Hz), 2.26 (2H, m), 2.05 (1H, m), 1.92 (3H, s), 1.69 (3H, s) 1.62 (3H, s), 1.74–1.92 (7H, om), 1.53 (1H, m), 1.34 (1H, m), 1.27 (3H, s), 1.23 (1H, m), 1.20 (1H, m), 0.83 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 148.1, 147.3, 146.6, 136.7, 133.8, 132.3, 126.7, 123.3, 121.9, 119.6, 118.8, 109.3, 80.9, 64.1, 61.9, 54.7, 43.0, 40.5, 38.7, 38.3, 36.6, 28.2, 26.5, 25.7, 22.9, 22.6, 17.7, 17.3, 13.9; HRMS m/z: $[M+Na]^+$, 489.2997, (calcd 489.2981).

3.5.3. 15-Benzylidene-14-deoxy-11,12-didehydroandrographolide (9b). Yield 90%; mp 127–129 °C; IR 3393, 2933, 2847, 1750, 1644, 1450, 1036, 942, 894, 758, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.77 (2H, d, J = 7.6 Hz), 7.40 (2H, m), 7.32 (1H, m), 7.12 (1H, s), 6.92 (1H, dd, J = 10.0, 15.7 Hz), 6.20 (1H, d, J = 15.7 Hz), 5.96 (1H, s), 4.80 (1H, s), 4.54 (1H, s), 4.24 (1H, br s), 3.49 (1H, br s), 3.38 (1H, br s), 2.46 (1H, d, J = 13.4 Hz), 2.36 (1H, d, J = 10.0 Hz), 2.27 (2H, br s), 2.05 (1H, t, J = 13.0 Hz), 1.8 (3H, m), 1.54 (1H, J = 13.0 Hz), 1.41 (1H, m), 1.38 (3H, s), 1.14 (2H, m), 0.84 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 148.0, 147.5, 137.6, 135.5, 133.2, 130.4, 128.9, 128.8, 127.0, 121.5, 113.1, 109.3, 80.8, 64.2, 61.9, 54.6, 13.0, 38.7, 38.3, 36.5, 28.1, 22.9, 22.8, 15.9; HRMS m/z: $[M+Na]^+$, 443.2187, (calcd 443.2199).

3.5.4. 14-Deoxy-11,12-didehydro-15-*p*-fluorobenzylidene andrographolide (9c). Yield 87%; mp 213.5–215.0 °C; IR 3293, 3081, 2944, 2849, 1747, 1642, 1600, 1507, 1449, 1418, 1232, 1362, 1038, 986, 943, 989 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.80 (2H, m), 7.73 (1H, s), 7.30 (2H, m), 6.83 (1H, dd, J = 10.1, 15.8 Hz), 6.35 (1H, s), 6.27 (1H, d, 15.8 Hz), 5.05 (1H, bs), 4.75 (1H, s), 4.45 (1H, s), 4.1 (1H, br s), 3.86 (1H, d, J = 10.9), 3.30 (1H, d, J = 13.0 Hz), 3.23 (1H, m), 2.43 (1H, d, J = 10.1 Hz), 2.38 (1H, br), 2.0 (1H, m), 1.71 (1H, br), 1.59 (2H, m), 1.38 (1H, m), 1.34 (1H, m), 1.20 (2H, m), 1.10 (3H, s), 0.79 (3H, s).^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 163.4, 160.9, 148.9, 147.3, 137.2, 132.6, 132.5, 130.1, 126.2, 121.5, 131.3, 116.1, 111.8, 108.4, 78.8, 62.9, 60.9, 53.9, 42.6, 38.7, 38.2, 36.4, 27.8, 23.3, 23.2, 15.7; HRMS m/z: $[M+Na]^+$ 461.2130 (calcd 461.2104).

