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Synthesis and Biological Evaluation of Andrographolide *C*-Glycoside Derivatives as *α*-Glycosidase Inhibitors

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A series of new andrographolide *C*-glycoside derivatives were synthesized by a facile route. The new compounds showed higher potency than the parent andrographolide evaluated as *α*-glycosidase inhibitors in the preliminary study.

Keywords andrographolide, *β*-*C*-glycosidic ketone, *α*-glycosidase inhibitor

Introduction

Traditionally natural products have been an excellent and reliable source for the development of new drugs. Some natural products have been used directly while others have served as intermediates in semi-synthetic pathways or as the source of structural or functional templates for drug design. In recent years, the intense interest of glucosidase inhibitors[1] 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 the development of potential pharmaceuticals.[2] In our previous study on searching for glucosidase inhibitors, some andrographolide derivatives have been proved to be potent and specific *α*-glucosidase inhibitor.[3,4] SAR analyses indicated that (a) replacing the C-8 ethylene moiety with an 8,17-epoxy resulted in a decrease of activity; (b) esterification of 3,19-hydroxyl groups and (c) the aromatic group at 3,19-hydroxyls were favorable to the activity; (d) 15-ene-substituted derivatives of 14-deoxy-11,12,13,14-tetradehydroandrographolide significantly increased the *α*-glucosidase inhibitory activities. Furthermore, 15-alkylidene derivatives showed best inhibition activity among the published work. It is worth pointing out that although many 15-alkylidene andrographolide derivatives have been synthesized in our previous reports, the substitution groups at C-15 were all highly lipophilic bulky groups. Based on these results we decided to introduce hydrophilic group (such as carbohydrates) at C-15 in order to increase their hydrophilicity and bioactivity. On the other hand, carbohydrates and glycoconjugates are a very important class of carbohydrate-processing enzyme inhibitors and are known to display potent activity towards glycosidases. Among the most common and potent classes of glycosidase inhibitors are glycosides, aldono-1,5-lactones, aldono-1,5-lactams and dideoxyimino alditols (azasugars).[5] Recently, there have been a rapid extension in the field of glycobiology with carbohydrate-derived therapeutics now entering clinical trials,[6-9] such as acarbose (Glucobay^{TM}), voglibose (Basen^{TM}) and miglitol (Glyset^{TM}), which have been utilized medicinally in the treatment of type 2 diabetes for many years. In an effort to look for possible glucosidase inhibitors, we were interested in the incorporation of andrographolide derivatives with hydrophilic carbohydrate groups at the position of C-15 by aklylidene. At the same time, in our previous reports, we prepared some hydrophilic *β*-*C*-glycosidic ketones by a facile route.[10] So three series of andrographolide *C*-glycoside derivatives were designed and synthesized.

Results and Discussion

15-Alkylidene derivatives **3**—**6** (Scheme 1) were synthesized by the reaction of compound **2** and *β*-*C*-glycosidic ketones according to previous method.[11] Compound **2** was obtained by refluxing andrographolide **(1)** in pyridine in the presence of Al_2O_3.[12] *β*-*C*-Glycosidic ketones were prepared following the literature procedures.[10]

The structures of andrographolide *C*-glycoside derivatives were elucidated by the analysis of NMR, IR and HRMS spectra. In the HRMS spectrum of **3**, the M＋Na^+ peak at *m*/*z* 575.2382 and the M＋Na^+＋2 peak at *m*/*z* 577.2376, as well as the 3∶1 ratio of the heights of the two peaks (corresponding to Cl-35 and Cl-37

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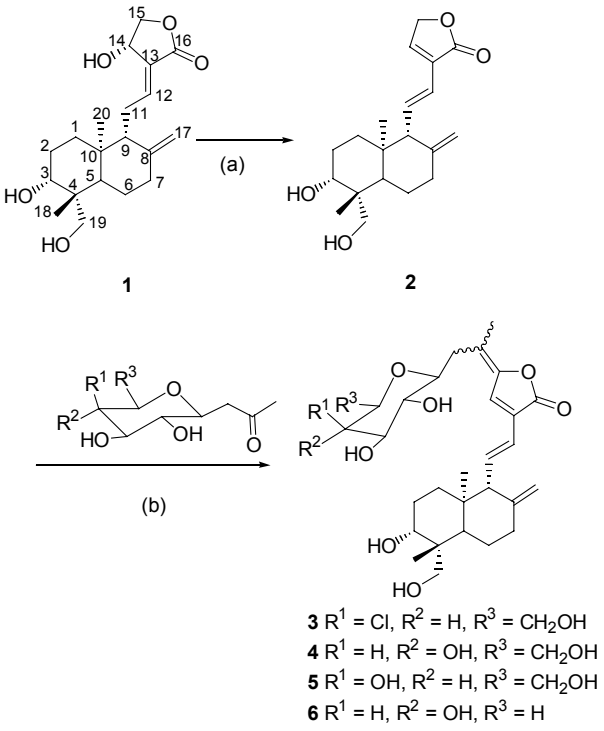
Scheme 1 Synthesis of compounds **2**—**6**



