東北医科薬科大学

審査学位論文（博士）要旨

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New Types of Protein Tyrosine Phosphatase 1B Inhibitors from Marine and Terrestrial Organisms

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Marine and terrestrial organisms are a rich source of biologically active metabolites and have been used for the development of new therapeutic agents and their lead compounds. In the course of the search for new types of protein tyrosine phosphatase (PTP) 1B inhibitors from marine and terrestrial organisms, the EtOH extract from fruiting bodies of a mushroom *Rusulla lepida* collected in Sendai, Japan and a marine sponge *Petrosia* sp. collected at Manado in North Sulawesi, Indonesia, were found to inhibit the PTP1B activity.

PTPs, one of the major families of phosphatases, consist of more than 100 members including PTP1B and regulate various cellular functions. PTP1B plays a significant role in the insulin and leptin signal transduction pathways as a negative regulator. Therefore, the inhibitors of PTP1B are expected to be a new type of therapeutic agents for the type 2 diabetes mellitus and obesity.

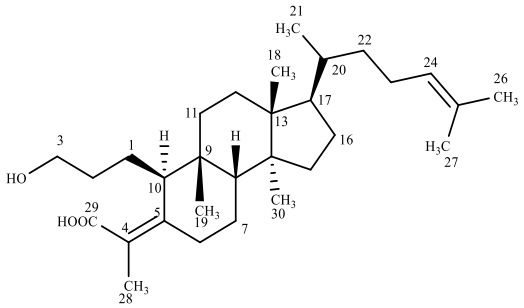
Chemical investigation on the mushroom *R. lepida* led to the isolation of three new terpenes, (24*E*)-3,4-seco-cucurbita-4,24-diene-3-hydroxy-26,29-dioic acid (**1**), (+)-1,2-didehydro-9-hydroxy-aristlone (**2**) and (+)-12-hydroxy-aristlone (**3**), together with two known compounds, (24*E*)-3,4-seco-cucurbita-4,24-diene-3,26,29-trioic acid (**4**) and (+)-aristlone (**5**). The structures of new compounds (**1**-**3**) were assigned on the basis of their spectroscopic data. Compound **1** showed a moderate inhibitory activity against PTP1B with an IC_{50} value of 20.4 μM. On the other hand, compound **4** potently inhibited the PTP1B activity with an IC_{50}

value of 0.4 μM. Oleanolic acid, a positive control, showed the IC_{50} value of 1.1 μM in the same bioassay.

Compounds **1** and **4** were not cytotoxic against five cancer cell lines, Huh-7 (hepatocarsinoma), EJ-1 (bladder), A549 (lung adenocarcinoma), MCF-7 (breast adenocarcinoma), and K562 (erythroleukemia), at 50 μM.

The selectivity against several PTPs was examined, and compound **4** inhibited the T-Cell PTP (TCPTP) activity similar to PTP1B and exhibited 3-fold greater selectivity against PTP1B than *vaccinia* H-1-related phosphatase (VHR), one of the dual specificity phosphatase.

TCPTP is also a negative regulator of insulin and leptin signaling pathways, and recent studies indicated that dual inhibitors against PTP1B and TCPT are expected to be drug candidates without major side effects. Compound **4** may be a candidates of lead compound for the development of drugs for the type 2 diabetes and obesity.



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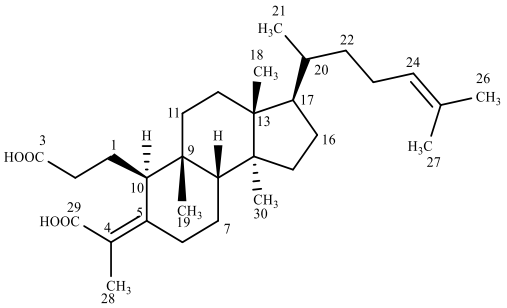
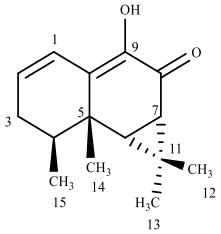


(24*E*)-3,4-seco-cucurbita-4,24-diene-3,26,29-trioic acid (**4**)



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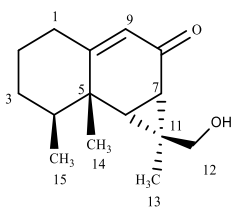

