Modification of 15-akylidene andrographolide derivatives as alpha-glucosidase inhibitor

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ABSTRACT: 15-Alkylidene andrographolide derivatives were specific alpha-glucosidase inhibitors. Semi-synthetic studies of these derivatives led to new alpha-glucosidase inhibitors. Their alpha-glucosidase inhibitory activity was evaluated. Bioactivity results indicated that most of the derivatives were excellent alpha-glucosidase inhibitors. Among them, 6c displayed the best alpha-glucosidase inhibitory bioactivity with an IC_{50} value of 8.3 μM.

Key Words: Synthesis, andrographolide derivative, alpha-glucosidase inhibitor

Introduction

Intense interest in glucosidase inhibitors in chemistry, biochemistry, and pharmacology has led to many types of natural and synthetic inhibitors, which aid in both unraveling the mechanism of glucosidase action and development of potential pharmaceuticals such as antitumour agents (*1-3*), antiviral agents (*4,5*), antidiabetics (*6-9*), and immunoregulatory agents (*10*). Various types of inhibitors have also been designed based on structures that resemble the glycosylcations in a transition state of hydrolysis by glucosidase (*11*).

The plant *Andrographis paniculata* (*12,13*) and its constituent andrographolide (**3**) are used extensively in traditional Chinese medicine (*14,15*). Extracts of the plant and the constituents are reported to exhibit a wide spectrum of biological activities including antibacterial (*16,17*), anti-inflammatory (*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 the current authors' study of glucosidase inhibitors, some andrographolide derivatives have been proven to be potent and specific α-glucosidase inhibitors (*31*). Previous results indicated that (a) the γ-alkylidene butenolide moiety of andrographolide derivatives and (b) the aromatic group at 3,19-hydroxyls favored α-glucosidase inhibitory activity while (c) the epoxidation of double bonds ($\Delta^{8(17)}$) hampered α-glucosidase inhibitory activity (*31*).

Among the two series of 15-alkylidene derivatives cited in previous work, compounds **1** and **2** were the best α-glucosidase inhibitors with an IC_{50} value of 16 μM and 6 μM, respectively (Figure 1) (*32*).

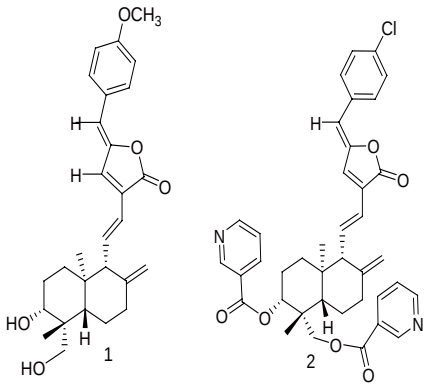

Figure 1. α-glucosidase inhibitors with an IC_{50} value of 16 μM and 6 μM, respectively.

This paper focuses on synthesizing more 15-alkylidene andrographolide analogues and investigating the contribution of ketal to inhibitory activity. Hence, a new series of derivatives were designed and synthesized based on the 15-aklylidene andrographolide derivatives concerned instead of the compound **1,** which displayed excellent bioactivity (IC_{50}, 16 μM).

Materials and Methods

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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. ^{1}H- and ^{13}C-NMR spectra were recorded on a Brüker DPX-400 spectrometer at 400 and 100MHz with TMS as the internal standard. Mass spectra were taken with a Waters Q-Tof micro mass spectrometer. The absorbance at 405 nm was measured with a PowerWaveX Microplate Scanning Spectrophotometer (BIO-TEK INSTRUMENTS, INC).

