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REVIEW

Protein tyrosine phosphatase 1B inhibitors from natural sources

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Abstract Since PTP1B enzyme was discovered in 1988, it has captured the research community's attention. This landmark discovery has stimulated numerous research studies on a variety of human diseases, including cancer, inflammation, and diabetes. Tremendous progress has been made in finding PTP1B inhibitors and exploring PTP1B regulatory mechanisms. This review investigates for the natural PTP1B inhibitors, and focuses on the common characteristics of the discovered structures and structure–activity relationships. To facilitate understanding, all the natural compounds are here divided into five different classes (fatty acids, phenolics, terpenoids, steroids, and alkaloids), according to their skeletons. These PTP1B inhibitors of scaffold structures could serve as a theoretical basis for new concept drug discovery and design.

Keywords PTP1B inhibitors · Natural sources · Chemical structure · Structure–activity relationships

Introduction

Protein tyrosine phosphatases (PTPs; EC 3.1.3.48) are a large family of enzymes that remove phosphate groups from tyrosine phosphorylated proteins. These enzymes play an important role in cell growth regulation, proliferation, and transformation. Among the PTPs family, Protein-tyrosine phosphatase 1B (PTP1B) is a classical enzyme, also called protein tyrosine phosphatase non-receptor type 1 (Barrett et al. 1999). It is widely expressed in human tissues such as adipose tissue, liver, muscle, and brain (Zabolotny et al. 2008). For the first time, Tonks et al. (1988) purified and identified PTP1B enzyme from human placenta (Sun et al. 2016). Chernoff et al. and Brown-Shimer et al. then determined the sequence of amino acids for PTP1B in 1990 (Frangioni et al. 1992). To clarify the role of PTP1B as a negative regulator of the insulin receptor (IR), Elchebly et al. (1999) proved this theory using PTP1B gene lacked mice (Goldstein et al. 1998; Zabolotny et al. 2002). After several years of research, PTP1B was found to be associated with various diseases. In previous reports, the PTP1B enzyme was mainly used as a target for the treatment of diabetes or obesity. Substantial evidence indicates that PTP1B enzyme takes part in insulin and leptin signaling regulations. In the insulin signaling pathway, PTP1B dephosphorylated IR or insulin receptor substrate 1 (IRS-1), thus further reducing insulin sensitivity or shutting down signaling. Consequently, PTP1B inhibitors have emerged as potential and novel target drugs for the treatment of obesity and T2DM (Cho 2013). In the leptin signaling pathway, PTP1B has the function of dephosphorylation for leptin receptor (LepR) and janus kinase 2 (JAK2). This mechanism is used not only in obesity but also in Alzheimer's disease (Bence et al. 2006; Vieira et al. 2017). In addition, the PTP1B enzyme is also

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involved in cancer and inflammation, controlling cytokine signaling pathways by the dephosphorylation of JAK2, tyrosine kinase 2 (TYK2), and signal transducer and activator of transcription 5 (STAT5) (Traves et al. 2014; Song et al. 2016). Moreover, many researches have reported that PTP1B is relevant to inflammatory cytokines such as interleukin 4 (IL-4), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), extracellular signal-regulated kinase (ErK), protein kinase B (PKB/AKT), human epidermal growth factor receptor 2 (HER2) and Nuclear factor kappa B (NFκB) (Camer and Huang 2014; Traves et al. 2014; Rivera-Franco et al. 2016).

The negative regulation effect of PTP1B in insulin signaling pathway is considered to be a potential therapeutic target for obesity, and T2DM. Up to the present, how to efficiently develop highly selective PTP1B inhibitors remains a hot research issue. Thus far, there is no listed PTP1B inhibitor drug, and just a few prodrugs are in the phase of clinical trials. Ertiprotafib (Wyeth-Ayerst Co.) was discontinued in Phase II clinical trial due to insufficient efficacy and dose-dependent side effects (Shrestha et al. 2007; He et al. 2014). Furthermore, trodusquemine (MSI-1436) was isolated from the liver of the dogfish shark (*Squalus acanthias*), which was well tolerated by patients in phase I clinical trial (Rao et al. 2000; Smith et al. 2017). Significantly, this precursor drug is originated from nature, rather than synthetic pathway (Fig. 1).

Although some progress has been made in the study of the structure, catalytic mechanism, regulation, and localization of the general class of protein tyrosine phosphatases, the inhibitors of PTP1B that have been discovered so far have shown significant limitations. For example, there has been very limited success to date in achieving high selectivity with respect to T cell phosphatase (TC-PTP), which is nearly identical to PTP1B. Thus, there remains a need for potent and selective PTP inhibitors in general and PTP1B inhibitors specifically. Recently, many researches have been focused on the discovery of PTP1B inhibitors from a variety sources, such as plants, microorganism, and animals. Around 56 families of genera from the natural source were found to have PTP1B inhibitory activity (Table 1). Although these PTP1B inhibitors have very good inhibitory effect, but their clinical availability remains limited. Because of the PTP1B enzyme is widely distributed in the body, so it is difficult to achieve efficacy simply using conventional drug delivery systems (Zabolotny et al. 2008). Future efforts will probably develop the PTP1B inhibitors as the new drug with desirable in vivo efficacy by improving the pharmacological properties and pharmaceutical dosage form (Zhang and Zhang 2007).

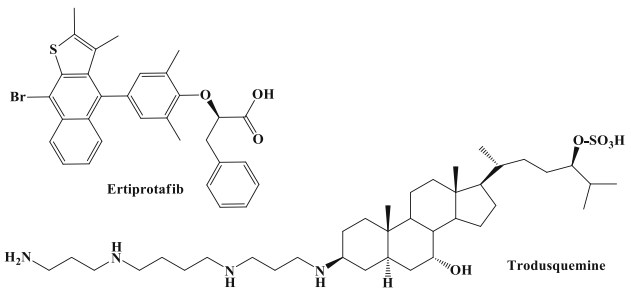


Fig. 1 The clinical-stage PTP1B inhibitors

Above all, it is necessary to search, arrange and integrate such a huge amount of data for natural PTP1B inhibitors. Nearly 500 natural compounds are here reviewed in five different classes (fatty acids, phenolics, terpenoids, steroids, and alkaloids), according to their skeletons. We hope this review will serve as a useful tool for innovative PTP1B inhibitors discovery.

