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# Sesquiterpene Lactones from the Roots of *Ixeris sonchifolia*

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**Abstract** – Three known sesquiterpene lactones were isolated from the *n*-BuOH fraction of the roots of *Ixeris sonchifolia*. Their structures were identified as macrocliniside A (**1**), glucozaluzanin C (**2**), and ixerin H (**3**), by spectral analyses. Compounds **1** and **2** are guaiane-type, while compound **3** is a germacrane-type sesquiterpene lactone. Compounds **1-3** are first isolated from *I. sonchifolia*.
**Keywords** – *Ixeris sonchifolia*, Compositae, sesquiterpene lactone, macrocliniside A, glucozaluzanin C, ixerin H

## Introduction

*Ixeris sonchifolia* is an important food source and a folk medicine for digestive, diuretic, and anti-inflammatory activities. Previous study on the chemical constituents of *I. sonchifolia* revealed several sesquiterpene lactones like ixerin X, ixerin Z, and ixerin Z1, as well as saponins, steroids, and flavonoids (Ma *et al.*, 1998; Feng *et al.*, 2001; Suh *et al.*, 2002). Some of the sesquiterpene lactones are reported to have diverse biological activities, such as cytotoxicity (Seto *et al.*, 1988), ant-repellent and antifeedant properties (Isman and Rodriguez, 1983; Okunade and Wiemer, 1985; Srivastava *et al.*, 1990).

In the present study, we report the isolation of three known sesquiterpene lactones (**1-3**) from the *n*-BuOH fraction of the roots of *I. sonchifolia*. These compounds are first isolated from this plant.

## Experimental

**Instruments and reagents** – $^1$H- and $^{13}$C-NMR spectra were measured on Varian UNITY INOVA 500 and Bruker AC 200 spectrometers. The chemical shifts were given in values (ppm) relative to tetramethylsilane (TMS) as an internal standard. LRFAB Mass spectra were recorded on a JEOL JMS 110/110 instrument. IR spectrum was recorded on JASCO FT/IR-410 in KBr disc method. JASCO DIP-370 digital polarimeter was used to measure optical rotation.

**Plant material** – The roots of *Ixeris sonchifolia* (Compositae) were harvested from the cultivated field in Hadong, Kyungnam and identified taxonomically with respect to morphology. The voucher specimen is deposited in Natural Product Chemistry Laboratory, Pusan National University.

**Extraction and isolation** – The dried roots of *Ixeris sonchifolia* (1.8 kg) were extracted three times with MeOH by refluxing for 5 hrs. After removal of the solvent *in vacuo*, the residue was suspended in water and successively extracted with $Et_2O$, EtOAc, and *n*-BuOH.

The *n*-BuOH fraction was subjected to reversed-phase MPLC with a $H_2O$-MeOH gradient solvent system to give five fractions (A-E). Fraction B was chromatographed on silica gel column with a gradient system of $CHCl_3$-MeOH (20 : 1 → 10 : 1 → 5 : 1), and purified by HPLC with 45% aqueous MeOH on $C_{18}$ column to afford compound **1** (14.1 mg). Fraction E was subjected to silica gel column chromatography with the solvent system of $CHCl_3$-MeOH-$H_2O$ (15 : 3 : 1, lower phase), and HPLC on $C_{18}$ column with 55% aqueous MeOH to give compounds **2** (4.9 mg) and **3** (1.4 mg).

**Macrocliniside A (1)**: Amorphous solid. $[\alpha]_D$ −4.6° (*c* 0.87, MeOH). IR $\nu_{max}$ cm$^{-1}$: 3450, 1760. LRFABMS *m/z*: 447 $[M + Na]^+$. $^1$H-NMR (500 MHz, $CD_3OD$): see Table 1. $^{13}$C-NMR (125 MHz, $CD_3OD$): see Table 2.

**Glucozaluzanin C (2)**: Amorphous solid. $[\alpha]_D$ −18.4° (*c* 0.93, MeOH). IR $\nu_{max}$ cm$^{-1}$: 3400, 1755. $^1$H-NMR (500 MHz, $CD_3OD$): see Table 1. $^{13}$C-NMR (125 MHz, $CD_3OD$): see Table 2.

**Ixerin H (3)**: Amorphous solid. $[\alpha]_D$ +43.6° (*c* 0.51, MeOH). IR $\nu_{max}$ cm$^{-1}$: 3400, 1740. $^1$H-NMR (500 MHz, $CD_3OD$): see Table 1. $^{13}$C-NMR (50 MHz, $CD_3OD$): see Table 2.