General procedure for α-glucosidase inhibition assay

The inhibition rate was determined at 37ºC in 0.067 M K_2HPO_4/KH_2PO_4 buffer (pH 6.8).The reaction mixture contained 4 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). One mM acarbose (extracted from Glucobay tablets, Bayer Pharmaceuticals Corporation) was tested as a positive control. Both the inhibitor and substrate were first dissolved in dimethyl sulfoxide (DMSO) and then diluted with 0.067 M K_2HPO_4/KH_2PO_4 buffer so that the final concentration of DMSO was 10%. The enzymatic reaction was started after incubation of the enzyme (0.04 units/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 37ºC 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 served as the relative rate for the hydrolysis of the substrate. All experiments were carried out in triplicate.

Synthesis of compound 4 (*33*)

Synthesis of compound 5

Compound **4** (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 produce a white powder. The white powder was dissolved in $CHCl_3$. The $CHCl_3$ phase was extracted with brine and water and dried with Na_2SO_4. The solvent was evaporated to produce **5.**

General procedure for the synthesis of compound 6

5 (100 mg, 0.3 mmol) and variant aldehydes (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 produce the corresponding product by flash chromatography or crystallization from methanol.

6a Yield 89%; m.p.: 153.8~156.5ºC; IR 2939, 2847, 1757, 1643, 1449, 1165, 1101, 1029, 941, 900 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.77 (2H, d, *J* = 7.5Hz), 7.38 (1H, t, *J* = 7.3Hz), 7.30 (2H, t, *J* = 7.3Hz), 7.10 (1H, s), 6.97 (1H, dd, *J* = 10.0, 15.6Hz), 6.23 (1H, d, *J* = 15.6Hz), 5.95 (1H, s), 4.93 (1H, d, *J* = 6.5Hz), 4.81 (2H, od), 4.57 (1H, s), 4.06 (1H, d, *J* = 11.2Hz), 3.50 (1H, dd, *J* = 4.6, 13.2Hz), 3.46 (1H, d, *J* = 11.2Hz), 2.50 (1H, dd, *J* = 1.6, 13.7Hz), 2.24 (1H, m), 2.04 (1H, m), 1.76 (1H, m), 1.64 (2H, om), 1.47 (1H, br), 1.42 (3H, s), 1.31 (1H, m), 1.22 (1H, m), 1.14 (1H, m), 0.97 (3H, s); ^{13}C-NMR (100.6MHz, $CDCl_3$): δ 168.8, 147.8, 147.6, 137.5, 135.5, 133.3, 130.4, 128.8, 128.7, 127.7, 127.1, 113.0, 109.6, 87.7, 79.8, 69.1, 61.8, 54.5, 38.7, 37.7, 37.3, 36.3, 25.8, 21.8, 20.9, 16.0. HRMS m/z: $[M+Na]^+$ 455.2189 (calcd.455.2198).

6b Yield 87%; m.p.: 187.0~189.4ºC; IR: 2940, 2847, 1752, 1645, 1596, 1462, 1300, 1245, 1165, 1100, 1029, 939, 752 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ 8.18 (1H, dd, *J* = 1.2, 8.0Hz), 7.28 (1H, m), 7.13 (1H, s), 7.01 (1H, t, *J* = 7.6Hz), 6.92 (1H, dd, *J* = 10.1, 15.8Hz), 6.89 (1H, d, *J* = 8.4Hz), 6.5 (1H, s), 6.29 (1H, d, *J* = 15.6Hz), 4.95 (1H, d, *J* = 6.4Hz), 4.80 (2H, om), 4.57 (1H, s), 4.06 (1H, d, *J* = 11.2Hz), 3.87 (3H, s), 3.50 (1H, dd, *J* = 4.4, 8.8Hz), 3.46 (1H, d, *J* = 11.6Hz), 2.49 (1H, m), 2.46 (1H, d, *J* = 10Hz), 2.26 (1H, m), 2.06 (1H, m). 1.79 (1H, m), 1.64~1.57 (2H, om), 1.41 (3H, s), 1.30 (1H, m), 1.21~1.13 (2H, om), 0.96 (3H, s); ^{13}C-NMR (100.6MHz, $CDCl_3$): δ 168.9, 157.3, 147.9, 147.4, 136.9, 136.1, 131.5, 130.3, 126.4, 122.3, 121.8, 121.1, 110.5, 109.6, 106.9, 87.7, 79.8, 69.1, 61.8, 55.6, 38.7, 37.7, 37.3, 36.3, 25.8, 21.8, 20.9, 16.0.