Natural PTP1B inhibitors

Fatty acid

Fatty acids are considered to be the most common compounds in nature. They play an important physiological function in supporting human health (Gill and Valivety 1997). In addition, these compounds are known to be involved in cellular and tissue metabolism of thermal adaptation and membrane fluidity transformation (Funk 2001). Fatty acids may improve the lipid metabolism of diabetes, as well as insulin sensitivity, through different ways. This compound group may reduce the incidence of obesity, facilitate weight loss, or help maintenance of body weight (Nettleton and Katz 2005). Fatty acids are abundant in the nonpolar part of the material. The increased plasma free fatty acid levels are related to mechanisms of insulin resistance, and could be affected by increased lipid flux (Koves et al. 2008). The accumulation of lipid promotes insulin resistance via fatty acid synthesis, metabolism, and storage pathway. Thus, the presence of increased lipid not only enhanced phosphorylation, but also enhanced PTP1B phosphorylation (Obanda and Cefalu 2013). The PTP1B inhibitory effect was also found in fatty acids, including myristic acid (**1**), palmitic acid (**3**), stearic acid (**6**), oleic acid (**8**), linoleic acid (**10**), linolenic acid (**11**), and behenic acid (**15**). In this, a drastic inhibition of PTP1B activity was obtained with stearic acid (**6**), oleic acid (**8**), linoleic acid (**10**), and linolenic acid (**11**) at a concentration of 10 μM, reaching over 90% inhibition rates, as well as myristic acid (**1**), palmitic acid (**3**), and behenic acid (**15**) at the same concentration reaching 52% to 54% of inhibition rates. In mechanism study, this report suggested that unsaturated and saturated fatty acids could activate Akt through PI3K/

Table 1 Recent research on PTP1B from natural source over three years period from 2014 to 2017

Family/scientific names	Part of plants	References	Family/scientific names	Part of plants	References
Agelasidae			Daphniphyllaceae		
Agelas nakamurai	Sponge	Abdjul et al. (2015a)	*Daphniphyllum himalense*	Twigs and leaves	Zhang et al. (2015, 2016)
Alaeocarpaceae			Dysideidae		
Elaeocarpus grandiflorus	Fruits	Saifudin et al. (2016b)	*Dysidea* sp.	Sponge	Abdjul et al. (2016b)
Alcyoniidae			Ellisellidae		
Sarcophyton trocheliophorum	Sorals	Chen et al. (2014c)	*Dichotella gemmacea*	Sorals	Zhou et al. (2014)
Sinularia flexibilis			Ericaceae		
Amaryllidaceae			*Rhododendron capitatum*	Aerial parts	Liao et al. (2015)
Allium cepa L.	Seeds	Li et al. (2014a)	*Rhododendron principis*		Liu et al. (2014)
Apiaceae			Euphorbiaceae		
Angelica keiskei	Stems	Li et al. (2015a)	*Euphorbia neriifolia*	Twigs and leaves	Zhao et al. (2014)
Aplidiidae			*Macaranga denticulata*	Leaves	Lei et al. (2016)
Sidnyum elegans	Corals	Imperatore et al. (2016)	Fabaceae		
Araliaceae			*Flemingia philippinensis*	Roots	Wang et al. (2016b)
Acanthopanax senticosus	Roots and stems	Li et al. (2015b)	Fagaceae		
Panax ginseng C.A. Meyer	Roots	Yang et al. (2016)	*Quercus infectoria*	Gums	Saifudin et al. (2016b)
Panax notoginseng	Leaves	Li et al. (2014b)	Ganodermataceae		
Asteraceae			*Ganoderma lucidum*	Fruits	Pan et al. (2014); Ma et al. (2015)
Elephantopus scaber	Aerial parts	Saifudin et al. (2016b)	Glyptocidaridae		
Gynura divaricata		Chen et al. (2014a)	*Glyptocidaris crenularis*	Urchins	Zhou et al. (2014)
Botryosphaeriaceae			Hericiaceae		
Guignardia sp.	Cultured medium	Ai et al. (2014)	*Hericium erinaceus*	Fruits	Wang et al. (2015a)
Caprifoliaceae			Juglandaceae		
Lonicera japonica	Flower buds	Liu et al. (2016)	*Juglans regia* L.	Leaves	Pitschmann et al. (2014)
Caulerpaceae			Lamiaceae		
Caulerpa racemosa	Algae	Yang et al. (2015)	*Origanum vulgare*	Aerial parts	Bower et al. (2014)
Chloranthaceae			*Origanum majorana*		
Chloranthus oldhamii	Roots	Xiong et al. (2015)	*Rosmarinus officinalis*		
Clusiaceae			*Persea Americana Mill*	Leaves	Marrero-Faz et al. (2014)
Garcinia hanburyi	Gum	Tan et al. (2017)	*Cinnamomum osmophloeum*	Twigs and branches	Lin et al. (2016)
Combretaceae			Leguminosae		
Anogeissus acuminata	Leaves/barks	Navale and Paranjape (2016)	*Glycyrrhiza uralensis* Fisch	Rhizomes	Guo et al. (2015)
Commelinaceae			*Glycyrrhiza glabra*	Roots	Li et al. (2017a)
Tradescantia spathacea Sw.	Aerial parts	Vo et al. (2015)	*Glycyrrhiza uralensis*	Aerial parts	Ji et al. (2016)