3.5.5. 14-Deoxy-11,12-didehydro-15-trimethoxylbenzylidene andrographolide (9d). Yield 76%; mp 131–132 °C; IR 3431, 2936, 2845, 1760, 1643, 1578, 1505, 1455, 1422, 1335, 1250, 1328, 1038, 892 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.10 (1H, s), 7.02 (2H, s)6.90 (1H, dd, J = 10.1, 15.6 Hz), 6.21 (1H, d, J = 15.7 Hz), 5.88 (1H, s), 4.80 (1H, s), 4.52 (1H, s), 4.22 (1H, d, J = 10.7 Hz), 3.90 (9H, od), 3.50 (1H, J = 5.8 Hz), 3.36 (1H, d, J = 10.7 Hz); 2.47 (1H, d, J = 13.2 Hz), 2.36 (1H, d, J = 10.0 Hz), 2.06 (1H, br), 1.80 (3H, br), 1.54 (1H, d, J = 13.2 Hz), 1.35 (1H, m), 1.27 (3H, s), 1.24–1.13 (2H, m), 0.84 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 153.3, 148.0, 147.1, 137.5, 135.4, 128.9, 126.6, 121.5, 114.9, 113.1, 109.3, 107.8, 106.5, 80.8, 64.2, 61.9, 60.9, 56.2, 54.7, 43.0, 38.8, 38.3, 36.6, 28.1, 22.9, 22.6, 15.9; HRMS m/z: $[M+Na]^+$, 533.2510, (calcd 533.2515).

3.5.6. 14-Deoxy-11,12-didehydro-15-*p*-chlorobenzylidene andrographolide (9e). Yield 84%; mp *237–239* °C; IR 3413, 2934, 1749, 1632, 1490, 1442, 1090, 1035, 891 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.77 (2H, d, J = 6.8 Hz), 7.40 (3H, m), 6.86 (1H, dd, J = 10.0, 15.6 Hz), 6.24 (1H, d, J = 16.0 Hz), 6.17 (1H, s), 4.76 (1H, s), 4.48 (1H, s), 4.03 (1H, d, J = 10.8 Hz), 3.31 (1H, t, J = 7.2 Hz), 3.25 (1H, d, J = 10.8 Hz), 2.41 (2H, m), 2.03 (1H, m), 1.78 (1H, m), 1.64 (2H, m), 1.44 (1H, m), 1.35 (1H, m), 1.23 (2H, m), 1.17 (3H, s), 0.82 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 148.9, 148.1, 137.7, 136.5, 131.7, 131.2, 129.9, 126.9, 121.5, 111.5, 108.8, 79.5, 63.4, 61.6, 54.3, 42.7, 38.8, 38.4, 36.6, 28.1, 23.2, 15.9; HRMS m/z: $[M+Na]^+$, 477.1803, (calcd 477.1809).

3.5.7. 15-*m*-Bromoacylbenzylidene-14-deoxy-11,12-didehydroandrographolide (9f). Yield 85%. mp 217–219 °C; IR 3400, 2929, 1762, 1629, 1474, 1421, 1034, 892 cm^{-1}; ^1H NMR (400 MHz, DMSO) 7.15 (1H, d, J = 1.6 Hz), 6.89 (1H, d, J = 7.9 Hz), 6.66 (1H, dd, J = 0.9, 7.4 Hz), 6.64 (1H, s), 6.50 (1H, t, J = 7.9 Hz), 6.16 (1H, dd, J = 10.1, 15.7 Hz), 5.47 (1H, d, J = 15.7 Hz), 5.33 (1H, s), 3.97 (1H, s), 3.76 (1H, s), 3.33 (1H, d, J = 13.0 Hz), 2.60 (1H, br), 2.58 (1H, d, J = 13.0 Hz), 1.64 (2H, m), 1.20 (1H, m), 1.01 (1H, m), 0.91 (2H, m), 0.68 (1H, m), 0.60 (1H, m), 0.49 (1H, m), 0.45 (1H, m), 0.42 (3H, s), 0.06 (3H, s); ^{13}C NMR (100 MHz, DMSO): δ 170.2, 150.1, 150.0, 139.3, 137.5, 137.2, 133.7, 132.6, 131.5, 130.1, 128.7, 123.7, 122.7, 112.3, 109.2, 81.2, 65.0, 63.1, 55.8, 43.8, 39.9, 39.6, 37.8, 28.9, 24.4, 23.3, 16.3; HRMS m/z: $[M+Na]^+$, 521.1307, (calcd 521.1304).