6c Yield 57%; m.p.: 175.0~176.4ºC; IR 2941, 2849, 1742, 1601, 1565, 1525, 1366, 1165, 1100, 1063, 940, 810 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.70 (2H, d, *J* = 8.8Hz), 7.09 (1H, s), 6.84 (1H, dd, *J* = 10.1, 15.8Hz), 6.70 (2H, d, *J* = 8.8Hz), 6.21 (1H, d, *J* = 15.8Hz), 5.90 (1H, s), 4.94 (1H, d, *J* = 6.4Hz), 4.81 (2H, od), 4.58 (1H, s), 4.06 (1H, d, *J* = 11.2Hz), 3.51 (1H, om), 3.43 (1H, d, *J* = 11.2Hz), 3.0 (6H, od), 2.49 (1H, d, *J* = 13.5Hz), 2.36 (1H, d, *J* = 10Hz), 2.26 (1H, m), 2.10 (1H, m). 1.79 (1H, m), 1.65~1.57 (2H, om), 1.41 (3H, s), 1.28~1.13 (3H, om), 0.96 (3H, s); ^{13}C-NMR (100.6MHz, $CDCl_3$): δ 169.4, 150.5, 148.0, 144.8, 135.7, 135.2, 132.2, 130.4, 124.2, 122.1, 121.4, 114.6, 111.9, 109.6, 87.7, 79.8, 69.1, 61.8, 34.3, 40.1, 38.6, 37.7, 37.2, 36.3, 25.8, 21.8, 20.8, 16.1.

6d Yield 69%; m.p.: 164.8~170.2ºC; IR: 2942, 2847, 1750, 1638, 1599, 1507, 1233, 1161, 1099, 1028, 941, 892 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.83 (2H, om), 7.11 (3H, om), 6.98 (1H, dd, *J* = 10.1, 15.8Hz), 6.23 (1H, d, *J* = 15.8Hz), 5.9 (1H, s), 4.94 (1H, d, *J* = 6.4Hz), 4.82 (2H, od), 4.56 (1H, s), 4.06 (1H, d, *J* = 11.2Hz), 3.51 (1H, om), 3.46 (1H, d, *J* = 11.2Hz), 2.49 (1H, d, *J* = 13.6Hz), 2.46 (1H, d, *J* = 10.0Hz), 2.26 (1H, m), 2.06 (1H, m), 1.78 (1H, br), 1.61 (2H, om), 1.42 (3H, s),

1.31 (1H, m), 1.22 (1H, m), 1.14 (1H, m), 0.97 (3H, s); ^{13}C-NMR (100.6MHz, $CDCl_3$): δ 168.6, 164.0, 161.5, 147.8, 147.1, 137.5, 135.5, 132.3, 129.5, 126.8, 121.6, 116.0, 115.8, 111.8, 109.6, 87.7, 79.7, 69.1, 61.8, 54.3, 38.7, 37.7, 37.3, 36.3, 25.8, 21.8, 20.8, 16.1.