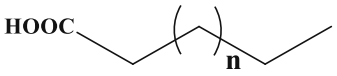
Table 1 continued

Family/scientific names	Part of plants	References	Family/scientific names	Part of plants	References
Cucurbitaceae			*Pueraria lobata*	Roots	Seong et al. (2016)
Gynostemma pentaphyllum	Roots	Li et al. (2014d)	Liliaceae		
Momordica charantia L	Furits	Zeng et al. (2014)	*Veratrum nigrum*	Roots	Kang et al. (2015)
Magnoliaceae			Rhodomelaceae		
Magnolia officinalis	Barks	Sun et al. (2015)	*Laurencia okamurai*	Algae	Li et al. (2017b)
Schisandra chinensis	Fruits	Fang et al. (2014)	Rosaceae		
Malvaceae			*Agrimonia pilosa*	Aerial parts	Na et al. (2016)
Helicteres isora	Aerial parts	Saifudin et al. (2016b)	*Cydonia oblonga* Mill.	Seeds	Tang et al. (2016)
Theobroma cacao L.	Seeds	Żyżelewicz et al. (2016)	*Crataegus pinnatifida*	Fruits	Chowdhury et al. (2014)
Meliaceae			*Prunus dulcis*	Fruits	Qureshi et al. (2016)
Cipadessa cinerascens	Leaves	Yu et al. (2016a)	Russulaceae		
Moraceae			*Russula lepida*	Fruits	Lee et al. (2016)
Cudrania tricuspidata	Leaves	Kim et al. (2016)	Scrophulariaceae		
Morus notabilis	Root barks	Wang et al. (2015b)	*Eremophila aff.*	Aerial parts	Wubshet et al. (2016)
Mycalidae			*Eremophila gibbosa*		
Mycale sp.	Sponge	Zhou et al. (2014)	*Eremophila glabra*		
Myoporaceae			Selaginellaceae		
Eremophila lucida	Leaves	Tahtah et al. (2016)	*Selaginella tamariscina*	Aerial parts	Nguyen et al. (2015a)
Myrtaceae			Simaroubaceae		
Eucalyptus robusta	Leaves	Yu et al. (2016b)	*Ailanthus altissima*	Barks	Sasaki et al. (2015)
Eugenia jambolana	Seeds	Liu et al. (2017)	*Eurycoma longifolia*		
Melaleuca leucadendron	Fruits/leaves	Saifudin et al. (2016a)	*Picrasma javanica*		
Syzygium cumini	Seeds	Sawant et al. (2015)	*Picrasma quassioides*		
Nymphaeaceae			*Simarouba amara*		
Euryale ferox	Shells	Yuan et al. (2014)	*Simaba cuspidata*		
Orchidaceae			*Quassia amara*		
Anoectochilus chapaensi	Aerial parts	Cai et al. (2015)	Smilacaceae		
Petrosiidae			*Smilax china* L.	Leaves	Zhao et al. (2016)
Strongylophora strongilata	Corals	Lee et al. (2015)	Spongiidae		
Xestospongia testudinaria	Sponge	Zhou et al. (2014)	*Hyattella* sp.	Sponge	Abdjul et al. (2015b)
Pleurotaceae			Theaceae		
Pleurotus cystidiosus	Fruits	Tao et al. (2016)	*Camellia japonica*	Fruit peels	Uddin et al. (2014)
Polyporaceae			Trichocomaceae		

Table 1 continued

Family/scientific names	Part of plants	References	Family/scientific names	Part of plants	References
Antrodiella albocinnamomea	Cultured medium	Chen et al. (2014d)	*Isaria fumosorosea*	Cultured medium	Liu et al. (2015)
Ranunculaceae			*Penicillium verruculosum*		Yamazaki et al. (2015)
Coptis chinensis Franch	Rhizomes	Choi et al. (2015)	Umbelliferae		
Nigella glandulifera	Seeds	Chen et al. (2014b, 2017)	*Angelica decursiva*	Whole plants	Ali et al. (2016)
Rhizophoraceae			Verbenaceae		
Rhizophora apiculata	Leaves	Selvaraj et al. (2016)	*Lippia graveolens*	Aerial parts	Bower et al. (2014)

PDK1/Akt pathway in association with PTP1B inhibition (Shibata et al. 2013). Also, Steinmann et al. (2012) showed that saturated fatty acids as potential PTP1B inhibitors, including pentadecyclic acid (**2**, IC_{50}: 8.1 μM), palmitic acid (**3**, IC_{50}: 8.8 μM), margaric acid (**5**, IC_{50}: 3.8 μM), stearic acid (**6**, IC_{50}: 2.3 μM), nonadecyclic acid (**12**, IC_{50}: 1.8 μM), and arachidic acid (**13**, IC_{50}: 1.6 μM), exhibited strong inhibition of PTP1B effects. Meanwhile, unsaturated fatty acid compounds also displayed strong PTP1B inhibitory effects, such as palmitoleic acid (**4**, IC_{50}: 16.1 μM), petroselinic acid (**7**, IC_{50}: 6.2 μM), oleic acid (**8,** IC_{50}: 6.2 μM), vaccenic acid (**9**, IC_{50}: 10.2 μM), linoleic acid (**10,** IC_{50}: 6.4 μM), linolenic acid (**11,** IC_{50}: 9.7 μM), and eicosenoic acid (**14**, IC_{50}: 1.4 μM) from the bark of *Phellodendron amurense* Rupr. The interesting results from this study indicate that the PTP1B inhibitory effects from these fatty acids are independent of the number of double bonds (one double bond **4**, **7**, **8**, **9** and **14**; two double bonds **10**; three double bonds **11**); rather, they depend on the number of carbon atoms. In other words, as the number of carbon increases, the activity slightly increases (**13** ≈ **12** > **6** > **5** > **2** ≈ **3**). In the compounds containing 18 carbon atoms, the results demonstrated that saturated fatty acids (**6**) seem to have a stronger effect than their unsaturated derivatives (**7**–**11**). On the other hand, oleic acid was also found to inhibit PTP1B, as well as to increase the insulin-induced phosphorylation of insulin. The results suggested that oleic acid could activate insulin receptors in associated PTP1B inhibition (Tsuchiya et al. 2014). Several PTP1B inhibitors were isolated from the green alga of *Caulerpa racemosa* with moderate inhibition, and contained (9*R*,10*E*)-9-hydroxyoctadec-10-enoic acid (**16**, IC_{50}: 35.2 μM), (9*R*,10*E*,12*Z*)-9-hydroxyoctadeca-10,12-dienoic acid (**17**, IC_{50}: 40.3 μM), and (8*E*)-heptadec-8-en-7-one (**19**, IC_{50}: 47.4 μM) (Liu et al. 2013). One of our studies regarding PTP1B inhibitors from *Agrimonia pilosa* revealed that palmitic acid (**3**) and methyl-2-hydroxyl tricosanoate (**18**) exhibited IC_{50} values of 0.10 and 36.39 μM, respectively. Therefore, further study was carried out to determine the inhibition mode of an active compound **3** by Lineweaver–Burk and Dixon plot. The result indicated the competitive inhibition mode of compound **3** with *K*i value of 9.2 μM (Na et al. 2016). The PTP1B inhibitory effect was also found in the mediterranean ascidian *Sidnyum elegans*, characterized by phosphoeleganin (**20**, IC_{50}: 11.0 μM) (Imperatore et al. 2016). From the acetone extract of marine sponge *Xestospongia testudinaria*, methyl 18-bromo-(17*Z*)-octadeca-l7-ene-5,7,15-triynoate (**21**) was isolated and evaluated for PTP1B inhibitory activity with an IC_{50} value of 5.3 μM (He et al. 2015). The result opened further study, and evaluation of its PTP1B activity could lead to this compound becoming a new target for the treatment of PTP1B-related diseases.