3.5.8. 14-Deoxy-15-(*p*-(dimethanylamino)-benzylidene)-11,12-didehydroandrographolide (9g). Yield 83%; mp 223–225 °C; IR 3424, 2928, 2847, 1742, 1601, 1560, 1444, 1366, 1386, 1368, 1036, 894 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.68 (2H, d, J = 8.9 Hz), 7.08 (1H, s), 6.80 (1H, dd, J = 10.0, 15.7 Hz), 6.69 (2H, d,

J = 8.8 Hz), 6.18 (1H, d, J = 15.7 Hz), 5.90 (1H, s), 4.79 (1H, s), 4.56 (1H, s), 4.24 (1H, d, J = 13.1 Hz), 3.50 (1H, dd, J = 4.4, 13.4 Hz), 3.37 (1H, d, J = 13.1 Hz), 3.02 (6H, s), 2.46 (1H, d, J = 12.3 Hz), 2.34 (1H, d, J = 10.2 Hz), 2.08 (1H, m), 1.82 (1H, m), 1.74 (2H, m), 1.53 (1H, m), 1.36 (1H, m), 1.27 (3H, s), 1.23 (1H, m), 1.20 (1H, m), 0.83 (3H, s); HRMS *m/z*: $[M+H]^+$, 464.2799, (calcd 464.2801).

3.5.9. 14-Deoxy-11,12-didehydro-15-*p*-methoxylbenzylidene andrographolide (9h). Yield 93%; mp 211–213 °C; IR 3291, 2927, 2851, 1747, 1642, 1603, 1510, 1457, 1257, 1377, 1035, 941, 900 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.73 (2H, d, J = 8.8 Hz), 7.10 (1H, s), 6.92 (2H, d, J = 8.8 Hz), 6.87 (1H, dd, J = 10.1, 15.8 Hz), 6.19 (1H, d, J = 15.8 Hz), 5.92 (1H, s), 4.79 (1H, d, J = 0.89 Hz), 4.55 (1H, d, J = 0.89 Hz), 4.22 (1H, d, J = 13.0 Hz), 3.84 (3H, s), 3.48 (1H, m), 3.35 (1H, d, J = 13.0 Hz), 2.45 (1H, m), 2.35 (1H, d, J = 10.0 Hz), 2.04 (1H, m), 1.79 (2H, m), 1.74 (1H, m), 1.54 (1H, m), 1.34 (1H, m), 1.27 (3H, s), 1.24 (1H, m), 1.15 (1H, m), 0.84 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 160.2, 148.1, 146.2, 136.8, 135.6, 132.2, 126.2, 125.9, 121.6, 114.4, 113.1, 109.3, 80.8, 64.2, 61.9, 55.3, 54.7, 43.0, 38.7, 38.3, 36.6, 28.1, 22.9, 22.6, 15.9. HRMS *m/z*: $[M+Na]^+$, 473.2315, (calcd 473.2304).

3.5.10. 15-(Benzo[1,3]dioxole-5-methanylidene)-14-deoxy-11,12-didehydroandrographolide (9i). Yield 82%; mp 225–227 °C; IR 3412, 2942, 1734, 1641, 1619, 1498, 1447.1383, 1263, 1033, 942, 904 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.46 (1H, d, J = 1.6 Hz), 7.44 (1H, dd, J = 1.6, 8.2, Hz), 7.08 (1H, s), 6.88 (1H, dd, J = 10.0, 15.8 Hz), 6.82 (1H, d, J = 8.1 Hz), 6.20 (1H, d, J = 15.8 Hz), 6.0 (2H, s), 5.88 (1H, s), 4.79 (1H, d, J = 1.2 Hz), 4.54 (1H, d, J = 1.2 Hz), 4.22 (1H, d, J = 13.1 Hz), 3.49 (1H, dd, J = 4.5, 13.5 Hz), 3.36 (1H, d, J = 13.1 Hz), 2.45 (1H, m), 2.35 (1H, d, J = 15.8 Hz), 2.05 (1H, m), 1.75 (3H, m), 1.54 (1H, m), 1.18 (1H, m), 1.27 (3H, s), 1.23 (1H, m), 1.20 (1H, m), 0.84 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 148.5, 148.3, 148.1, 146.4, 137.1, 135.5, 127.8, 126.3, 125.9, 121.6, 113.1, 109.9, 109.3, 108.6, 101.5, 80.9, 64.2, 62.0, 54.8, 43.1, 38.8, 38.4, 36.6, 28.2, 23.0, 22.7, 15.9. HRMS *m/z*: $[M+Na]^+$ 487.2090, (calcd 487.2097).