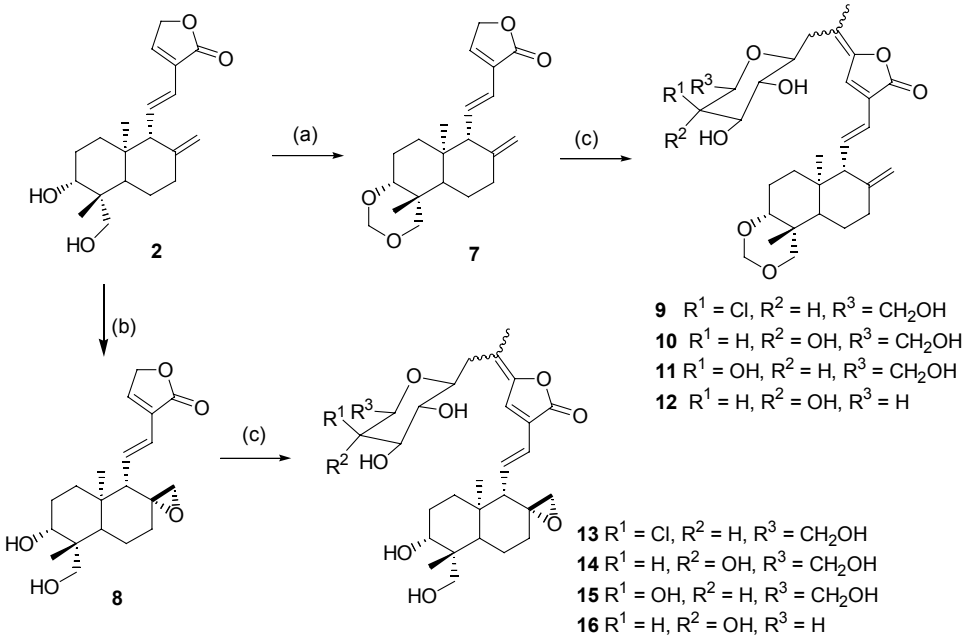
Reagents and conditions: (a) xylene, pyridine, Al_2O_3, reflux, 6—10 h; (b) 1,2-diaminoethane, methanol, refluxing, 3—5 h

isotopes respectively), indicated that the formula of **3** should be $C_{29}H_{41}ClO_8$. The ^{1}H NMR spectrum of **3** revealed the presence of the characteristic of carbohydrates (δ 3—5) and the disappearation of H-15 signal (δ 4.8). All of these indicated that **3** is a *C*-glycoside derivative of **2**. But it is worth pointing out that the product **3** is a mixture of two isomers in the ratio of 1∶1 based on their ^{1}H NMR integrals. Similarly, the structures of **4**, **5** and **6** were elucidated by the analysis of NMR, IR and HRMS spectra.

Correspondingly, other andrographolide *C*-glycoside derivatives **9**—**16** were also synthesized by the vinylogous aldol reaction. The synthetic pathways used in the present work are outlined in Scheme 2. Compound **7** was obtained by heating **2** and paraform in THF in the presence of H_2SO_4 in excellent yield. Compound **8** was prepared by the expoxidation reaction of compound **2** with *m*CPBA. Fortunately, following the vinylogous aldol reaction, most of the desired products could be obtained with good yield. After chromatography, compounds **9**—**16** were obtained as mixtures of isomers based on the analysis of the NMR spectra.