	n	Total carbon, $\Delta^{\text{double-bond position}}$
1	10	14
2	11	15
3	12	16
4	12	16, Δ^{9}
5	13	17
6	14	18
7	14	18, Δ^{6}
8	14	18, Δ^{9}
9	14	18, Δ^{11}
10	14	18, $\Delta^{9,12}$
11	14	18, $\Delta^{9,12,15}$
12	15	19
13	16	20
14	16	20, Δ^{11}
15	18	22

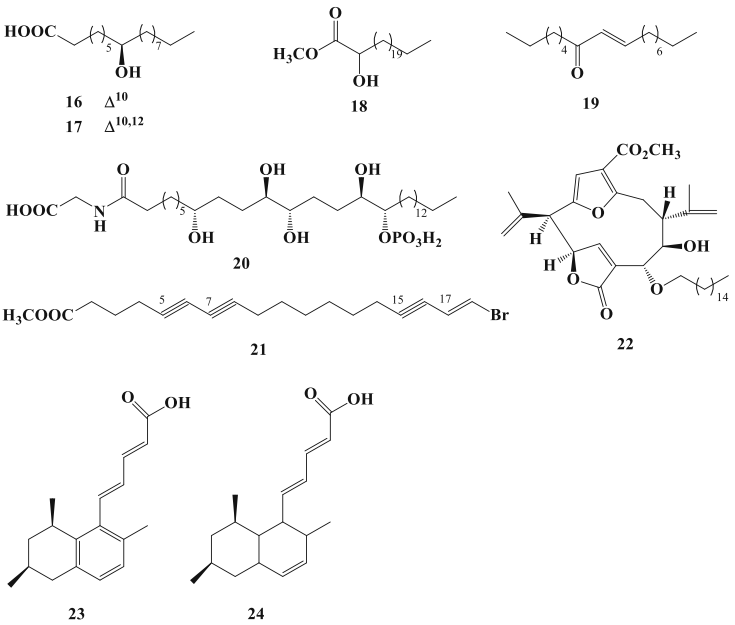


Fig. 2 Structures of fatty acids **1–24**

This result contributed to the active PTP1B compounds of natural sources from marine animals. New lipidyl pseudopterane A (**22**), which was isolated from the marine gorgonian coral *Pseudopterogorgia acerosa*, contained significant PTP1B inhibitory activity, with an IC_{50} value of 71.0 μg/mL (Kate et al. 2008). Compounds **23** and **24** had side chain of unsaturated fatty acids, were isolated from a marine-derived fungus *Penicillium* sp. SF-6013. Compounds **23** and **24** showed strong inhibitory effects against PTP1B activity with same IC_{50} values of 8.2 μM, and also inhibited the production of nitric oxide (NO) with IC_{50} values of 7.1 μM and 42.5 μM, respectively (Quang et al. 2014). There are limited reports on the PTP1B inhibitory activity of fatty acid derivatives that are identified from natural sources. Table S1 lists the resulting activity data, while Fig. 2 shows the structures of fatty acids. According to the above data, the strong discoveries and finding of new PTP1B inhibitors are attracting scientists worldwide. In addition, these inhibitors require much more attention for clarification of their mechanism for inhibiting action, and the development of new drugs for the treatment of diabetes and obesity.

Phenolics

Phenolic compounds are the most numerous and ubiquitously distributed group in the natural sources of PTPs. These have at least one aromatic ring, with one or more hydroxyl groups attached. They can be divided into simple molecules (phenolic acids, phenylpropanoids, flavonoids, etc.), and highly polymerized compounds (lignans, tannins, etc.) (Soobratee et al. 2005; Del Rio et al. 2013). Phenolic compounds have wide pharmacological activities, such as anti-oxidant, anti-hyperlipidemia, anti-virus, anti-inflammation, and anti-bacteria (Kil et al. 2017). In this review article, the phenolics part was divided into eight groups (alpha-pyrones, benzofurans, bromophenols, flavonoids, lignans, phenolic acids, tannins, and other phenolics) according to the structural properties, and was described in the alphabetical order form. Furthermore, the alpha-pyrones, benzofurans, and bromophenols groups have many compounds, and such group names were recurrently mentioned in previous papers. So we separated them with other phenolic groups and explained.