3.5.11. 14-Deoxy-11,12-didehydro-15-(-2-furanmethanylidene)-andrographolide (9j). Yield 82%; mp*136–138* °C; IR 3421, 2930, 2851, 1768, 1748, 1645, 1470, 1284, 1037, 948, 884, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.49 (1H, d, J = 1.6 Hz), 7.08 (1H, s), 7.02 (1H, d, J = 3.6 Hz), 6.88 (1H, dd, J = 10.0, 15.6 Hz), 6.54 (1H, dd, J = 1.6, 3.6 Hz), 6.19 (1H, d, J = 15.6 Hz), 6.00 (1H, s), 4.80 (1H, s), 4.53 (1H, d, J = 1.2 Hz), 4.22 (1H, d, J = 13.2 Hz), 3.48 (1H, m), 3.35 (1H, d, J = 13.2 Hz), 2.48 (1H, m), 2.35 (1H, d, J = 10.0 Hz), 2.05 (1H, m), 1.80 (2H, br), 1.74 (1H, m), 1.53 (1H, m), 1.35 (1H, m), 1.27 (3H, s), 1.23 (1H, m), 1.15 (1H, m), 0.84 (3H, s); HRMS *m/z*: $[M+Na]^+$ 433.1992, (calcd 433.1991).

3.5.12. 14-Deoxy-11,12-didehydro-3,19-dinicotinateandrographolide (10). Compound **5** (5 g, 15 mmol) and nicotinic chloride (8 g, 57 mmol) in $CHCl_3$ were refluxed for 3 h under Ar_2 in the presence of Na_2CO_3. The reaction mixture was extracted with aq Na_2CO_3, brine, and water successively. The $CHCl_3$ phase was dried over Na_2SO_4, filtered, and concentrated to give crude product which was crystallized from methanol to give **10** (7.5 g, 92%). Mp: 229.7–230.8 °C; IR 3429, 2938, 1748, 1715, 1643, 1592, 1420, 1298, 1119, 1089, 1025, 992 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.15 (2H, d, J = 6.4 Hz), 8.76 (1H, d, J = 4.0 Hz), 8.75 (1H, d, J = 4.0 Hz), 8.22 (1H, d, J = 8.0 Hz), 8.18 (1H, d, J = 8.0 Hz), 7.35 (1H, m), 7.27 (1H, s), 7.21 (1H, m), 6.97 (1H, dd, J = 10.0, 15.6 Hz), 6.19 (1H, d, J = 15.6 Hz), 5.00 (1H, s), 4.84 (4H, om), 4.57 (2H, m), 2.53 (1H, d, J = 16.0 Hz), 2.42 (1H, d, J = 10.0 Hz), 2.11 (1H, m), 2.06 (1H, m), 1.89 (2H, m), 1.70 (1H, m), 1.87 (1H, m), 1.50 (1H, m), 1.41 (1H, m), 1.25 (3H, s), 0.99 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 172.2, 165.2, 164.8, 153.4, 150.8, 150.7, 147.5, 143.4, 137.1, 137.0, 135.3, 129.1, 126.0, 123.4, 123.2, 121.6, 109.7, 81.1, 69.6, 65.5, 61.6, 54.9, 42.1, 38.7, 38.2, 36.5, 24.4, 23.9, 22.7, 15.4.