The α-glucosidase inhibition activities of the synthetic compounds were tested with the acarbose as positive control. The compounds concerned for β-glucosidase showed no inhibition activity. The bioactivity results showed that compounds **3, 4, 13**—**16** displayed selective α-glucosidase inhibitory activity (Table 1), and their α-glucosidase inhibitory activity is better than that of the parent compound **2**, which has 16.5% of inhibiton at 100 μmol/L. Among them, compounds **3**, **4**, **13** with 56, 78, 72 μmol/L of IC_{50} respectively, showed better activity than acarbose which is useful in reducing peak postprandial blood glucose (PPBG) concentrations. In the above study, all the derivatives with hydrophilic β-C-glycosidic substitutions at C-15 were found to be less active compared to the previous derivatives with

Scheme 2 Synthesis of compounds **7**—**16**



Reagents and conditions: (a) THF, H_2SO_4, paraform, reflux, 1 h; (b) $CHCl_3$, *m*CPBA, r.t., 2 h; (c) β-*C*-glycosidic ketone, 1,2-diaminoethane, methanol, refluxing, 3—5 h.

Table 1 *α*-Glucosidase inhibition activity of andrographolide *C*-glycoside derivatives[a]

α-Glucosidase inhibition activity[b] [IC_{50}/(μmol/L)]			
Compound	*α*-Glucosidase	Compound	*α*-Glucosidase
2	16.5%	**10**	Ni
3	77.1% (56)	**11**	Ni
4	64.8% (78)	**12**	Ni
5	Ni[c]	**13**	61.9% (72)
6	Ni	**14**	42.4% (100)
7	Ni	**15**	50.8% (89)
8	Ni	**16**	50.7% (91)
9	Ni		

[a] Acarbose was taken as positive control. The inhibition percentage of 1 mmol/L acarbose was 56.5%. [b] % Inhibition determined at 100 μmol/L concentration of compound. [c] No inhibition at 100 μmol/L.

lipophilic aromatic groups at C-15, indicating that the hydrophilic groups of C-15 are bad to the activity. Interestingly, **3** and **13**, which contained chlorine-substituted C-glycosidic at C-15 were found to possess potent activity against *α*-glucosidase inhibitory activity compared to **2** and **8**, indicating that the presence of chlorine-substituted functionality at C-15 is essential for improving the activity. In general, introduction of halogen atom may significantly modify the chemical, physical and biological activities of the natural substances.[13,14] In view of this observation, a number of compounds which have halogen atom side chains at C-15 are in progress.

In conclusion, series of new andrographolide *C*-glycoside derivatives were synthesized using *β*-*C*-glycosidic ketones as building blocks in one pot under mild conditions. Some of them showed *α*-glucosidase inhibition activity. Although, none of them showed better inhibitory activity than the andrographolide derivative we have reported, the above study made the structure-activity relationship of andrograholide derivatives for *α*-glucosidase inhibition activity more complete.

Experimental

General methods

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVANCE DPX-400 spectrometer with tetramethylsilane as internal standard and using $CDCl_3$ or DMSO as solvent. Chemical shifts (*δ*) were expressed downfield from internal TMS. IR spectra were recorded on a Nicolet IR 200 spectrophotometer. HRMS (high-resolution mass spectra) were taken with a Q-Tof Micromass spectrometer. Thin-layer chromatography (TLC) was performed on glass plates precoated with silica gel (5—40 μm) to monitor the reactions and certify the purity of the reaction products. Visualization was accomplished by spraying the chromatograms with 10% ethanolic sulfuric acid and charring them on a hot plate. Column chromatography was carried out on silica gel (200—300 mesh).

General procedure for *α*-glucosidase inhibition assay

Inhibition rate was determined at 37 ℃ in 0.067 mol/L 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 mmol/L) (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 mol/L 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 mmol/L) by the addition of substrate (0.5 mmol/L). The mixture was incubated at 37 ℃ for 5 min, and the reaction was quenched by the addition of 0.1 mol/L 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. The IC_{50} value is the concentration of inhibitor at 50% of enzyme activity.