6e Yield 90%; m.p.: 198.2~199.7ºC; IR 2953, 2939, 2849, 1758, 1637, 1488, 1458, 1161, 1097, 1043, 1023, 942, 891, 811 cm^{-1}; H-NMR (400MHz, $CDCl_3$): δ 7.71 (2H, d, *J* = 8.8Hz), 7.36 (2H, d, *J* = 8.8Hz), 7.10 (1H, s), 6.99 (1H, dd, *J* = 10.1, 15.6Hz), 6.23 (1H, d, *J* = 15.8Hz), 5.92 (1H, s), 4.94 (1H, d, *J* = 6.4Hz), 4.81 (2H, od), 4.56 (1H, s), 4.06 (1H, d, *J* = 11.2Hz), 3.51 (1H, dd, *J* = 4.4, 12.8Hz), 3.46 (1H, d, *J* = 11.2Hz), 2.50 (1H, m), 2.46 (1H, d, *J* = 10Hz), 2.29 (1H, m), 2.08 (1H, m). 1.79 (1H, m), 1.63~1.58 (2H, om), 1.42 (3H, s), 1.32 (1H, m), 1.22~1.11 (2H, om), 0.96 (3H, s); ^{13}C-NMR (100.6MHz, $CDCl_3$): δ 168.5, 147.82, 147.86.

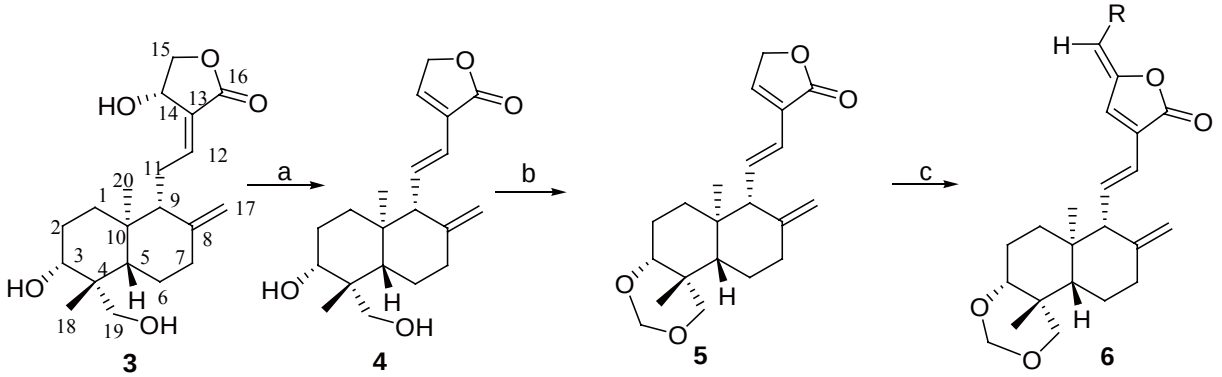
6f Yield 77%; m.p.: 168.4~170.2ºC; IR 2970, 2941, 2847, 1761, 1628, 1443, 1261, 1101, 1030, 944, 892 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ 8.25 (1H, d, *J* = 7.7Hz), 7.41 (1H, d, *J* = 7.8Hz), 7.31 (1H, m), 7.24 (1H, m), 7.22 (1H, s), 7.00 (1H, dd, *J* = 10.0, 15.8Hz), 6.45 (1H, s), 6.25 (1H, d, *J* = 15.8Hz), 4.9 (1H, d, *J* = 6.4Hz), 4.8 (2H, od), 4.56 (1H, s), 4.06 (1H, d, *J* = 11.2Hz), 3.51 (1H, dd, *J* = 4.4, 12.8Hz), 3.47 (1H, d, *J* = 11.2Hz), 2.50 (1H, d, *J* = 13.6Hz), 2.38 (1H, d, *J* = 10.1Hz), 2.24 (1H, m), 2.07 (1H, m), 1.78 (1H, m), 1.61 (2H, om), 1.42 (3H, s), 1.31~1.14 (3H, om), 0.97 (3H, s); ^{13}C-NMR (100.6MHz, $CDCl_3$): δ 168.5, 148.5, 147.8, 138.1, 135.8, 134.1, 131.9, 131.0, 129.7, 129.6, 127.5, 127.2, 121.5, 109.7, 105.2, 87.7, 79.7, 69.1, 61.8, 54.2, 38.7, 37.7, 37.2, 36.2, 25.8, 21.8, 20.8, 16.1.