3.5.13. 14-Deoxy-11,12-didehydro-3,19-dinicotinate-15-(2,8-dimethanyl-2,7-octanedieneylidene)-andrographolide (11a). A mixture of 15(E) and 15(Z)-isomers (1/1), yield: 35%; IR 3425, 2938, 2854, 1758, 1720, 1591, 1422, 1376, 1284, 1115, 1025, 988 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.15 (2H, br), 8.72 (2H, br), 8.22 (2H, br), 7.40 (0.5H, s), 7.35 (1H, m), 7.22 (1H, m), 7.04 (0.5H, s), 6.98 (0.5H, dd, J = 10.0, 15.2 Hz), 6.94 (0.5H, dd, J = 10.0, 15.2 Hz), 6.46 (1H, m), 6.25 (0.5H, d, J = 15.6 Hz), 6.23 (0.5H, d, J = 15.6 Hz), 6.13 (0.5H, d, J = 12.0 Hz), 5.99 (0.5H, d, J = 12.0 Hz), 5.10 (1H, m), 5.02 (1H, m), 4.85 (2H, m), 4.61 (1H, s), 4.58 (1H, d, J = 12.0 Hz), 2.53 (1H, d, J = 13.6 Hz), 2.45 (1H, m), 2.26 (1H, m), 2.23 (1H, m), 1.97–1.85 (8H, om), 1.75 (6H, om) 1.65 (3H, m), 1.54 (1H, d, J = 13.1 Hz), 1.39 (1H, m), 1.25 (3H, s), 1.00 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 168.5, 165.1, 164.6, 153.1, 150.6, 150.4, 147.5, 147.4, 137.4, 137.3, 136.3, 136.0, 134.3, 129.5, 126.6, 126.2, 123.6, 123.3, 122.4, 118.9, 117.9, 111.9, 111.0, 109.8, 81.3, 65.5, 61.8, 54.9, 42.4, 40.60, 40.56, 38.9, 38.2, 36.6, 26.5, 25.7, 24.4, 23.9, 22.8, 17.7, 17.4, 17.2, 15.4. HRMS *m/z*: 677.3595 ($M+H^+$), (calcd 677.3591).

3.5.14. 15-Benzylidene14-deoxy-11,12-didehydro-3,19-dinicotinateandrographolide (11b). Yield: 75%; mp: 188.9–191.6 °C; IR: 3429, 2937, 2849, 1751, 1712, 1644, 1592, 1419, 1281, 1114, 1043, 992, 940, 892 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.16 (2H, om), 8.73 (2H, om), 8.23 (2H, om), 7.78 (2H, d, J = 7.2 Hz), 7.40 (3H, om), 7.29 (2H, m), 7.16 (1H, s), 7.00 (1H, dd, J = 10.0, 15.6 Hz), 6.28 (1H, d, J = 15.6 Hz), 5.99 (1H, s), 5.02 (1H, m), 4.85 (2H, om), 4.83 (1H, s), 4.57 (1H, d, J = 12.0 Hz), 2.55 (1H, br), 2.48 (1H, d, J = 10.0 Hz), 2.15 (1H, br), 2.0 (1H, br), 1.89 (2H, br), 1.72 (1H, m), 1.69 (1H, m), 1.52 (1H, d, J = 10.8 Hz), 1.40 (1H, m), 1.26 (3H, s), 1.02 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ: 168.8, 165.1, 164.6, 153.2, 150.5, 150.4, 147.5, 147.4, 137.3, 137.0, 136.9, 135.9, 133.3, 130.5, 128.9, 128.8, 126.8,

126.0, 123.5, 123.2, 122.0, 114.9, 113.3, 109.8, 81.2, 65.5, 61.9, 54.9, 42.2, 38.9, 38.2, 36.6, 24.4, 23.9, 22.8, 15.5; HRMS *m*/*z*: ($M+H^+$)631.2803 (calcd 631.2808).