14-Deoxy-11,12-didehydroandrographolide (2)[12]

14-Deoxy-11,12-didehydro-3,19-metheneandrographolide (7) Compound **2** (1.7 g, 5 mmol) and paraform (182 mg, 6 mmol) in THF (20 mL) were refluxed for 1 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 organic phase was evaporated *in vacuo* to afford **7** (1.6 g, 4.8 mmol 95%) by crystallization from EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.15 (s, 1H), 6.57 (dd, *J*=10.0, 15.6 Hz, 1H), 6.17 (d, *J*=15.6 Hz, 1H), 4.93 (s, 2H), 4.84 (s, 2H), 4.78 (d, *J*=1.5 Hz, 1H), 4.54 (d, *J*=1.48 Hz, 1H), 4.22 (d, *J*=13.1 Hz, 1H), 3.50 (dd, *J*=13.4, 4.7 Hz, 1H), 3.35 (d, *J*=4.5 Hz, 1H), 2.48—2.46 (m, 1H), 2.33 (d, *J*=9.8 Hz, 1H), 2.06—2.04 (m, 1H), 1.83—1.81 (m, 1H), 1.79—1.77 (m, 2H), 1.54—1.52 (m, 1H), 1.35—1.33 (m, 1H), 1.26 (s, 3H), 1.26—1.24 (m, 1H), 1.21—1.98 (m, 1H), 0.82 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ*: 172.8, 144.9, 131.5, 129.4, 124.9, 88.4, 80.3, 70.3, 69.7, 59.8, 58.7, 54.7, 51.8, 39.6, 38.3, 37.7, 36.1, 26.6, 21.1, 21.0, 16.8; IR (KBr) *v*: 3337, 3080, 2928, 2855, 1746, 1642, 1445, 1375, 1073, 1034, 896 cm^{-1}; HRMS calcd for $C_{21}H_{28}NaO_4$ 367.1885, found 367.1889.

14-Deoxy-11,12-didehydro-8,17-epoxyandrographolide (8) Compound **2** (5.0 g, 15 mmol) and *m*CPBA (2.5 g, 16 mmol) in $CHCl_3$ (35 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 **8** (5.0 g, 14 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.16 (s, 1H), 6.51 (dd, J=10.0, 15.6 Hz, 1H), 6.15 (d, J=16.0 Hz, 1H), 4.79 (s, 2H), 4.22 (d, J=10.8 Hz, 1H), 3.46 (dd, J=4.0, 11.2 Hz, 1H), 3.37 (d, J=11.2 Hz, 1H), 2.80 (d, J=3.6 Hz, 1H), 2.56 (d, J=4.0 Hz, 1H), 2.16 (d, J=9.8 Hz, 1H), 1.27 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 172.0, 143.8, 130.7, 128.4, 123.7, 80.2, 69.4, 63.8, 58.9, 57.9, 54.0, 50.7, 42.5, 38.6, 37.7, 35.2, 27.3, 22.5, 21.0, 15.8; IR (KBr) v: 3392, 2979, 2934, 2854, 1723, 1672, 1458, 1368, 1221, 1080, 1035, 983, 894 cm^{-1}; HRMS calcd for $C_{20}H_{28}NaO_5$ 371.1834, found 371.1836.

General procedure for synthesis of 14-deoxy-11, 12-didehydro-15-isopro-*C*-glycosideandrographolide analogues

14-Deoxy-11,12-didehydro-andrographolide derivatives (0.45—0.9 mmol) and various β-*C*-glycosidic ketones (0.3 mmol) in dry methanol were refluxed in the presence of 1,2-diaminoethane (0.09 mmol). After completion of the reaction, the reaction mixture was concentrated under reduced pressure and diluted with $CHCl_3$ (10 mL) and washed with water. The organic phase was evaporated *in vacuo* to afford corresponding product by flash chromatography.

14-Deoxy-11,12-didehydro-15-isopro-*C*-glycosideandrographolide analogue (3) Yield 71%; ^{1}H NMR (400 MHz, DMSO) δ: 8.01 (s, 1H), 7.80 (s, 1H), 6.76 (dd, J=10.4, 15.6 Hz, 2H), 6.16 (dd, J=12.8, 15.6 Hz, 2H), 5.39—5.35 (m, 2H), 5.21—5.17 (m, 2H), 5.08—5.06 (m, 2H), 4.79—4.77 (m, 2H), 4.78 (s, 2H), 4.44 (s, 2H), 4.34 (d, J=2.8 Hz, 2H), 4.04—4.02 (m, 2H), 3.85 (d, J=10.8 Hz, 2H), 3.63 (d, J=5.6 Hz, 4H), 3.42—3.17 (m, 13H), 2.86 (d, J=13.6 Hz, 1H), 2.69 (d, J=13.6 Hz, 1H), 2.39—2.35 (m, 4H), 1.99—1.98 (m, 9H), 1.10 (s, 6H), 0.77 (s, 6H); ^{13}C NMR (100.6 MHz, DMSO) δ: 168.9, 168.7, 149.2, 145.9, 145.3, 136.0, 135.9, 133.2, 132.9, 126.2, 125.8, 125.2, 124.4, 121.8, 121.6, 108.4, 79.2, 79.1, 78.8, 77.3, 73.2, 73.0, 70.8, 70.1, 64.7, 62.9, 60.9, 60.0, 53.9, 42.6, 39.5, 39.3, 39.1, 38.7, 38.2, 36.5, 27.9, 23.4, 23.3, 17.5, 17.2, 15.7, 14.3; IR (KBr) v: 3391, 2935, 1744, 1077, 1031 cm^{-1}; HRMS calcd for $C_{29}H_{41}ClNaO_8$ 575.2388, found 575.2382.

