67. Structure of Globularidin: An Unusual Iridoid Glucoside from *Globularia alypum* L.[1])

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Summary

A novel iridoid glucoside, named globularidin, lacking the typical double bond between C(3) and C(4), has been isolated from the whole plant of *Globularia alypum* by the combination of open column- and high-performance liquid chromatography. The structure of this compound was established by chemical transformation and spectral data.

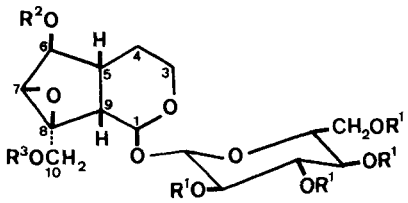
Previous investigation on *Globularia alypum* L. reported the isolation and characterization of globularin and catalpol [1]. In addition the presence of aucubin, catalposide, monotropein, and asperuloside in this species was reported by *Wiefering* [2] which was subsequently contradicted [1]. Reinvestigation in this species by the present authors resulted in the isolation of a novel iridoid which we named globularidin (**1**). We also sorted out, on the basis of HPLC [3], the above mentioned contradictory reports about the other iridoids and established their absence in this species. We report here the structure elucidation of globularidin.

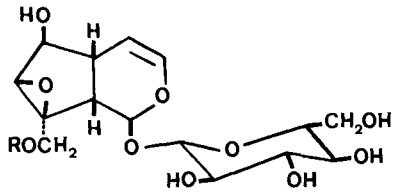
An ethanolic extract of *G. alypum* (whole plant) was processed for iridoids in the usual way. The crude iridoid fraction was initially separated into five broad fractions (A–E) by column chromatography using $CH_2Cl_2/CH_3OH/H_2O$ 8:2:0.2, 7:3:0.3 and 6:4:0.4. Likewise, further fractionation of B, followed by preparative HPLC [3] using reversed phase C_{18} column and CH_3OH/H_2O 3:7 allowed the isolation of globularidin. The structure elucidation of this compound is based upon the following evidence.

Globularidin (**1**), $C_{24}H_{30}O_{11}$, $[\alpha]_D^{20} = -57.65$ ($c = 0.51$, CH_3OH), on hydrolysis with emulsin yielded D-glucose. The IR. (KBr) spectrum of **1** showed bands, with their assignment in parenthesis, at 3410 (OH), 1705 (C(=O)–O), 1635 (C=C), 1580, 1500 and 1450 cm^{-1} (aromatic ring). In agreement with IR. data, the UV. spectrum of **1** showed absorption, λ_{max} (CH_3OH): 216 ($\log\varepsilon$ 4.02), 221 sh. and 278 (4.46), attributable to the presence of cinnamoyl ester group in the molecule. **1** showed positive test with sodium thiosulfate, specific for epoxides

[1]) Part 1 in the series, 'Glycosides of *Globulariaceae*'.

[4]. Acetylation under mild conditions provided a pentaacetate **2** (^{1}H-NMR.), demonstrating the presence of a hydroxy group on the aglucone.





1 Globularidin
$R^1 = R^2 = H$; $R^3 = C_6H_5-CH=CH-CO$

2 Globularidin pentaacetate
$R^1 = R^2 = Ac$; $R^3 = C_6H_5-CH=CH-CO$

3 Tetrahydroglobularin
$R^1 = R^2 = H$; $R^3 = C_6H_5-CH_2-CH_2-CO$

4 Dihydrocatalpol
$R^1 = R^2 = R^3 = H$

5 Globularin
$R = C_6H_5-CH=CH-CO$

The ^{1}H-NMR. (100 MHz, CD_3OD) of **1** exhibited, besides the signals due to five aromatic and two olefinic protons arising from *trans*-cinnamoyl ester part of the molecule, signals at 4.80 (*d*, $J = 8$ Hz, 1 H, H–C(1)); 4.95 and 4.24 (*AB*-system, $J = 13$ Hz, 2 H, 2 H–C(10)); 4.16 (*d*, $J = 6$ Hz, 1 H, H–C(6)); 2.42 ($d \times d$, $J = 8$ Hz, 1 H, H–C(9)); 2.12 (*m*, 1 H, H–C(5)); 1.70 ppm (*m*, 4 H, 2 H–C(3) and 2 H–C(4)) and the signals arising from glucose protons[2]).

The ^{13}C-NMR. spectrum (25.2 MHz) of globularidin exhibited chemical shifts from which the following straightforward assignment [5] *(Table)* can be made. The position of cinnamoyl residue on the aglucone was unequivocally determined by ^{13}C-NMR. spectroscopy [6]. The spectrum of **1** differ from the spectrum of **4** in the chemical shift of C(10) and C(8): the C(10) have moved downfield by 3.07 ppm and the C(8), upfield by 2.71 ppm. Such changes in chemical shift can only be explained if the primary hydroxyl group at C(10) of **1** is esterified. This observation has been confirmed by comparing the data obtained [6] from a series of iridoid glucosides and their corresponding esters.

Table. ^{13}*C-NMR. Data of Globularidin* (**1**) *and Dihydrocatalpol* (**4**)[a])

Comp.	C(1)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)
1	98.05	62.80[b])	23.76	38.09	73.00	62.20[b])	63.27	43.33	64.27
4	97.78	62.89[c])	23.87	38.20	73.23	62.01[c])	65.98	43.47	61.20

[a]) The spectra were recorded in CD_3OD. Chemical shifts in ppm relative to internal $(CH_3)_4Si$. Additional signals arising from glucose. Comp. **1** in addition those from cinnamoyl ester part.
[b])[c]) These values could be interchanged.

[2]) Partly merged in the solvent signals. H–C(7) signal is overlapped with the glucose protons.

Definite proof for the structure **1** (including its configuration) for globularidin was gained from its chemistry, in particular its reduction over 10% Pd/C to tetrahydroglobularin **3** [7]. Additionally, hydrolysis of **1** with methanolic 0.1 N NaOH afforded cinnamic acid and **4** which was found identical in all respect with that of dihydrocatalpol [4] [7].

The iridoid glucoside lacking the double bond between C(3) and C(4), such as **1**, has not been encountered in nature[3]) [8].

The occurrence of **1** was unexpected and is of great biogenetic and chemotaxonomic interest, especially since the corresponding unsaturated iridoid globularin **5**, is present in relatively high amount in the same plant [1]. The presence of this and similar compounds in the genus *Globularia* is currently being investigated.

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3) Notable only exception villoside [8]. However, it lacks a hemiacetalic glucoside function at C(1).