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**Table 1.** $^1$H-NMR data of compounds **1-3** (500 MHz in $CD_3OD$)[a]

| No. | 1 | 2 | 3 |
|---|---|---|---|
| 1 | 3.69 (brq, 8.0) | 2.81 (t, 10) | 4.80 - 5.00 |
| 2a | 2.20 (m) | 2.37 (m) | 1.70 - 2.75 (m) |
| 2b | 2.44 (m) | 1.98 (m) | 1.70 - 2.75 (m) |
| 3 | 4.89 (brt, 6.0) | 4.66 (brt, 5.5) | 1.70 - 2.75 (m) |
| 5 | 2.97 (brt, 8.5) | 3.02 (m) | 4.80 - 5.00 |
| 6 | 4.24 (m) | 4.29 (tm, 9.5) | 4.80 - 5.00 |
| 7 | 3.42 (m) | 2.92 (m) | 1.70 - 2.75 (m) |
| 8a | 1.61 (brt, 11.5) | 2.30 (m) | 1.70 - 2.75 (m) |
| 8b | 2.48 (m) | 1.47 (m) | 1.70 - 2.75 (m) |
| 9 | 4.82 (t) | 2.53 (m), 2.22 (m) | 1.70 - 2.75 (m) |
| 11 | - | - | 1.70 - 2.75 (m) |
| 13a | 6.26 (d, 3.5) | 6.13 (d, 3.5) | 1.23 (dd, 6.5, 1.5) |
| 13b | 5.44 (d, 3.5) | 5.59 (d, 3.5) | |
| 14a | 5.19 (brs) | 5.04 (brs) | 1.42 (brs) |
| 14b | 5.16 (brs) | 4.94 (brs) | |
| 15a | 5.96 (brs) | 5.45 (brd, 1.5) | 3.98 (d, 12) |
| 15b | 5.56 (brs) | 5.38 (brd, 1.5) | 4.64 (d, 12) |
| 1' | 5.05 (d, 7.5) | 4.48 (d, 8.0) | 4.32 (dd, 8.0, 1.5) |
| 2' | 4.10 (brt, 7.5) | 3.22-3.39 | 3.22 (brt, 8.0) |
| 3' | 4.27 (m) | 3.22-3.39 | 3.26-3.42 |
| 4' | 4.27 (m) | 3.22-3.39 | 3.26-3.42 |
| 5' | 3.97 (m) | 3.22-3.39 | 3.26-3.42 |
| 6'a | 4.40 (m) | 3.68 (dd, 12, 5.5) | 3.68 (dd, 12, 4.0) |
| 6'b | 4.56 (m) | 3.89 (dd, 12, 2.0) | 3.89 (d, 12) |

[a]Coupling constants and multiplicities are in parentheses.

**Table 2.** $^{13}$C-NMR data of compounds **1-3** ($CD_3OD$)

| No. | 1[a] | 2[a] | 3[b] |
|---|---|---|---|
| 1 | 41.5 | 47.4[c] | 127.6 |
| 2 | 37.6 | 39.7 | 29.0[c] |
| 3 | 80.9 | 82.5 | 36.7 |
| 4 | 151.4 | 152.0 | 141.0 |
| 5 | 49.5 | 52.9 | 131.4 |
| 6 | 84.7 | 86.3 | 81.6 |
| 7 | 36.7 | 47.6[c] | 56.0 |
| 8 | 40.0 | 32.7 | 28.5[c] |
| 9 | 72.5 | 35.5 | 42.0 |
| 10 | 153.5 | 151.2 | 138.6 |
| 11 | 141.3 | 143.2 | 43.1 |
| 12 | 170.5 | 173.4 | 179.0 |
| 13 | 119.3 | 121.6 | 13.3 |
| 14 | 110.9 | 115.9 | 16.4 |
| 15 | 112.3 | 114.8 | 68.3 |
| 1' | 104.8 | 104.3 | 104.7 |
| 2' | 75.5 | 76.4 | 75.2 |
| 3' | 78.8 | 79.4 | 78.2 |
| 4' | 71.9 | 72.9 | 71.7 |
| 5' | 78.6 | 79.0 | 78.0 |
| 6' | 63.0 | 64.0 | 62.8 |

[a]Measured at 125 MHz. [b]Measured at 50 MHz. [c]Assignments with the same superscript within the same column may be interchanged.