14-Deoxy-11,12-didehydro-15-isopro-*C*-glycosideandrographolide analogue (4) Yield 74%; ^{1}H NMR (400 MHz, DMSO) δ: 8.00 (s, 1H), 7.85 (s, 1H), 6.77—6.75 (m, 1H), 6.16 (dd, J=7.8, 15.8 Hz, 1H), 4.74 (s, 1H), 4.44 (s, 1H), 3.85 (d, J=10.8 Hz, 1H), 3.59 (d, J=10.8 Hz, 1H), 3.23—3.19 (m, 9H), 2.71 (d, J=13.6 Hz, 1H), 1.90 (s, 3H), 1.10 (s, 6H), 0.77 (s, 6H); ^{13}C NMR (100.6 MHz, DMSO) δ: 168.9, 168.8, 149.2, 145.9, 145.2, 135.9, 135.8, 133.4, 133.0, 126.0, 125.8, 124.8, 121.9, 121.7, 108.4, 81.0, 80.8, 78.9, 78.4, 78.2, 73.9, 70.6, 70.5, 62.9, 61.5, 61.0, 60.9, 53.9, 42.6, 39.5, 39.3, 39.1, 38.7, 38.2, 36.5, 34.7, 27.9, 23.4, 23.3, 17.6, 17.3, 15.7; IR (KBr) v: 3403, 2935, 1749, 1081, 1037 cm^{-1}; HRMS calcd for $C_{29}H_{42}NaO_9$ 557.2727, found 557.2724.

14-Deoxy-11,12-didehydro-15-isopro-*C*-glycosideandrographolide analogue (5) Yield 69%; ^{1}H NMR (400 MHz, DMSO) δ: 7.95 (s, 1H), 7.82 (s, 1H), 6.73—6.71 (m, 1H), 6.12 (dd, J=6.4, 15.7 Hz, 1H), 4.70 (s, 1H), 4.40 (s, 1H), 3.82 (d, J=10.9 Hz, 1H), 3.23—3.19 (m, 9H), 2.49—2.47 (m, 1H), 2.35—2.33 (m, 1H), 1.94 (s, 3H), 1.09 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO) δ: 168.9, 168.8, 149.1, 146.0, 135.9, 133.4, 132.9, 126.2, 126.0, 124.6, 124.2, 121.7, 108.4, 82.1, 81.9, 81.1, 80.8, 78.9, 77.2, 77.0, 71.3, 71.1, 62.9, 61.0, 53.9, 42.6, 36.5, 27.9, 23.4, 23.3, 17.4, 15.7; IR (KBr) v: 3401, 2935, 1749, 1444, 1034 cm^{-1}; HRMS calcd for $C_{29}H_{42}NaO_9$ 557.2727, found 557.2729.

14-Deoxy-11,12-didehydro-15-isopro-*C*-glycosideandrographolide analogue (6) Yield 65%; ^{1}H NMR (400 MHz, DMSO) δ: 7.98 (s, 0.4H), 7.84 (s, 0.6H), 6.77—6.75 (m, 1H), 6.15 (dd, J=8.3, 15.7 Hz, 1H), 5.09—5.05 (m, 4H), 4.74 (s, 1H), 4.43 (s, 1H), 4.18—4.14 (m, 1H), 3.85 (d, J=10.8 Hz, 1H), 3.66—3.64 (m, 1H), 1.94 (s, 3H), 1.10 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO) δ: 169.1, 168.9, 149.4, 146.2, 145.8, 136.2, 136.1, 133.3, 133.1, 126.4, 126.2, 125.2, 124.6, 122.0, 121.8, 108.6, 79.1, 79.0, 74.8, 74.2, 70.3, 70.2, 63.1, 61.2, 54.2, 42.8, 38.5, 36.7, 28.1, 23.6, 23.5, 17.2, 15.9; IR (KBr) v: 3394, 2935, 1750, 1444, 1039 cm^{-1}; HRMS calcd for $C_{28}H_{40}NaO_8$ 527.2621, found 527.2628.

