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Antiproliferative glabretal-type triterpenoids from the root bark of *Dictamnus dasycarpus*

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ABSTRACT

Four new glabretal-type triterpenoids, dictabretols A–D (**1**–**4**), were isolated by activity-guided fractionation from the root bark of *Dictamnus dasycarpus* T. (Rutaceae) using an in vitro antiproliferative assay on T cells using splenocytes. The structures of these compounds were determined by spectroscopic methods, including 2D NMR experiments. Compounds were evaluated for their immunosuppressive activity on T cells and demonstrated inhibition of proliferation of activated T cells, up to IC_{50} of 1.5 μM.

Dictamnus dasycarpus T. (Rutaceae) is a perennial herb that is widespread across Asia and Europe; it is known as the 'gas plant' or 'burning-bush' because of the volatile oils it produces.[1,2] *D. dasycarpus* has been used as a traditional medicine for amenorrhea, anti-fertilization, cough, jaundice, rheumatism, and skin disorders. Phytochemical studies of the *Dictamnus* genus have shown it to contain alkaloids, limonoids, flavonoids, coumarins, sesquiterpene glycosides, and essential oils.[3–10]

Immunosuppressive agents have been used to treat immunologically mediated diseases and prevent activities related to the immune system, such as organ transplantation rejection. Among these agents, cyclosporin A and FK506, initially isolated from the fungus *Cylindrocarbon lucidum* and *Streptomyces tsukubaensis* is the most widely used and effective immunosuppressive drug in clinical use today.[11–14] Given its side effects on vascular tension and plasma lipoprotein, there is a need for new immunosuppressive agents.[15]

In our search for immunosuppressive agents from natural origin, methanolic extract of the root bark of *D. dasycarpus* was found to inhibit the proliferation of T cells. The bioassay-guided fractionation and purification of $CHCl_3$-soluble fraction led to the isolation of four new glabretal-type triterpenoids, dictabretols A–D (**1**–**4**).[16] The effects of the compounds on activated T cells were examined by measuring the proliferation of T cells and the secretion level of cytokines, IL-2 and IFN-γ.[17] This report describes the isolation and structure elucidation of **1**–**4** along with their biological evaluation (Fig. 1).

Dictabretol A (**1**)[18] was isolated as a white amorphous powder, mp 234.4 °C. The molecular formula was determined as $C_{35}H_{56}O_7$ by HRESIMS at *m/z* 587.3951 $[M-H]^-$ (calcd for $C_{35}H_{55}O_7$, 587.3948), with eight degrees of unsaturation in the molecule. The IR spectrum showed the presence of hydroxy (3402 cm^{-1}) and ester (1723 cm^{-1}) functionalities. The ^1H NMR spectrum of **1** (in $CDCl_3$, Table 1) displayed the signals for seven methyl groups at δ_H 0.88 (H-19), 1.31 (H-27), 0.84 (H-28), 0.87 (H-29), 1.04 (H-30), 0.96 (H-4′), and 0.95 (H-5′). Proton signals for six oxygenated methines at δ_H 4.65 (H-3), 3.75 (H-7), 5.43 (H-21), 3.94 (H-23), 3.18 (H-24), and 3.65 (H-26) as well as overlapping proton signals for aliphatic methines and methylenes were exhibited. In addition, characteristic signals were observed for a cyclopropyl methylene group in a relatively high-field region at δ_H 0.71 (2H, doublet, J = 4.5 Hz, H-18a) and 0.46 (2H, doublet, J = 5.0 Hz, H-18b). Detailed analysis of ^1H and ^{13}C NMR spectra (Tables 1 and 2) as well as the HMBC spectrum revealed that compound **1** has a glabretal triterpene skeleton.[19,20] The ^1H and ^{13}C NMR spectra of **1** displayed the signals of a trisubstituted epoxy group at C-24 [δ_H 3.18 (1H, doublet, J = 7.5 Hz) and δ_C 63.4] and C-25 (δ_C 60.7). In addition, the chemical shifts at δ_C 98.3 (C-21) and δ_H 5.43 (1H, overlap, H-21) suggested the presence of a hemi-acetal group. The ^1H NMR signals at δ_H 2.21 (2H, broad doublet, J = 7.0 Hz, H-2′), 2.13

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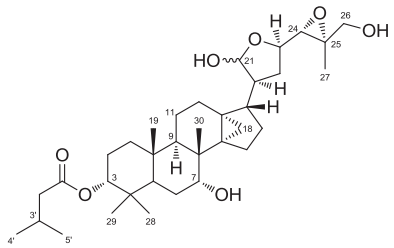

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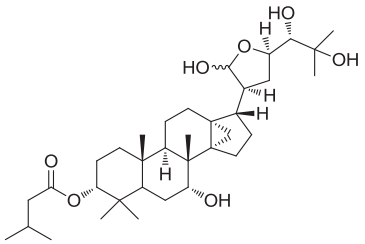