6g Yield 77%; m.p.: 179.3~182.7ºC; IR 2941, 2878, 2847, 1762, 1638, 1582, 1474, 1425, 1163, 1099, 1030, 943, 892 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.73 (1H, s), 7.67 (1H, d, *J* = 7.5Hz), 7.30 (2H, om), 7.11 (1H, s), 7.00 (1H, dd, *J* = 10.0, 15.6Hz), 6.24 (1H, d, *J* = 15.6Hz), 5.89 (1H, s), 4.94 (1H, d, *J* = 6.4Hz), 4.82 (2H, od), 4.56 (1H, s), 4.06 (1H, d, *J* = 11.2Hz), 3.51 (1H, dd, *J* = 4.4, 12.9Hz), 3.47 (1H, d, *J* = 11.2Hz), 2.50 (1H, d, *J* = 12.3Hz), 2.46 (1H, d, *J* = 10.0Hz), 2.24 (1H, m), 2.08 (1H, br), 1.78 (1H, m), 1.63 (2H, om), 1.42 (3H, s), 1.31 (1H, m), 1.22~1.14 (2H, om), 0.97 (3H, s); ^{13}C-NMR (100.6MHz, $CDCl_3$): δ 168.8, 148.7, 148.2, 138.6, 135.8, 135.4, 135.1, 130.43, 130.40, 129.2, 128.8, 128.0, 122.0, 111.8, 110.1, 88.1, 80.1, 69.5, 62.2, 54.7, 39.2, 38.1, 377, 36.7, 26.2, 22.2, 21.3, 16.5.

6h Yield 85%; m.p.: 203.2~203.8ºC; IR 2942, 2851, 1753, 1642, 1495, 1447, 1259, 1038, 940, 891 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.47 (1H, d, *J* = 1.4Hz), 7.15 (1H, dd, *J* = 1.4, 8.1Hz), 7.08 (1H, s), 6.95 (1H, dd, *J* = 10.1, 15.6Hz), 6.83 (1H, d, *J* = 8.1Hz), 6.22 (1H, d, *J* = 15.6Hz), 6.01 (2H, s), 5.89 (1H, s), 4.9 (1H, d, *J* = 6.3Hz), 4.82 (1H, d, *J* = 6.3Hz), 4.80 (1H, s), 4.57 (1H, s), 4.06 (1H, d, *J* = 11.2Hz), 3.51 (1H, m), 3.45 (1H, d, *J* = 11.1Hz), 2.49 (1H, dd, *J* = 1.5, 13.7Hz), 2.38 (1H, d, *J* = 10.0Hz), 2.24 (1H, br), 2.05 (1H, m), 1.76 (1H, m), 1.64~1.57 (2H, om), 1.42 (3H, s), 1.28 (1H, m), 1.22 (1H, m), 1.13 (1H, m), 0.96 (3H, s); ^{13}C-NMR (100.6MHz, $CDCl_3$): δ 169.0, 149.1, 148.9, 148.6, 147.0, 137.6, 136.4, 128.4, 126.6, 122.5, 113.9, 110.6, 110.4, 109.3, 102.2, 88.4, 80.5, 68.0, 62.5, 55.0, 39.4, 38.4, 38.0, 37.0, 26.5, 22.57, 21.6, 16.8.