14-Deoxy-11,12-didehydro-3,19-methene-15-isopro-*C*-glycosideandrographolide analogue (9) Yield 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28 (s, 1H), 6.91—6.89 (m, 1H), 6.14 (d, J=16.0 Hz, 1H), 4.92 (d, J=6.4 Hz, 1H), 4.80 (s, 2H), 4.56 (s, 1H), 4.43 (s, 1H), 4.13—4.11 (m, 1H), 4.04—4.02 (m, 1H), 3.78—3.66 (m, 14H), 2.05 (s, 3H), 1.24 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 169.8, 148.7, 147.4, 137.6, 137.2, 132.5, 127.6, 123.4, 122.8, 122.6, 110.4, 88.5, 80.6, 79.9, 75.1, 71.6, 69.9, 63.5, 63.2, 63.0, 62.5, 61.2, 55.1, 39.4, 38.5, 38.0, 37.1, 35.4, 26.6, 22.6, 21.8, 21.7, 18.6, 16.8, 14.9; IR (KBr) v: 3426, 2941, 1753, 1097 cm^{-1}; HRMS calcd for $C_{30}H_{41}ClNaO_8$ 587.2388, found 587.2387.

14-Deoxy-11,12-didehydro-3,19-methene-15-isopro-*C*-glycosideandrographolide analogue (10) Yield 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (s, 1H), 7.28 (s, 1H), 6.92—6.88 (m, 2H), 6.11 (d, J=15.6 Hz, 2H), 4.90 (d, J=5.4 Hz, 2H), 4.78 (s, 2H), 4.52 (s, 3H), 4.00 (d, J=10.4 Hz, 4H), 3.77—3.24 (m, 23H), 2.00 (s, 3H), 1.96 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 0.91 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 169.8, 168.8, 148.1, 146.5, 145.6, 136.7, 136.4, 131.9, 131.5, 126.8, 124.6, 122.8, 122.2, 121.7, 109.5, 87.7, 79.7, 79.3, 78.4, 77.3, 74.1, 73.6, 70.1, 69.7, 69.1, 61.7, 54.3, 46.4, 38.7, 37.7, 37.3, 36.4, 34.6, 25.9, 21.8, 20.9, 17.8, 17.6, 16.1; IR (KBr) v: 3420, 2939, 1753, 1094 cm^{-1}; HRMS calcd for $C_{30}H_{42}NaO_9$ 569.2727, found 569.2735.

14-Deoxy-11,12-didehydro-3,19-methene-15-iso-

pro-*C*-glycosideandrographolide analogue (11) Yield 69%; ^{1}H NMR (400 M Hz, $CDCl_3$) δ: 7.41 (s, 1H), 7.32 (s, 1H), 6.91—6.89 (m, 1H), 6.14 (d, J=15.6 Hz, 1H), 4.90 (s, 2H), 4.78 (s, 2H), 4.29 (s, 2H), 4.26—3.42 (m, 14H), 2.01 (s, 3H), 1.41 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 169.7, 148.8, 147.3, 147.1, 132.6, 132.3, 127.9, 127.7, 122.9, 110.3, 88.5, 87.3, 83.1, 81.0, 80.6, 79.9, 72.4, 69.9, 64.8, 62.5, 55.0, 39.5, 38.5, 38.0, 37.1, 26.6, 25.9, 22.6, 21.7, 18.5, 18.1, 16.8; IR (KBr) v: 3400, 2939, 1753, 1445, 1026 cm^{-1}; HRMS calcd for $C_{30}H_{42}NaO_9$ 569.2727, found 569.2740.