3.5.15. 15-(*p*-Chlorinebenzylidene)-14-deoxy-11,12-didehydro-3,19-dinicotinateandrographolide (11c). Yield: 80%; mp: 232.3–234.5 °C; IR: 3425, 2931, 2853, 1770, 1717, 1590, 1420, 1283, 1116, 1028, 990, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.16 (2H, m), 8.75 (1H, m), 8.68 (1H, m), 8.19 (2H, m), 7.71 (2H, d, J = 8.0 Hz), 7.36 (2H, d, J = 8.0 Hz), 7.31 (1H, m), 7.19 (1H, m), 7.14 (1H, s), 7.01 (1H, dd, J = 10.0, 15.6 Hz), 6.27 (1H, d, J = 15.6 Hz), 5.93 (1H, s), 5.01 (1H, t, J = 8.4 Hz), 4.85 (2H, om), 4.61 (1H, s), 4.57 (1H, d, J = 11.6 Hz), 2.54 (1H, br), 2.48 (1H, d, J = 10.0 Hz), 2.13 (1H, br), 2.02 (1H, br), 1.92 (2H, br), 1.69 (2H, om), 1.51 (1H, d, J = 12.0 Hz), 1.41 (1H, m), 1.26 (3H, s), 1.02 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ: 168.8, 165.1, 164.6, 153.2, 150.5, 147.5, 137.3, 137.0, 136.0, 133.3, 130.5, 129.1, 129.0, 128.8, 123.5, 122.0, 115.0, 113.3, 109.8, 81.2, 65.5, 61.9, 54.9, 42.2, 38.9, 38.2, 36.6, 24.4, 23.9, 22.8, 15.5; HRMS *m*/*z*: ($M+H^+$)665.2417, (calcd 665.2418).

3.5.16. 15-(*m*-Bromoacylbenzylidene)-14-deoxy-11,12-didehydro-3,19-dinicotinateandrographolide (11d). Yield: 53%; mp: 177.8–179.2 °C; IR: 3426, 2929, 2853, 1768, 1720, 1640, 1591, 1473, 1421, 1285, 1117, 990, 895, 742, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.14 (2H, br), 8.73 (2H, br), 8.26 (1H, d, J = 8.8 Hz), 8.22 (1H, d, J = 8.0 Hz), 7.86 (1H, s), 7.73 (1H, d, J = 8.0 Hz), 7.43 (1H, m), 7.38 (1H, m), 7.29 (1H, d, J = 7.9 Hz), 7.24 (1H, m), 7.13 (1H, s), 6.90 (1H, dd, J = 10.0, 15.6 Hz), 6.27 (1H, d, J = 15.6 Hz), 5.89 (1H, s), 5.02 (1H, t, J = 8.0 Hz), 4.86 (2H, om), 4.61 (1H, s), 4.57 (1H, m), 2.55 (1H, br), 2.48 (1H, d, J = 10.0 Hz), 2.16 (1H, br), 2.02 (1H, br), 1.91 (2H, br), 1.71 (2H, om), 1.52 (1H, d, J = 11.4 Hz), 1.29 (1H, m), 1.25 (3H, s), 1.02 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ: 168.4, 165.1, 164.7, 153.2, 150.6, 150.4, 148.3, 147.4, 137.7, 137.3, 137.2, 135.6, 135.3, 132.9, 131.7, 130.2, 128.8, 127.6, 126.2, 123.5, 123.2, 122.8, 121.9, 111.4, 109.9, 81.2, 65.5, 61.9, 54.9, 42.2, 38.9, 38.3, 36.6, 29.7, 24.4, 23.9, 22.8, 15.5; HRMS *m*/*z*: ($M+H^+$)709.1918 (calcd 709.1913).