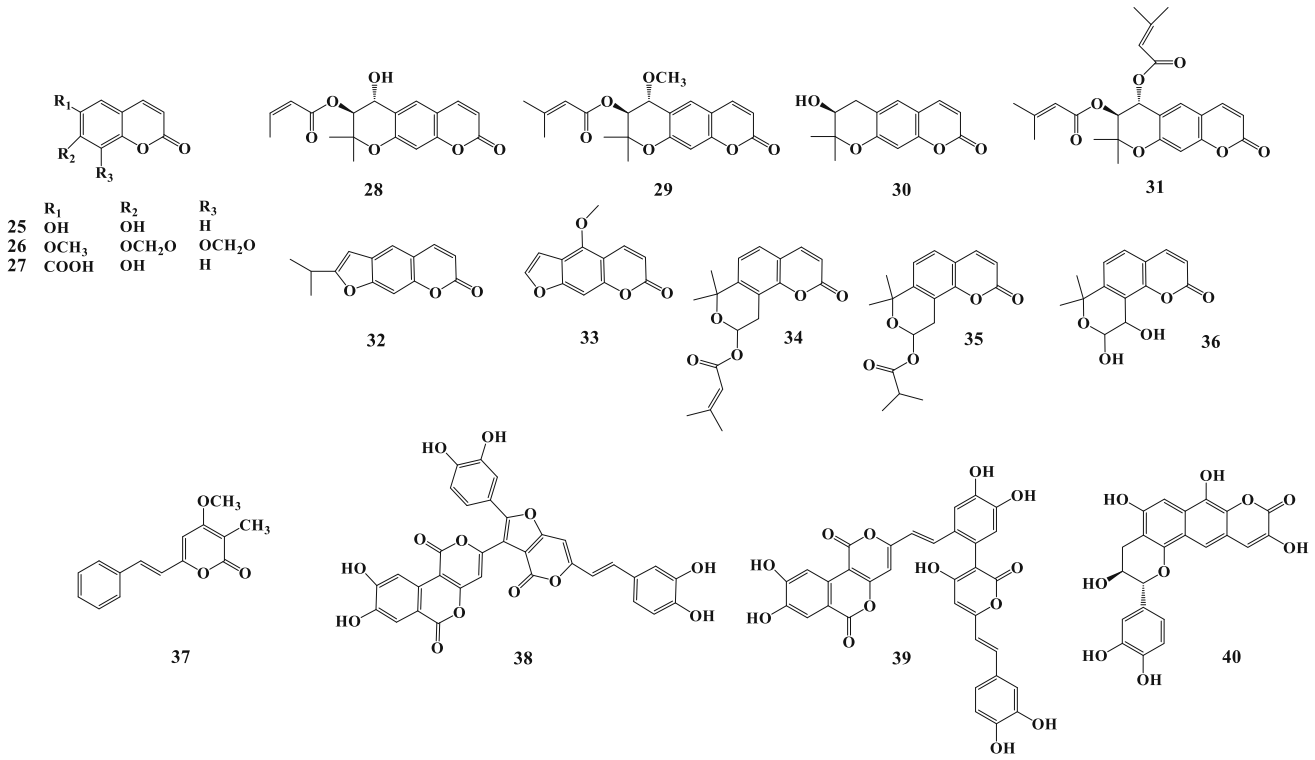


Fig. 3 Structures of alpha-pyrones **25–40**

Alpha-pyrones

The alpha-pyrones (or 2-pyrone), a very large class of compounds, have been found throughout the natural sources of PTPs. The most representative component is coumarin derivatives (Jain and Joshi 2012). Many coumarins have been reported to possess bioactivities, such as antimicrobial, anti-tumorous, anti-platelet aggregation, and anti-cancer activities (Ishita et al. 2016; Seo et al. 2016). Two coumarin derivatives **25** and **26** from *Artemisia capillaris* exhibited good inhibitory activity against PTP1B (IC_{50}: 10.1 and 27.6 μM, respectively) (Nurul-Islam et al. 2013). Ali et al. (2016) isolated six natural coumarin derivatives (**27–32**) from *Angelica decursiva*, and evaluated their PTP1B inhibitory activity. All the coumarins significantly inhibited the PTP1B enzyme. Compounds **27** (IC_{50}: 8.0 μM), **28** (IC_{50}: 5.4 μM), and **32** (IC_{50}: 10.8 μM) were the competitive type, with *K*i values of 6.5, 3.5, and 8.3 μM, respectively. Compounds **29** (IC_{50}: 6.6 μM) and **31** (IC_{50}: 11.2 μM) showed mixed type, with *K*i values of 9.6 and 26.4 μM, respectively. Compound **30** (IC_{50}: 58.9 μM) was determined as a noncompetitive inhibitor, with *K*i value of 41.1 μM. Compounds **33–36** were purified from the stems of *Angelica keiskei*. These cumarin derivative compounds **33–36** revealed inhibitory activity against PTP1B (IC_{50}: 2.5, 11.6, 9.6, and 10.4 μM, respectively) (Li et al. 2015a). A competitive PTP1B inhibitor **37** (IC_{50}: 5.3 μM) was obtained from the marine-derived fungus *Penicillum* sp. JF-55. This compound was not only a PTP1B inhibitor, but also a NO, PGE2, TNF-α, and IL-1β inhibitor via a NF-kB pathway. This result suggested that PTP1B is implicated in inflammation and diabetes (Lee et al. 2013). Two pyrano[4,3-*c*]isochromen-4-one derivatives of PTP1B inhibitors were found in the fungus of *Phellinus igniarius*. Compounds **38** and **39** displayed strong PTP1B inhibitory (IC_{50}: 3.1 and 3.0 μM, respectively), and anti-lipid peroxidase activities (Wang et al. 2007). Also, a mixed competitive type PTP1B alpha-pyrone inhibitor **40** (IC_{50}: 13.7 μM; *K*i: 10.3 μM) was found in the corks of *Euonymus alatus* (Jeong et al. 2015). Table S2 and Fig. 3 show all PTP1B inhibitors as alpha-pyrone.

Benzofurans

Benzofurans are the heterocyclic compound from simple phenols and olefins (Agasti et al. 2015). In previous research, these heterocyclic compounds showed anti-nociceptive, anti-inflammatory, anti-cancer, etc. (Ferreira-Júnior et al. 2015; Kapche et al. 2017). Three 2-arylbenzofurans **41–43** were identified as mixed-type PTP1B inhibitors from *Morus bombycis* (IC_{50}: 9.2, 2.7, and 2.7 μM, respectively). The PTP1B inhibitory activity for farnesyl group at C-2′ (R_6) in compound **42** was