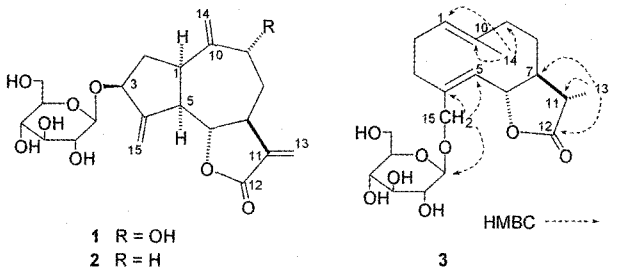


**Fig. 1.** Structures of compounds **1-3** and key HMBC correlations of compound **3**.

## Results and Discussion

A chromatographic separation of the *n*-BuOH fraction of *Ixeris sonchifolia* led to isolation of compounds **1-3**. These compounds were previously isolated from other *Ixeris* species.

The IR spectrum of compound **1** suggested the presence of hydroxyl (3400 $cm^{-1}$), an unsaturated γ-lactone (1750 $cm^{-1}$), and double bonds (1660, 1635 $cm^{-1}$) in the molecule. The $^1$H-NMR spectrum of **1** exhibited signals due to three exomethylene groups at δ 6.26 (d, $J$= 3.5 Hz, H-13a), 5.44 (d, $J$=3.5 Hz, H-13b); 5.19 (brs, H-14a), 5.16 (brs, H-14b); 5.96 (brs, H-15a), 5.56 (brs, H-15b), suggesting that **1** has a guaianolide skeleton. The $^{13}$C-NMR spectrum also indicated the presence of three exomethylene groups: 151.4 (C-4), 153.5 (C-10), 141.3 (C-11), 119.3 (C-13), 110.9 (C-14), 112.3 (C-15). By comparing $^1$H- and $^{13}$C-NMR data with those of literature (Ishihara *et al.*, 1987), **1** was identified as macrocliniside A. Compounds with different stereochemistry were excluded by comparing $^{13}$C-NMR data of those in the literature (Nishimura *et al.*, 1985; Adegawa *et al.*, 1987; Marco *et al.*, 1994; Kisiel and Kohlmunzer, 1989). Compound **1** was previously isolated from *Macroclinidium trilobum* MAKINO. (Miyase *et al.*, 1984b), *Ixeris stolonifera* A. GRAY (Nishimura *et al.*, 1985), *Lactuca saligna* (Kisiel and Gromek, 1993), and *Lactuca sativa* L. (Ishihara *et al.*, 1987).

The IR spectrum of compound **2** suggested the presence of hydroxyl groups (3400 $cm^{-1}$) and an unsaturated-lactone group (1755 $cm^{-1}$) in the molecule. The $^1$H-NMR spectrum of **2** also exhibited two doublets at 5.59 (1H, $J$=3.5 Hz) and 6.13 (1H, $J$=3.5 Hz), which are characteristic of exocyclic α-methylene γ-lactone, as in the $^1$H-

NMR spectrum of **1**. $^{1}$H- and $^{13}$C-NMR spectral data agreed well with those of glucozaluzanin C, which was previously isolated from *Ixeris dentata* NAKAI (Seto *et al.*, 1986), *Ixeris Debilis* (Warashina *et al.*, 1990), *Diaspananthus uniflorus* KITAM (Adegawa *et al.*, 1987), and *Ainsliaea acerifolia* (Miyase and Fukushima, 1984a; Jung *et al.*, 2000).

Compounds **1** and **2** are reported to have cytotoxic activity in the L-5178Y (mouse lymphoma) cultured cell system (Seto *et al.*, 1988).

The $^{1}$H-NMR spectrum of compound **3** showed a doublet of doublets methyl signal at δ 1.23 ($J$ = 6.5, 1.5 Hz), and a broad singlet methyl signal at δ 1.42. Also there were two AB-type doublets ($J$ = 12 Hz) at δ 3.98 and δ 4.64, which were deduced to be H-15a and H-15b. In the $^{13}$C-NMR spectrum, signals due to a glucosyl group were observed and the HMBC spectrum supported the position of glycosidation. From these spectral data, compound **3** was identified as ixerin H, which was previously isolated from *Ixeris dentata* NAKAI (Seto *et al.*, 1986) and *Ixeris tamagawaensis* KITAM. (Asada *et al.*, 1984). Compounds **1-3** are first isolated from the titled plant.