3.5.17. 14-Deoxy-11,12-didehydro-3,19-dinicotinate-15-(*p*(-dimethylamino)benzylidene)-andrographolide (11e). Yield: 61%; mp: 235.0–237.0 °C; IR: 3433, 2928, 2847, 2363, 1740, 1603, 1526, 1442, 1526, 1442, 1367, 1101, 813 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.25 (2H, br), 9.08 (2H, br), 8.32 (2H, br), 7.69 (1H, d, J = 8.9 Hz), 7.43 (2H, om), 7.30 (1H, br), 7.09 (1H, s), 6.82 (1H, dd, J = 10.0, 15.6 Hz), 6.69 (2H, d, J = 8.8 Hz), 6.18 (1H, d, J = 15.6 Hz), 5.91 (1H, s), 4.79 (1H, s), 4.56 (1H, s), 4.23 (1H, d, J = 10.8 Hz), 3.97 (6H, s), 3.51 (1H, m), 3.35 (1H, d, J = 10.8 Hz), 2.50 (1H, br), 2.34 (1H, d, J = 10.0 Hz), 2.10 (1H, br), 1.82–1.70 (5H, om), 1.55 (1H, br), 1.35 (1H, m), 1.27 (3H, s), 0.83 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.7, 153.3, 150.8, 148.2, 137.3, 135.6, 135.4, 132.2, 130.5, 123.4, 121.9, 114.5, 112.0, 109.3, 80.9, 64.2, 61.9, 54.7, 52.5, 43.0, 40.2, 38.7, 38.3, 36.6, 28.1, 23.0, 22.6, 16.0; HRMS *m*/*z*: ($M+H^+$)674.3226 (calcd 674.3230).

3.5.18. 14-Deoxy-11,12-didehydro-3,19-dinicotinate-15-(2-furanmethanylidene)-andrographolide (11f). Yield: 80%; mp: 232.3–234.8 °C; IR: 3426, 2934, 2852, 1770, 1719, 1643, 1590, 1475, 1424, 1396, 1296, 1023, 992, 948, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.15 (2H, br), 8.75 (2H, br), 8.24 (2H, m), 7.49 (1H, d, J = 1.6 Hz), 7.37 (1H, br), 7.26 (1H, br), 7.11 (1H, s), 7.03 (1H, d, J = 3.4 Hz), 6.96 (1H, dd, J = 10.0, 15.6 Hz), 6.55 (1H, m), 6.25 (1H, d, J = 15.7 Hz), 6.02 (1H, s), 5.01 (1H, t, J = 7.2 Hz), 4.85 (2H, om), 4.6–4.56 (2H, om), 2.55 (1H, d, J = 13.5 Hz), 2.46 (1H, d, J = 10.0 Hz), 2.13 (1H, br t), 1.98 (1H, om), 1.90 (2H, br), 1.70 (2H, om), 1.52 (1H, m), 1.39 (1H, m), 1.25 (3H, s), 1.01 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 168.2, 165.2, 164.7, 153.4, 150.7, 150.6, 149.3, 147.7, 145.6, 143.9, 136.9, 136.8, 136.7, 134.4, 127.0, 123.3, 123.1, 122.1, 115.0, 113.1, 109.8, 101.4, 81.1, 65.4, 61.8, 54.9, 42.2, 38.9, 38.2, 36.5, 24.3, 23.9, 22.7, 15.4. HRMS *m*/*z*: ($M+H^+$) 621.2603, (calcd 621.2601).

3.5.19. 14-Deoxy-11,12-didehydro-3,19-dinicotinate-15-*p*-methoxylbenzylidene andrographolide (11g). Yield 80%; mp: 167.0–169.0 °C; IR: 3440.3, 2938.6, 2849.1, 1763.8, 1716.9, 1639.9, 1593.7, 1465.9, 1287.9, 1248.1, 1194.5, 1115.6, 1027.9, 743.3 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.15 (2H, br), 8.75 (2H, br), 8.24 (2H, m), 7.73 (2H, d, J = 8.8 Hz), 7.39 (1H, br), 7.26 (1H, br), 7.12 (1H, s), 7.02 (1H, dd, J = 10.0, 15.6 Hz), 6.95 (2H, d, J = 8.8 Hz), 6.27 (1H, d, J = 15.4 Hz), 6.02 (1H, s), 5.02 (1H, t, J = 8.04), 4.85 (2H, om), 4.62–4.56 (2H, om), 3.85 (3H, s), 2.55 (1H, d, J = 13.3 Hz), 2.46 (1H, d, J = 10.0 Hz), 2.13 (1H, br), 1.98 (1H, br), 1.89 (2H, br), 1.68 (2H, om), 1.52 (1H, m), 1.39 (1H, m), 1.25 (3H, s), 1.01 (3H, s); MS *m*/*z*: ($M+H^+$) 661.3, (calcd 661.29).

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