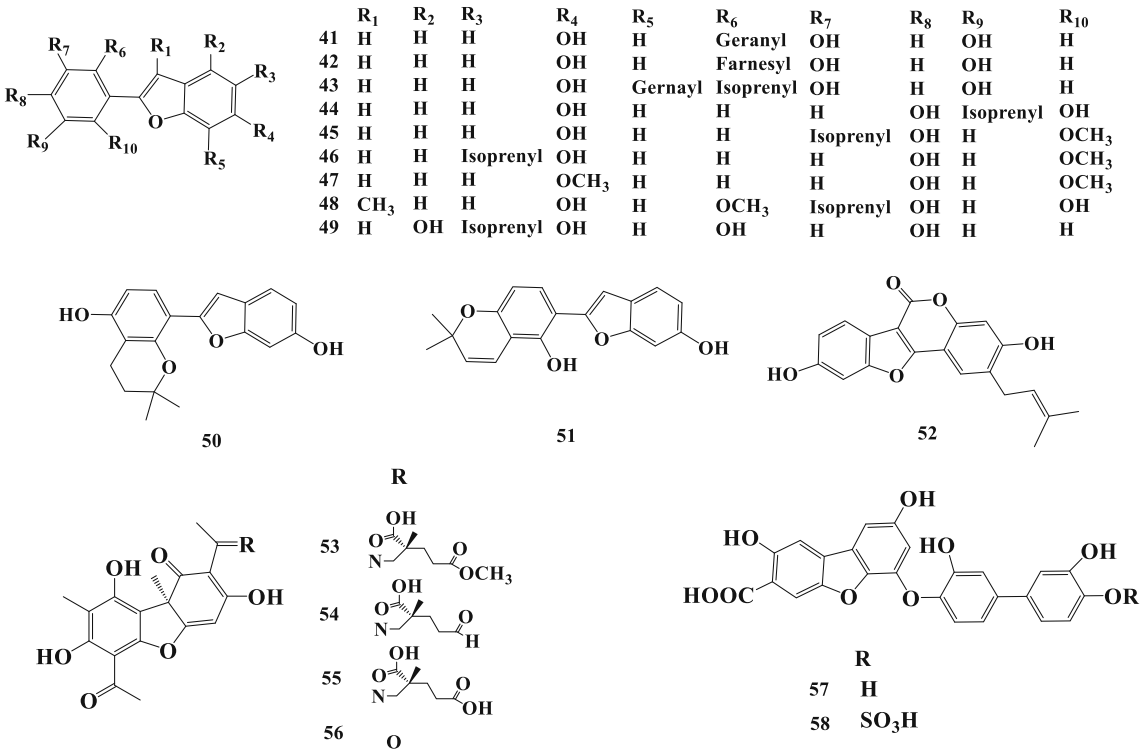


Fig. 4 Structures of benzofurans **41–58**

approximately 3-fold higher than that of the geranyl group at C-2′ in compound **41**. This result suggested that increasing the lipophilicity leads to stronger activity. In the enzyme kinetics experiment, these three benzofurans all showed mixture-type inhibitions against PTP1B (Hoang et al. 2009). Six 2-arylbenzofuran derivatives (**44–47, 50**, and **51**) were isolated from the stem bark of *Erythrina addisoniae*. Three 2-arylbenzofurans **44–46** (including prenyl groups) strongly inhibited a PTP1B enzyme (IC_{50}: 13.6, 17.5, and 15.7 μM, respectively), while compounds **47**, **50**, and **51** showed weak PTP1B inhibitory activity (IC_{50}: 74.1, 62.7, and 64.9 μM, respectively). In structure–activity relationship (SAR) investigation, the prenyl groups played an important role in suppressing PTP1B (Na et al. 2007). Compound **52,** which was acquired from the seeds of *Psoralea corylifolia,* showed strong non-competitive inhibitor (IC_{50}: 9.4 μM; *K*i: 8.9 μM) (Kim et al. 2005). Also, four dibenzofurans, **53–56**, from the Antarctic lichen (*Stereocaulon alpinum*), exhibited moderate PTP1B inhibitory activity. A PTP1B inhibitor **53** of the methoxy group at side chain (IC_{50}: 15.0 μM) was stronger than the compound with hydroxyl (**54**; IC_{50}: 27.7 μM) or hydrogen (**55**; IC_{50}: 23.2 μM) group at side chain (Seo et al. 2008b). Vanillic acid derivatives **57** and **58** were isolated from the algae of *Cladophora socialis*, and both showed potent PTP1B inhibitory activity, with IC_{50} values of 3.7 and 1.7 μM, respectively. This dibenzofuran and phenyl ring as skeleton system formed each binding site with the PTP1B enzyme. These results suggested that the presence of acidic functionality (carboxyl, phenolic hydroxyl, or sulfated group) may enhance PTP1B inhibitory activity (Feng et al. 2007). All the benzofuran-PTP1B inhibitors listed in Table S3 and Fig. 4.

Bromophenols

Bromophenols are ubiquitous components in marine algae. Recent evidence has indicated that the bromophenols have beneficial bioactivity, including antioxidant, anticancer, antidiabetic, and antimicrobial activities (Liu et al. 2011a). Eighteen bromophenol compounds (**59–76)** from algae were found as PTP1B inhibitors (Table S13; Fig. 5). Compounds **59**, **60**, and **72** were isolated from the algae of *Rhodomela confervoides* and *Leathesia nana*, and exhibited strong inhibitory activity, with IC_{50} values of 3.4, 4.5, and 2.8 μM, respectively (Shi et al. 2008a). Liu et al. (2011b) purified eight brominated phenols from the red algae of *Symphyocladia latiuscula*. Among these compounds, compounds **63–65** showed very potent PTP1B inhibitory activity, with IC_{50} values of 3.9, 4.3, and 3.5 μM, respectively. Compounds **61**, **62**, and **73** displayed moderate inhibitory activity, with IC_{50} values of 39.0, 19.4, and 25.6 μM, respectively. These preliminary data suggested that the number of bromine and side chains on

