[S3-4] [10/17/2002 (Thurs) 15:20~15:40/Hall A]

Biological Activity of Lanostane-type Triterpenes from *Ganoderma lucidum*

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The fruiting body of *Ganoderma lucidum* (Polyporaceae) is one of the valuable crude drugs, which has been used clinically in Korea, China, and Japan for a long time as a tonic and sedative, and for the treatment of hepatopathy, chronic hepatitis, nephritis, gastric ulcer, hypertension, arthritis, neurasthenia, insomnia, asthma, and poisoning and chronic bronchitis. Nowadays, this mushroom is used for leukopenia and paid much attention as a home remedy.

Over 130 highly oxygenated and pharmacologically active lanostane-type bitter triterpenes, and related compounds have been isolated from the cultured mycelium, fruiting body, and spore of *G. lucidum*. Some of them have been reported to have cytotoxic activity against hepatoma HTC (ganoderic acids U, V, W, X and Y), hepatoma PLC/PRF/5 and KB (ganoderic aldehyde A), and anti-histamine releasing activity in rat mast cells (ganoderic acids C and D), inhibitory activity against angiotensin converting enzyme (ganoderic acid F), hepatoprotective activity (ganoderic acid A), inhibitory effect on farnesyl protein transferase (ganoderic acid A and methyl ganoderate A), and anti-HIV-1 activity (ganoderiol F and ganodermanontriol).[1]

As part of continuing research to find pharmacologically active constituents from natural sources, thirteen new lanostane-type triterpenes, called lucidumols A–B (**1**–**2**), ganoderic acids β (**3**), γ (**4**), δ (**5**), ε (**6**), ζ (**7**), η (**8**) and θ (**9**), lucidenic acid SP1 (**10**), and lucialdehydes A–C (**11**–**13**), together with fourteen known triterpenes such as ganodermanondiol (**14**), ganoderiol F (**15**), ganodermanontriol (**16**), ganodermanonol (**17**), ganodermadiol (**18**), ganoderic acid A (**19**), ganoderic acid B (**20**), ganoderic acid B9 (**21**), ganoderic acid C1 (**22**), ganoderic acid C2 (**23**), ganoderic acid C6 (**24**), ganoderic acid G (**25**), ganolucidic acid A (**26**), and ganolucidic acid D (**27**)], isolated from the fruiting body and spore of *G. lucidum* and estimated for their biological acticity.[2–5]

1. Structural Determinations of New Triterpenes

The structures of the new triterpenes were determined by chemical and spectral means, which included the determination of a chiral center in the side chain by a modification of Mosher's method, such as ganoderic acids β (**3**), γ (**4**), ε (**6**) and η (**8**), and ganolucidic acid D (**27**).[2–3]

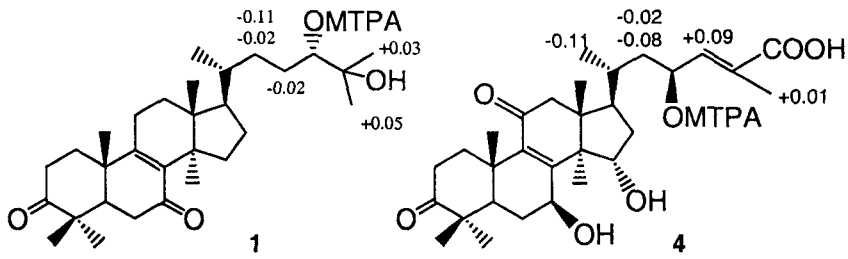

Fig. Chemical shift differnce for the (S)-MTPA Esters and (R)-MTPA Esters in ppm at 500 MHz

2. Anti-HIV-1 Protease Activity

Ten triterpenes were tested for their inhibitory activity against HIV-1 protease. Ganoderic acid β (**3**), lucidumol B (**2**), ganodermanondiol (**14**), ganodermanontriol (**16**), and ganolucidic acid A (**26**) showed significant inhibitory effects on HIV-1 protease with IC_{50} values of 20, 50, 90, and 70 μM, respectively. Ganoderic acids A (**19**), B (**20**), and C1 (**23**) moderately inhibited the enzyme activity (IC_{50} values, 140–430 μM). Of the tested compounds, **1** and **15** were devoid of any significant inhibitory effect. As to HIV-1 protease, could reach no conclusion on the structure-activity relatioship of tested compounds. However, hydroxy groups at C-3 or C-24 and C-25 of these triterpenes are essential cores showing inhibitory activity against HIV-1 protease.[2]

3. Anticomplement Activity

Tweleve triterpenes were tested for their anti-classical pathway (CP) complement activity. Ganoderiol F (**15**), ganodermanondiol (**14**) and ganodermanontriol (**16**) showed strong inhibitory activity against the CP system with IC_{50} values of 4.8, 41.7 and 16.2 μM, respectively, compared to rosmarinic acid (IC_{50}= 180.0 μM) and tiliroside (IC_{50}= 96.0 μ M) used as positive controls. On the other hand, lucidenic acid SP1 (**10**), ganoderic acids A (**19**), B (**20**), C1 (**22**) and C6 (**24**), ganolucidic acid A (**26**), and lucidumols A (**1**) and B (**2**) were completely incapable of inhibiting the CP activity. In this experiment, we found that $\Delta^{7(8)}$, $\Delta^{9(11)}$-lanostadiene type triterpenes (compounds **14**—**16**), which are present terminal hydroxyl and/or hydroxymethyl group in the side chain together with a carbonyl group at C-3, had relatively potent anticomplement activity. However, **2**, which is also $\Delta^{7(8)}$, $\Delta^{9(11)}$-lanostadiene type triterpene having a hydroxyl group C-3, was inactive in this system.[4]

4. Cytotoxic Activity

Twenty compounds from the spore of *G. lucidum* were tested for their cytotoxic activity against Meth-A (mouse, sarcoma) and LLC (mouse, lung carcinoma) tumor cells. Ganoderic alcohols, lucidumols A (**10**) and B (**10**), ganodermanondiol (**10**), ganoderiol F (**10**), and ganodermanontriol (**10**), showed cytotoxic effects on both cell lines. Ganoderic acids, including new ganoderic acids β–θ (**3–9**) and lucidenic acid SP1 (**10**) were inactive to both cell lines. Furthermore, three new lanostane-type triterpene aldehydes (**11–13**) isolated from the fruiting body of *G. lucidum* were evaluated for their cytotoxic effects on Meth-A, LLC, T-47D (human, carcinoma), and Sarcoma 180 (mouse, sarcoma).[3,5]

5. Antutumor Activity

Ganoderma alcohol- and acid-parts of the fruiting body of *G. lucidum* were investigated the antitumor effect against LLC cells *in vivo*. Two fractions, when given intraperitoneally once daily for the two weeks at dosages of 50 and 100 mg/kg, the body weights decreased down to 5 days, but then increased gradually becoming almost same to control body weights. The alcohol fraction exhibited the antitumor activity.

Many pharmacological studies of lanostane-type triterpenes are concentrated on the ganoderma acids, because these compounds are major lipophilic constituents of this mushroom. However, the recent studies revealed that ganoderma alcohols also showed significant anticomplement activity, anti-HIV-1 activity, and inhibitory activity against HIV-1 protease as well as cytotoxicity against mouse Meth-A and LLC tumor cells. Therefore, it is necessary, to focus more extensively the pharmacological activity of the Ganoderma alcohols form *G. lucidum*.

References

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