14-Deoxy-11,12-didehydro-3,19-methene-15-isopro-*C*-glycosideandrographolide analogue (12) Yield 59%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (s, 1H), 7.82 (s, 1H), 6.73—6.71 (m, 1H), 6.12 (dd, J=6.4, 15.7 Hz, 1H), 4.70 (s, 1H), 4.40 (s, 1H), 3.82 (d, J=10.9 Hz, 1H), 3.25—3.11 (m, 9H), 2.49—2.47 (m, 1H), 2.35—2.33 (m, 1H), 1.94 (s, 3H), 1.09 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 168.9, 168.8, 149.1, 146.0, 135.9, 133.4, 132.9, 126.2, 126.0, 124.6, 124.2, 121.7, 108.4, 82.1, 81.9, 81.1, 80.8, 78.9, 77.2, 77.0, 71.3, 71.1, 62.9, 61.0, 53.9, 42.6, 36.5, 27.9, 23.4, 23.3, 17.4, 15.7; IR (KBr) v: 3425, 2939, 1751, 1063 cm^{-1}; HRMS calcd for $C_{29}H_{40}NaO_8$ 539.2621, found 539.2630.

14-Deoxy-11,12-didehydro-8,17-epoxy-15-isopro-*C*-glycosideandrographolide analogue (13) Yield 71%; ^{1}H NMR (400 MHz, DMSO) δ: 7.95 (s, 1H), 6.29 (dd, J=10.0, 15.6 Hz, 1H), 6.07 (dd, J=12.4, 15.6 Hz, 1H), 5.32 (d, J=4.4 Hz, 1H), 5.17 (d, J=5.6 Hz, 1H), 5.01 (d, J=4.4 Hz, 1H), 4.75—4.73 (m, 1H), 4.29 (d, J=3.6 Hz, 1H), 4.12 (d, J=5.2 Hz, 1H), 3.98 (dd, J=7.2, 14.0 Hz, 1H), 3.80 (d, J=10.8 Hz, 1H), 3.59—3.57 (m, 2H), 3.39—3.37 (m, 1H), 3.33—3.28 (m, 5H), 3.24—3.16 (m, 2H), 2.80 (d, J=12.8 Hz, 1H), 2.65 (d, J=4.4 Hz, 1H), 2.49—2.46 (m, 2H), 2.34 (dd, J=9.4, 14.2 Hz, 1H), 2.19—2.17 (m, 1H), 1.95 (s, 3H), 1.06 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO) δ: 168.9, 145.4, 132.9, 132.1, 126.1, 125.2, 123.7, 79.2, 78.7, 77.3, 73.2, 70.9, 64.7, 62.9, 61.0, 60.0, 58.6, 53.6, 49.9, 42.5, 38.0, 35.7, 34.6, 27.4, 23.3, 21.8, 17.3, 15.8, 14.3; IR (KBr) v: 3410, 2938, 1742, 1038 cm^{-1}; HRMS calcd for $C_{29}H_{41}ClNaO_9$ 591.2337, found 591.2325.

14-Deoxy-11,12-didehydro-8,17-epoxy-15-isopro-*C*-glycosideandrographolide analogue (14) Yield 78%; ^{1}H NMR (400 MHz, DMSO) δ: 7.95 (s, 1H), 7.81 (s, 1H), 630 (dd, J=9.9, 15.6 Hz, 1H), 6.12 (dd, J=6.7, 15.6 Hz, 1H), 3.99 (dd, J=7.0, 14.2 Hz, 1H), 3.81 (d, J=12.4 Hz, 1H), 3.56—3.17 (m, 10H), 2.99—2.97 (m, 1H), 2.89—2.85 (m, 2H), 2.66—2.64 (m, 1H), 2.48 (d, J=4.5 Hz, 1H), 2.18 (dd, J=4.1, 9.7 Hz, 1H), 1.95 (s, 3H), 1.06 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO) δ: 169.1, 169.0, 146.2, 145.4, 133.5, 133.1, 132.1, 132.0, 126.1, 126.0, 125.9, 125.1, 124.1, 123.9, 81.2, 81.0, 78.9, 78.5, 74.8, 74.1, 63.1, 61.7, 60.2, 58.8, 53.8, 50.1, 45.9, 42.7, 38.2, 35.9, 34.9, 27.6, 23.5, 21.9, 21.2, 17.8, 17.5, 16.0, 14.5; IR (KBr) v: 3409, 2933, 1747, 1038 cm^{-1}; HRMS calcd for $C_{29}H_{42}NaO_{10}$ 573.2676, found 573.2662.