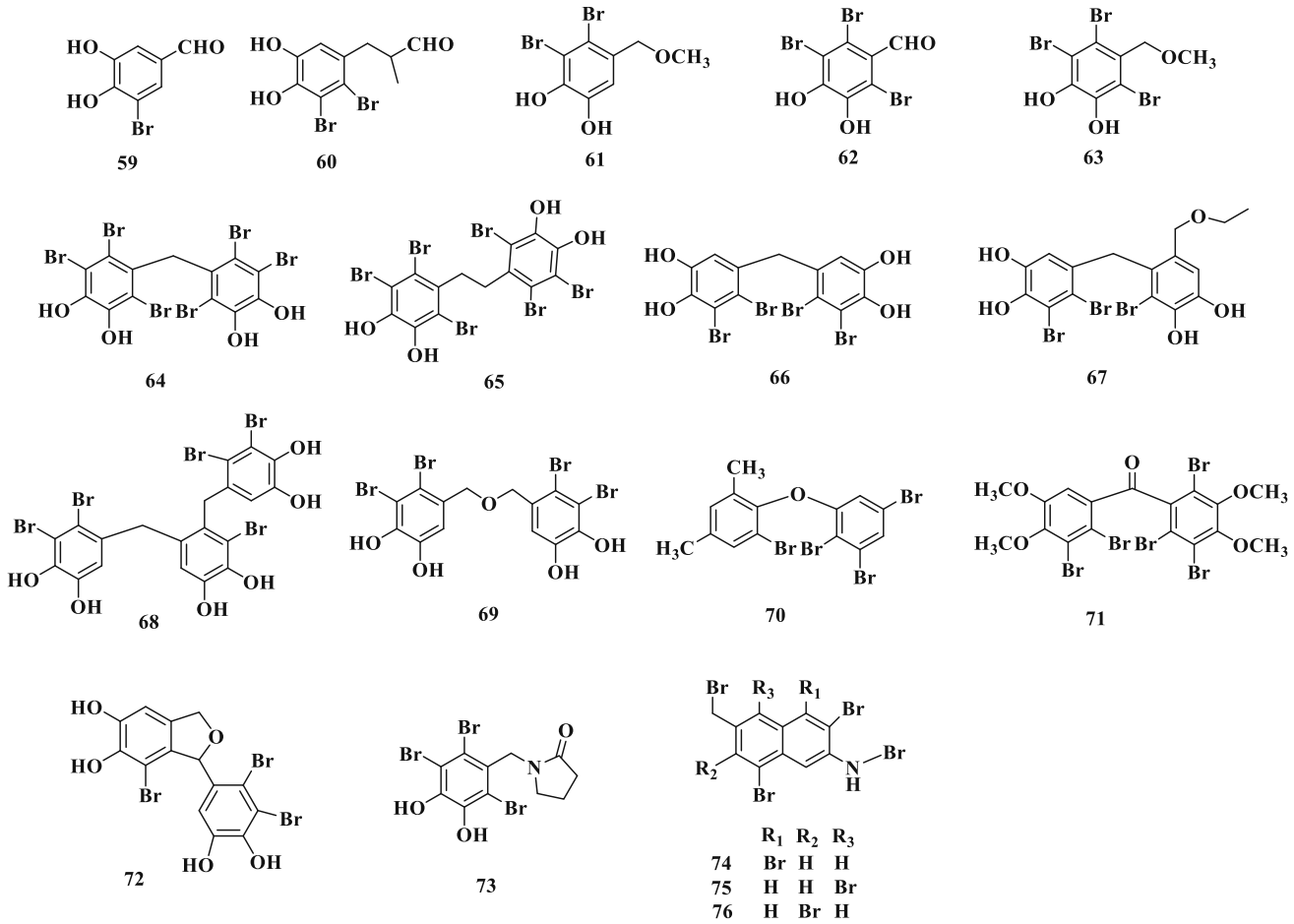
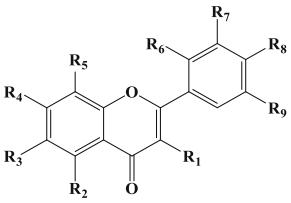


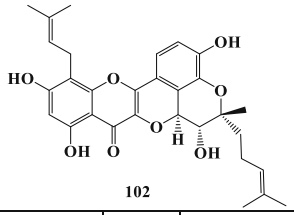
Fig. 5 Structures of bromophenols **59–76**

bromophenol derivatives might affect PTP1B inhibitory activity. Zhu et al. (2015) also came to a similar conclusion about the PTP1B inhibitory effects for bromophenol derivatives. They reported that the Br atom in benzene ring and the length of alkyl chain from bromophenol derivatives are pivotal roles against PTP1B enzyme. Shi et al. (2008b) investigated the PTP1B inhibitory activity and anti-hyperglycemic effect for red algae of *R. confervoides*, along with four bromophenol derivatives. All of the compounds **66–69** showed very potent inhibitory activity against PTPB (IC_{50}: 2.4, 0.8, 1.7, and 1.5 μM, respectively). Meanwhile, the anti-hyperglycemic activity of the *R. confervoides* extracts was corroborated using in vivo test by streptozotocin (STZ)-diabetic rat model. Five highly brominated compounds (**70, 71**, and **74–76**) were obtained from the red algae of *Laurencia similis*, and were evaluated for their PTP1B inhibitory activity. Compounds **70** and **71** showed strong inhibitory activities for the PTP1B enzyme, with IC_{50} values of 3.0, and 2.7 μM, respectively. The other three compounds, **74–76** (IC_{50}: 102.0, 65.3, and 69.8 μM, respectively), were expressed as moderate PTP1B inhibitory activity (Qin et al. 2010).

Flavonoids

Flavonoids are natural polyphenolic compounds that are comprised of 15 carbons, with two phenyl rings (A-ring and B-ring) connected by a three-carbon bridge. This carbon structure can be abbreviated as C6–C3–C6. They are ubiquitous in plants, and include chalcone, dibezylmethane, flavanone, dihydroflavonol, isoflavanone, isoflavone, flavone, pterocarpan, coumestan, aurone, dihydrochalcone, biflavonoid, and flavonoid glycoside (Halbwirth 2010; Tsao 2010). They have wide biological properties, including anti-oxidative, anti-allergic, anti-inflammatory, anti-diabetic, anti-proliferative, hepato- and gastro-protective, anti-viral, anti-neoplastic, and anti-PTP1B activities (Kumar and Pandey 2013; Inamullah et al. 2017). Among the many classes of flavonoids, those of particular interest to this review are flavonols, isoflavones, flavanones, isoflavanones, chalcones, and biflavonoids. In flavanoid compounds, we searched for more than 100 PTP1B inhibitors. Given the large number of the flavonoid family, these researches represent merely a small fraction.





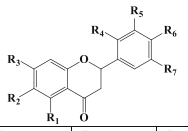
102

No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9
77	H	H	Isoprenyl	OH	H	H	Isoprenyl	OH	H
78	OH	OH	Isoprenyl	OH	H	H	H	OH	H
79	OCH_3	OH	Isoprenyl	OH	H	H	H	OH	H
80	OCH_3	OH	H	OH	H	H	Isoprenyl	OH	H
81	OH	OH	H	OH	H	H	Isoprenyl	OH	H
82	H	H	Isoprenyl	OH	H	H	H	OH	H
83	OH	OH	H	OH	H	H	OH	OH	Isoprenyl
84	H	OH	H	*O*-GlcA-6"-methyl ester	H	H	H	OH	H
85	*O*-Rha	OH	H	OH	H	H	H	OH	H
86	OH	OH	H	OH	H	H	OH	OH	H
87	OH	OH	H	OH	H	H	OCH_3	OH	H
88	*O*-Glc	OH	H	OH	H	H	OCH_3	OH	H
89	*O*-Glc-Rha	OH	H	OH	H	H	OCH_3	OH	H
90	OH	OH	H	OH	1,1-Dimethyl allyl	H	OH	OH	Isoprenyl
91	OH	OH	H	OH	H	OH	H	OH	H
92	OH	OH	H	*O*-Rha	H	H	H	OH	H
93	OH	OH	H	OH	H	H	OH	*O*-Glc	H
94	*O*-GlcA	OH	H	OH	H	H	OH	OH	H
95	*O*-GlcA	OH	H	OH	H	H	OH	OH	OH
96	H	OH	H	OH	H	H	H	OH	H
97	H	OH	H	OH	*C*-Glc	H	H	OH	H
98	H	OH	*C*-Glc	OH	H	H	H	OH	H
99	H	OH	H	OH	H	H	OH	OH	H
100	H	OH	H	OH	*C*-Glc	H	OH	OH	H
101	H	OH	*C*-Glc	OH	H	H	OH	OH	H