6i Yield 75%; m.p.: 203.6~205.0ºC; IR 2943, 2851, 1761, 1636, 1573, 1503, 1457, 1422, 1332, 1248, 1156, 1121, 1027, 937, 896 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.09 (1H, s), 7.02 (2H, s), 6.94 (1H, dd, *J* = 10.1, 15.8Hz), 6.23 (1H, d, *J* = 15.8Hz), 5.87 (1H, s), 4.93 (1H, d, *J* = 6Hz), 4.81 (2H, om), 4.5 (1H, s), 4.06 (1H, d, *J* = 11.6Hz), 3.90 (9H, s), 3.50 (1H, m), 3.46 (1H, d, *J* = 11.6Hz), 2.49 (1H, d, *J* = 12.4Hz), 2.4 (1H, d, *J* = 10.0Hz), 2.26 (1H, m), 2.01 (1H, m), 1.79 (1H, m), 1.64~1.57 (2H, o0m), 1.42 (3H, s), 1.31 (1H, m), 1.22~1.14 (2H, om), 0.96 (3H, s); ^{13}C-NMR (100.6MHz, $CDCl_3$): δ 168.7, 153.2, 147.9, 147.0, 139.0, 137.3, 135.5, 128.8, 126.5, 121.6, 113.1, 109.6, 107.6, 87.7, 79.5, 69.1, 61.7, 61.0, 56.2, 54.3, 38.7, 37.7, 37.3, 36.3, 25.8, 21.8, 20.8, 16.0.

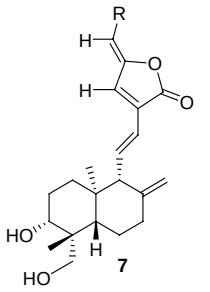
6j A mixture of two isomers (1/3); ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.83 (0.3H, s), 7.52 (0.3H, d, *J* = 1.2Hz), 7.50 (0.7H, d, *J* = 1.2Hz), 7.09 (0.7H, s), 7.03 (0.7H, d, *J* = 3.6Hz), 6.99 (03H, dd, *J* = 10.1, 15.6Hz), 6.95 (0.7H, dd, *J* = 10.1, 15.6Hz), 6.55 (0.7H, m), 6.51 (0.3H, d, *J* = 3.2Hz), 6.49 (0.3H, m), 6.35 (0.3H, s), 6.27 (0.3H, d, *J* = 15.6Hz), 6.22 (0.7H, d, *J* = 15.6Hz), 6.01 (0.7H, s), 4.93 (1H, d, *J* = 6.4Hz), 4.81 (2H, om),



Scheme 1. Synthesis of compound 6. Reagents and conditions: a) xylene, pyridine, Al_2O_3, reflux, 6~10 h. b) THF, H_2SO_4, paraform, reflux, 1 h; c) aldehydes, Na_2CO_3, methanol, reflux, 3~5 h.

Table 1. Structures and α-glucosidase inhibitory activity of compounds **1, 2, 3, 4, 6, and 7**

Comp	R	Bioactivity (IC_{50} μM)	Comp	R	Bioactivity (IC_{50} μM)
1	-	16	**3**	-	Ni [a]
2	-	6	**4**	-	18.5 [b]
6a	C_6H_5	49.1	**7a**	C_6H_5	58
6b	*o*-$OMeC_6H_4$	15.7	**7b**	*o*-$OMeC_6H_4$	Nd [c]
6c	*p*-(*N*,*N*-dimethyl)-C_6H_4	8.3	**7c**	*p*-(*N*,*N*-dimethyl)-C_6H_4	70
6d	*p*-F-C_6H_4	14.1	**7d**	*p*-F-C_6H_4	Ni
6e	*p*-Cl-C_6H_4	> 100	**7e**	*p*-Cl-C_6H_4	Ni
6f	*o*-Cl-C_6H_4	> 100	**7f**	*o*-Cl-C_6H_4	Ni
6g	*m*-Cl-C_6H_4	24.6	**7g**	*m*-Cl-C_6H_4	Nd
6h	benzo[13]dioxole-5-methanyl	> 100	**7h**	benzo[13]dioxole-5-methanyl	82
6i	2,4,5-triMeO-C_6H_4	> 100	**7i**	2,4,5-triMeO-C_6H_4	84
6j	furoyl	Nd	**7j**	furoyl	100



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Acarbose served as a positive control. The percentage of inhibition of 1 mM acarbose was 56.5%.
[a] No inhibition at100 μM.
[b] % Inhibition determined at 100 μM compound concentration.
[c] No determination.