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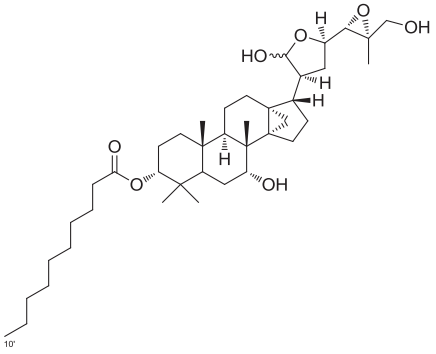

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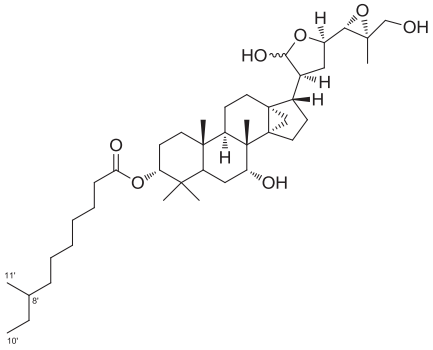

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Figure 1. Structures of compounds **1**–**4**.

Table 1
^{1}H NMR data for compounds **1**–**4**[a]

No.	1	2	3	4
1	1.36 m, 1.13 m	1.37 m, 1.15 m	1.35 m, 1.12 m	1.36 m, 1.13 m
2	1.89 m, 1.58 m	1.89 m, 1.58 m	1.88 m, 1.56 m	1.89 m, 1.58 m
3	4.65 br s	4.65 br s	4.63 br s	4.65 br s
4				
5	1.96 m [1.93 m]	1.95 m	1.96 m [1.93 m]	1.96 m [1.95 m]
6	1.61 m	1.61 m	1.56 m	1.63 m
7	3.75 br s	3.75 br s	3.75br s	3.76 br s
8				
9	1.30 overlap	1.32 m	1.30 overlap	1.31 m
10				
11	1.30 overlap	1.29 overlap	1.30 overlap	1.33 m
12	2.12 m; 1.79 m	2.10 m; 1.77 m		2.09 m; 1.77 m
13				
14				
15	1.93 m; 1.55 m	1.93 m	1.93 m; 1.55 m	1.93 m; 1.55 m
16	1.64 m	1.66 m	1.63 m	1.64 m
17	2.18 m [2.02 m]	2.17 m	2.20 m	2.21 m [2.04 m]
18	0.71 d (4.5); 0.46 d (5.0) [0.79 d (5.0); 0.49 (5.0)]	0.72 br d (4.5), 0.47 d (4.5)	0.70 d (4.5); 0.46 d (4.5) [0.78 d (5.0); 0.48 (5.0)]	0.72 d (4.5); 0.48 d (5.0) [0.81 d (4.5); 0.50 d (4.5)]
19	0.88 s	0.89 s	0.88 s	0.90 s
20	1.86 m [2.13 m]	1.86 m	1.86 m [2.14 m]	1.88 m [2.15 m]
21	5.43 overlap [5.43 overlap]	5.35 br s	5.43 overlap [5.42 overlap]	5.44 overlap [5.45 overlap]
22	1.96 m; 1.68 m	1.85 m, 1.98 m	1.98 m; 1.69 m	1.98 m; 1.70 m
23	3.94 dt (9.5, 7.0) [4.03 ddd (10.5, 7.5, 5.0)]	4.48 t (7.5)	3.93 dt (9.5, 7,5)[4.03 ddd (10.5, 7.5, 5.5)]	3.97 dt (9.5, 7.5) [4.05 ddd (10.5, 7.5, 5.0)]
24	3.18 d (7.5) [3.06 d (7.5)]	3.15 s	3.17 d (7.5) [3.05 d (7.5)]	3.17 d (7.5) [3.07 d (7.5)]
25				
26	3.65 d (12.5) [3.57 d (12.5)]	1.28 s	3.64 d (12.5) [3.56 d (12.5)]	3.67 d (12.0) [3.59 d (12.0)]
27	1.31 s	1.26 s	1.30 s	1.33 s
28	0.84 s	0.85 s	0.83 s	0.85 s
29	0.87 s	0.88 s	0.87 s	0.89 s
30	1.04 s [1.03 s]	1.04 s	1.03 s [1.02 s]	1.06 s [1.05 s]
1′				
2′	2.21 br d (7.0)	2.23 br d (6.0)	2.32 m	2.34 t (7.5) [2.34 t (7.5)]
3′	2.13 m	2.13 m	1.61 m	1.62 m
4′	0.96 d (6.5)	0.97 d (7.0)	1.26 m	1.31 m
5′	0.95 d (6.5)	0.97 d (6.5)	1.26 m	1.26 m
6′			1.26 m	1.29 m