14-Deoxy-11,12-didehydro-8,17-epoxy-15-isopro-*C*-glycosideandrographolide analogue (15) Yield 74%; ^{1}H NMR (400 MHz, DMSO) δ: 7.98 (s, 0.3H), 7.88 (s, 0.7H), 6.34—6.32 (m, 1H), 6.10—6.08 (m, 1H), 5.20—5.16 (m, 2H), 5.03 (d, J=4.2 Hz, 1H), 4.56 (s, 1H), 4.15 (s, 1H), 4.15—3.65 (m, 5H), 1.97 (s, 3H), 1.13 (s, 6H), 0.90 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO) δ: 168.7, 145.9, 132.8, 132.0, 131.8, 123.8, 81.9, 81.0, 80.7, 79.4, 78.6, 77.0, 71.1, 62.9, 58.5, 53.6, 53.0, 49.9, 45.9, 42.5, 40.3, 38.0, 36.3, 35.6, 27.4, 23.3, 21.7, 17.3, 15.7; IR (KBr) v: 3403, 2935, 1748, 1038 cm^{-1}; HRMS calcd for $C_{29}H_{42}NaO_{10}$ 573.2676, found 573.2662.

14-Deoxy-11,12-didehydro-8,17-epoxy-15-isopro-*C*-glycosideandrographolide analogue (16) Yield 67%; ^{1}H NMR (400 MHz, DMSO) δ: 7.92 (s, 0.4H), 7.80 (s, 0.6H), 6.31—6.29 (m, 1H), 6.09—6.07 (m, 1H), 5.04—4.98 (m, 4H), 4.14—4.12 (m, 1H), 3.81 (d, J=10.9 Hz, 1H), 3.64—3.62 (m, 1H), 3.38—3.17 (m, 6H), 3.17—3.15 (m, 1H), 3.07—3.05 (m, 1H), 2.91—2.89 (m, 1H), 2.67—2.64 (m, 2H), 2.46—2.44 (m, 1H), 2.19—2.17 (m, 1H), 1.91 (s, 3H), 1.06 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO) δ: 168.7, 146.0, 145.6, 133.1, 132.8, 132.0, 126.1, 125.8, 125.1, 124.5, 123.8, 123.7, 78.8, 78.5, 78.4, 74.6, 74.0, 70.1, 70.0, 62.9, 58.6, 58.5, 53.6, 49.9, 42.5, 38.0, 35.7, 35.0, 27.4, 23.3, 21.7, 17.0, 15.8; IR (KBr) v: 3410, 2933, 1748, 1038 cm^{-1}; HRMS calcd for $C_{28}H_{40}NaO_9$ 543.2570, found 543.2568.

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References

[1] de Melo, E. B.; Gomes, A. D.; Carvalho, I. *Tetrahedron* **2006**, *62*, 10277.
[2] Hughes, A. B.; Rudge, A. *J. Nat. Prod. Rep.* **1994**, *11*, 135.
[3] Dai, G. F.; Xu, H. W.; Wang, J. F.; Liu, F. W.; Liu, H. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2710.
[4] Xu, H. W.; Dai, G. F.; Liu, G. Z.; Wang, J. F.; Liu, H. M. *Bioorg. Med. Chem.* **2007**, *15*, 4247.
[5] Gabriela, P. B.; Rawle, I. H. *Tetrahedron* **2001**, *57*, 8773.
[6] Hakomori, S.; Zhang, Y. *Chem. Biol.* **1997**, *4*, 97.
[7] Alper, J. *Science* **2001**, *291*, 2338.
[8] Dove, A. *Nat. Biotechnol.* **2001**, *19*, 913.
[9] Dwek, R. A.; Butters, T. D. *Chem. Rev.* **2002**, *102*, 283.
[10] Yan, L.; Liu, F. W.; Yang, J. L.; Liu, H. M. *J. Carbohydr. Chem.* **2007**, *26*, 339.
[11] Xu, H. W.; Wang, J. F.; Liu, G. Z.; Hong, G. F.; Liu, H. M. *Org. Biomol. Chem.* **2007**, *5*, 1247.
[12] Xu, H. W.; Zhang, J.; Liu, H. M.; Wang, J. F. *Synth. Commun.* **2006**, *36*, 407.
[13] Tsuchiya, T. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 91.
[14] Hazeldine, S. T.; Polin, L.; Kushner, J.; White, K.; Corbett, T. H.; Biehl, J.; Horwitz, J. P. *Bioorg. Med. Chem.* **2005**, *13*, 1069.

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