4.57 (0.3H, s), 4.56 (0.7H, s), 4.06 (1H, d, *J* = 11.2Hz), 3.51 (1H, m), 3.46 (1H, d, *J* = 11.2Hz), 2.49 (1H, m), 2.36 (1H, d, *J* = 10Hz), 2.26 (1H, m), 2.07 (1H, m). 1.76 (1H, m), 1.63~1.58 (2H, om), 1.41 (3H, s), 1.28 (1H, m), 1.22~1.13 (2H, om), 0.96 (3H, s); ^{13}C-NMR (100.6MHz, $CDCl_3$): δ 168.3, 168.0, 149.7, , 87.7, 79.7, 69.1, 61.8, 54.3, 38.7, 37.7, 37.2, 36.3, 25.8, 21.8, 20.149.3, 147.88, 147.84, 147.3, 145.6, 144.3, 143.9, 138.0, 137.3, 134.1, 132.3, 128.9, 127.0, 122.1, 121.8, 114.9, 114.5, 113.1, 112.4, 109.6, 101.8, 101.38, 16.0.

Results and Discussion

Compound **4** was obtained by refluxing andrographolide (**3)** in a mixture of xylene and pyridine in the presence of Al_2O_3. Compound **5** was obtained in an excellent yield by heating **4** and paraform in THF in the presence of H_2SO_4. Compound **6** was synthesized by vinylogous aldol reaction of **4** and varied aldehydes (Scheme 1, Table 1). The structure of **6** was elucidated by NMR and IR spectral analysis. Conjugated olefinic protons in ^{1}H-NMR spectrum of **6** were detected at δ 6.8 (H-11), 6.1 (H-12), 7.2 (H-14) and about δ 5.9~6.5 (H-21). The signal of H-15 (δ 4.8) disappeared in ^{1}H-NMR of **6**. Based on the coupling constant $\boldsymbol{J_{H\text{-}11,H\text{-}12}}$ (15.6Hz), the conformation of double bonds $\Delta^{11(12)}$ was assumed to be **E**. The geometry of double bonds ($\Delta^{15(21)}$) in **6** was confirmed to be a **Z** conformation according to previous research (*32*). Of the **6** compounds, **6j** was a mixture of two isomers (1/3), which differed from the corresponding compound **7j**. The reason for the difference has yet to be indicated.

Bioactivity results showed that compound **6** displayed selective α-glucosidase inhibitory activity. The ketal derivative was able to enhance α-glucosidase inhibitory activity (Table 1). The bioactivities of **6a~g** were better than those of their corresponding compounds **7a~g** (*31*,*32*). **6c** is more effective than other **6** compounds. However, the ketal derivatives **6h** and **6i** of **7h** and **7i** displayed a lower IC_{50} value among the compounds concerned. The above results suggested that the ketal of hydroxyls at C-3 and C-19 favored inhibitory activity.

Comparing the activities of **6** indicated that mono-substitution in the aromatic ring displayed a higher affinity than disubstitution or trisubstitution. On the other hand, substitution of a simple chloro group at the 3-position of the aromatic ring was more effective than at the 2- or 4-position. Introduction of a strong electron-donor displayed the best inhibitory activity.

In α-glucosidase inhibitory activity testing, acarbose served as a positive control. The percentage of inhibition of 1 mM acarbose was 56.5%. Most 15-alkylidene andrographolide derivatives (**6** and **7**) displayed better activity than acarbose, which has proven useful in reducing peak postprandial blood glucose (PPBG) concentrations.

In summary, a new series of 15-alkylidene andrographolide derivatives were designed and synthesized as α-glucosidase inhibitors. Their structures were identified by IR and NMR spectral analysis. Several products exhibited good α-glucosidase inhibition activity. Among the inhibitors, the best was **6c** (8.3 μM), which should prove useful in developing new drugs such as diabetes, anti-tumor, and anti-antiviral medications.

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