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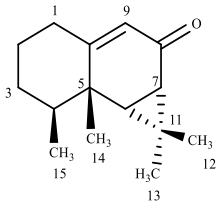
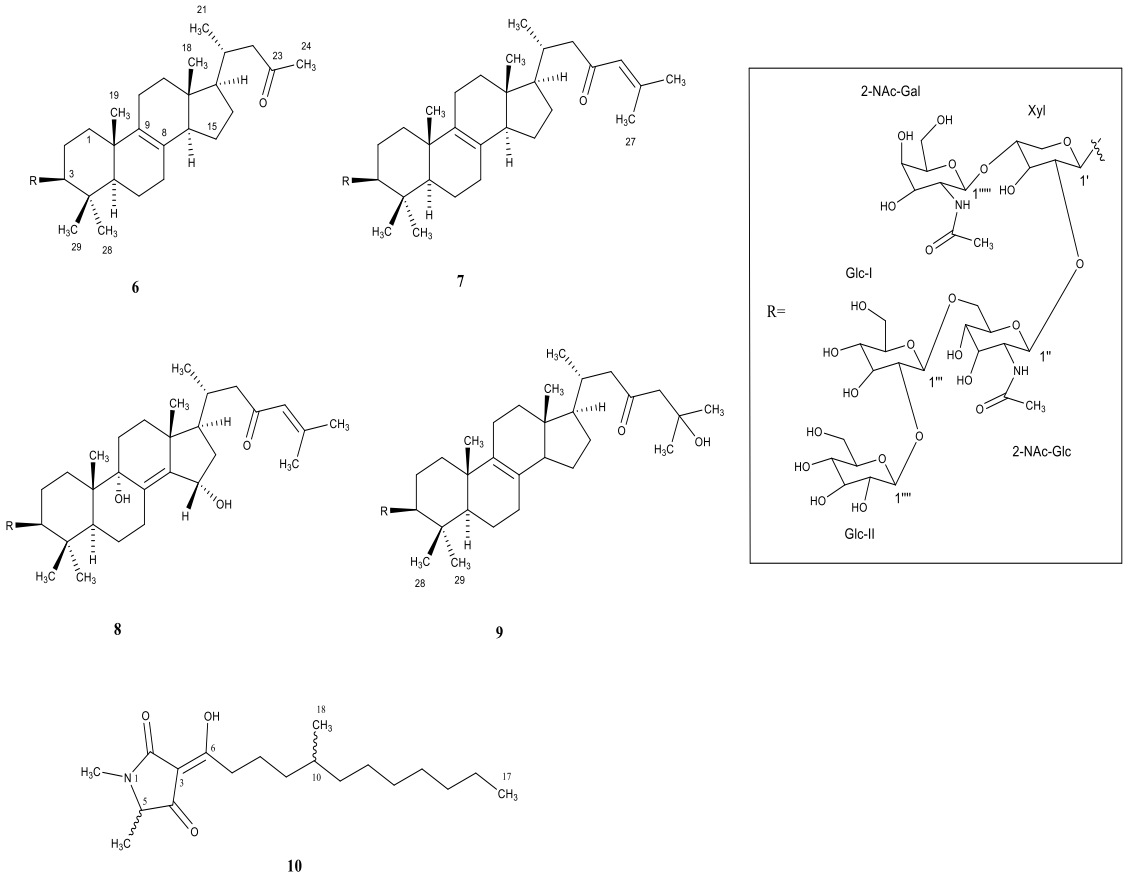


(+)-aristlone (**5**)

Structures of compounds **1-5** isolated from fruiting bodies of *R. lepida*

A new nortriterpene, named as sarasinoside S (**6**), was isolated from the EtOH extract of an Indonesia marine sponge *Petrosia* sp. together with four known sarasinosides A_1 (**7**), I_1 (**8**) and J (**9**). A known tetramic acid derivative, melophlin C (**10**), was obtained from the EtOH extract as an active component against PTP1B and showed the IC_{50} value of 14.6 μM. Compounds **6-9** did not inhibit the PTP1B activity at 15.2-16.0 μM and the cell proliferation of two human solid cancer cell lines, Huh-7 and A549, at 50 μM. The bioactivity of the other melophlin derivatives will be an interesting future study.

The structure of new compound, sarasinoside S (**6**), was determined by the analysis of its spectroscopic data and comparison with the other sarasinoside derivatives. Sarasinoside S (**6**) is the first example of a nortriterpene with a degraded side chain in the sarasinoside family.



Structures of compounds **6-10** isolated from an Indonesian marine sponge *Petrosia* sp.

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