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## References

Adegawa, S., Miyase, T., and Ueno, A., Sesquiterpene lactones from *Diaspananthus uniflorus* (SCH. BIP.) KITAM. *Chem. Pharm. Bull.* **35**, 1479-1485 (1987).

Asada, H., Miyase, T., and Fukushima, S., Sesquiterpene lactones from *Ixeris tamagawaensis* KITAM. III. *Chem. Pharm. Bull.* **32**, 3403-3409 (1984).

Feng, X. Z., Xu, S. X., and Dong, M., A new sesquiterpene lactone glucoside from *Ixeris sonchifolia. J. Asian Nat. Prod. Res.* **3**, 247-251 (2001).

Ishihara N., Miyase, T., and Ueno A., Sesquiterpene lactones from *Lactuca sativa* L. *Chem. Pharm. Bull.* **35**, 3905-3908 (1987).

Isman, M.B. and Rodriguez, E., Larval growth inhibitors from species of *Parthenium. Phytochemistry.* **22**, 2709-2713 (1983).

Jung, C. M., Kwon, H.C., Choi, S.Z., Lee, J.H., Lee, D.J., Ryu, S. N., and Lee, K.R., Phytochemical constituents of *Ainsliaea acerifolia. Kor. J. Pharmacogn.* **31**, 125-129 (2000).

Kisiel, W. and Kohlmunzer, S., A sesquiterpene lactone glycoside from *Crepis tectorum. Phytochemistry.* **28**, 2303-2304 (1989)

Kisiel, W. and Gromek, D., Sesquiterpene lactones from *Lactuca saligna. Phytochemistry.* **34**, 1644-1646 (1993).

Marco, J.A., Sanz-Cervera, J.F., Yuste, A., and Oriola, M.C., Sesquiterpene lactones and dihydroflavonols from *Andryala and Urospermum* species. *Phytochemistry.* **36**, 725-729 (1994).

Ma, J.Y., Wang, Z.T., Xu, L.S., Xu, G.J., Kadota, S., and Namba, T., Sesquiterpene lactones from *Ixeris sonchifolia. Phytochemistry.* **43**, 201-203 (1998).

Miyase, T. and Fukushima, S., Sesquiterpene lactones from *Ainsliaea acerifolia* SCH. BIP. and *A. dissecta* FRANCH. et SAV. *Chem. Pharm. Bull.* **32**, 3043-3046 (1984a).

Miyase, T., Yamaki, K., and Fukushima, S., Studies on sesquiterpenes from *Macroclinidium trilobum* MAKINO. I. *Chem. Pharm. Bull.* **32**, 3912-3917 (1984b).

Nishimura, K., Miyase, T., Ueno, A., Noro, T., Kuroyanagi, M., and Fukushima, S., Sesquiterpene lactones from *Ixeris stolonifera* A. GRAY. *Chem. Pharm. Bull.* **33**, 3361-3368 (1985).

Okunade, A.L. and Wiemer, D.F., Ant-repellent sesquiterpene lactones from *Eupatorium quadrangularae. Phytochemistry.* **24**, 1199-1201 (1985).

Seto, M., Miyase, T., and Fukushima, S., Sesquiterpene lactones from *Ixeris dentata* NAKAI. *Chem. Pharm. Bull.* **34**, 4170-4176 (1986).

Seto, M., Miyase, T., Umehara, K., and Ueno, A., Sesquiterpene lactones from *Cichorium endivia* L. and *C. intybus* L. and cytotoxic activity. *Chem. Pharm. Bull.* **36**, 2423-2429 (1988).

Srivastava, R., Proksch, P., and Wray, V., Toxicity and antifeedant activity of a sesquiterpene lactone from *Encelia* against *Spodoptera Littoralis. Phytochemistry.* **29**, 3445-3448 (1990).

Suh, J. Y., Jo, Y.M., Kim, N.D., Bae, S.J., Jung, Jee H., and Im, K.S., Cytotoxic constituents from the leaves of *Ixeris sonchifolia. Arch. Pharm. Res.* **25**, 289-292 (2002).

Warashina, T., Ishino, M., Miyase, T., and Ueno, A., Sesquiterpene glycosides from *Ixeris Debilis* and *Ixeris repens. Phytochemistry.* **29**, 3217-3224 (1990).

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