Screening and Identification of PTP1B Inhibitory Natural Products for the Treatment of Type 2 Diabetes

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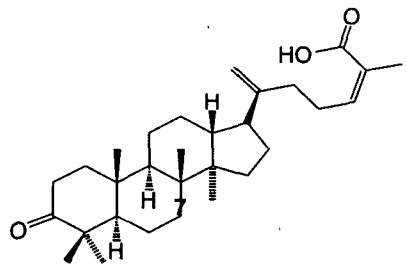
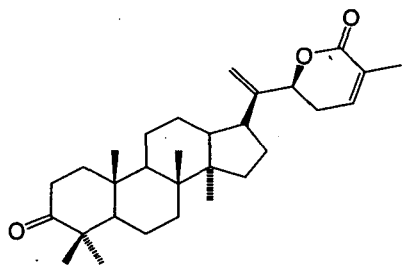
The incidence of diabetes is rapidly increasing in industrialized countries, and type 2 diabetes particularly accounts for more than 90% of cases. In type 2 diabetes, insulin-resistance is one of the characteristic types of pathogenesis, and several drugs that act by increasing the insulin sensitivity are currently being used in the clinic. However, currently available drugs for type 2 diabetes have a number of limitations, such as adverse side-effects and high rates of secondary failure.

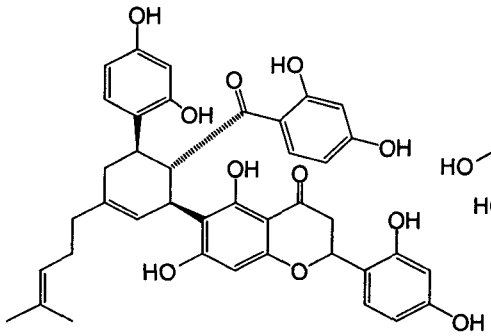
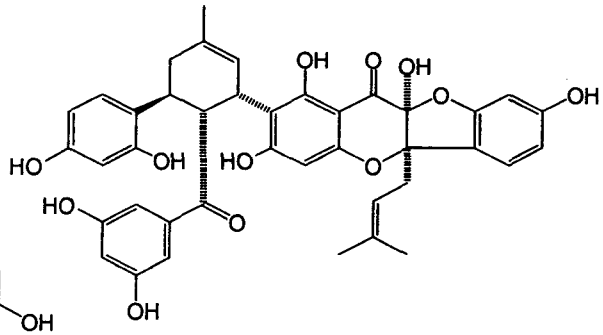
Protein tyrosine phosphatase1B (PTP1B) is a major nontransmembrane phosphotyrosine phosphatase in human tissues and a negative regulator of the insulin-stimulated signal transduction pathway. On the basis of a number of biochemical studies demonstrating that PTP1B is a major negative regulator of insulin receptor signaling, PTP1B is now considered as an attractive target in efforts to develop new treatments for type 2 diabetes and related metabolic syndromes.

Although there have been a number of reports on the designing and development of synthetic PTP1B inhibitors, little has been studied for PTP1B inhibitors derived from natural resources such as plant or microbial resources. Considering the track record of success in the development of a number of useful therapeutics, it seems reasonable to search for PTP1B inhibitors from natural resources.

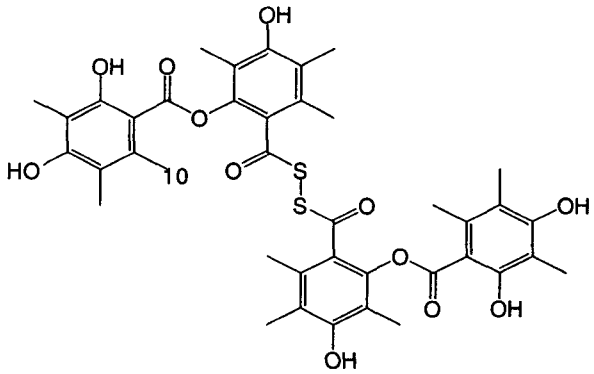
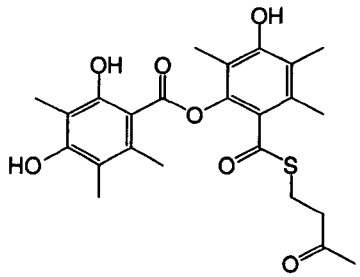
In the course of the screening for PTP1B inhibitors from plant and microbial resources, several organic extracts were selected on the basis of their potent inhibitory effects against PTP1B. Bioassay-guided investigation on these extracts afforded several classes of compounds, such as flavonoids, terpenoids, and depsides, as PTP1B inhibitors (Fig. 1). The structures of PTP1B inhibitors were mainly determined by various spectroscopic analyses such as MS and NMR data. Details of isolation of the active compounds and their PTP1B inhibitory activities will be presented.

dammarane triterpenes from the seeds of *Torreya nucifera*

Prenylated flavonoids from the roots of *Morus* sp.

Sulfur-conaining depsides from fungusf *Micromucor* sp.

Fig. 1. Selected PTP1B inhibitors from plants and microbial sources