Fig. 6 Structures of flavonols **77–102**

Flavonols

Flavonol compounds (**77–101**) were found to possess potent PTP1B inhibitory activity (Chen et al. 2002; Li et al. 2010b; Zhang et al. 2010; Choi et al. 2014a, b; Cai et al. 2015; Guo et al. 2015; Wang et al. 2015c; Ji et al. 2016; Na et al. 2016; Zhao et al. 2016). Table S2 lists the activity data for flavanol PTP1B inhibitors, while Fig. 3 shows their structures. Amongst them, compounds **87** (IC_{50}: 1.8 μM), **88** (IC_{50}: 1.2 μM), **89** (IC_{50}: 1.2 μM), **93** (IC_{50}: 0.9 μM), and **102** (IC_{50}: 0.9 μM) are the most active against PTP1B. This indicates that the finding of flavonols as PTP1B inhibitor is a promising strategy for the development of drugs. In the structure–activity relationship (SAR) study of flavonoids, Ji et al. (2016) reported that their inhibitory activities would be increased when the isoprenyl group occurred in B ring (**79**; 52%) rather than A ring (**80**; 85%). The same 3′,4′,5,7-tetrahydroxy-flavonol skeletons of compounds **83** (IC_{50}: 21.5 μM), **86** (IC_{50}: 23.3 μM), and **90** (IC_{50}: 4.3 μM) are attached to the isoprenyl, *O*-GlcA-6″-metthyl ester, and 1,1-demethylallyl groups, respectively. These data showed that their PTP1B inhibitory activities would be increased with more nonpolar substituents (Chen et al. 2002). Zhang et al. (2010) reported that compound **95** (IC_{50}: 9.5 μM), with one more OH group at C-5′, was less active than **94** (IC_{50}: 7.4 μM) on PTP1B enzyme assay. These data indicated that the OH group to C-5′ (R_9) in the B ring may be responsible for the decrease of activity. Additionally, the authours suggested that sugar configuration played an important role in the PTP1B inhibitory activity. However, not all the glycosylated compounds possess the same role above for PTP1B. In two studies of Choi et al. (2014a, b), the role of the sugar group based on PTP1B inhibitory activity seems to be an irregularity. The PTP1B inhibitory activity was found as vitexin (**97**; 8-glc) > isovitexin (**98**; 5-glc) > apigenin (**96**) from apigenin derivatives. But the luteolin derivatives with free sugar moiety showed stronger activity than the sugar modifed compounds, such as luteolin (**99**) > isoluteolin (**101**; 5-glc) > orientin (**100**; 8-glc) (Table S5; Fig. 6).



No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7
103	OH	H	OH	Isoprenyl	OH	OH	Isoprenyl
104	OH	H	OH	H	OH	OH	Isoprenyl
105	OH	H	OH	H	OCH_3	OH	Isoprenyl
106	OH	H	OH	H	Isoprenyl	OH	2-Hydroxy-3-methylbut-3-enyl
107	H	H	OH	H	OCH_3	OH	Isoprenyl
108	H	H	OH	H	H	OCH_3	Isoprenyl
109	H	H	OH	H	H	OH	Isoprenyl
110	OH	H	OH	Isoprenyl	Isoprenyl	OH	OH
111	H	H	OH	H	OH	OCH_3	Isoprenyl
112	OH	H	OH	H	Isoprenyl	OCH_3	Isoprenyl
113	H	H	OH	H	Isoprenyl	OCH_3	Isoprenyl
114	OH	H	OH	H	Isoprenyl	OH	Isoprenyl
115	H	H	OH	H	Isoprenyl	OH	Isoprenyl
116	OH	Isoprenyl	OH	OH	H	OH	Isoprenyl
117	OH	H	OH	Isoprenyl	OCH_3	OH	H
118	OH	H	OH	Isoprenyl	OH	OH	H
119	OH	H	*O*-Glc	H	H	OH	H

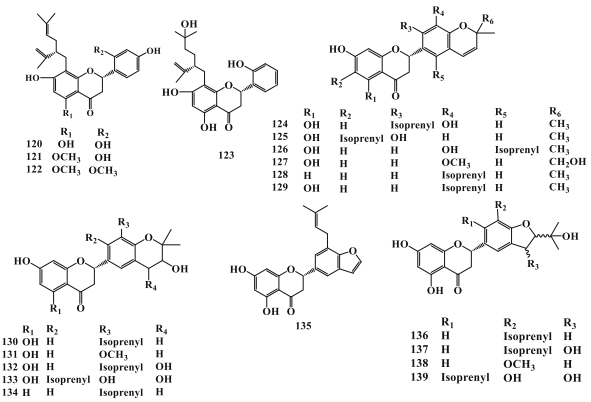
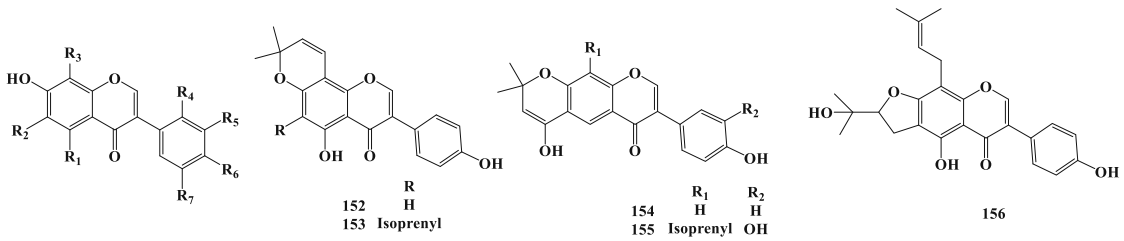


Fig. 7 Structures of flavanones **103–139**



No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7
140	OH	Isoprenyl	H	OH	Isoprenyl	OH	H
141	OH	H	Isoprenyl	H	Isoprenyl	OH	H
142	OH	H	Isoprenyl	OH	Isoprenyl	OH	H
143	OH	Isoprenyl	H	H	OH	OH	Isoprenyl
144	OH	Isoprenyl	Isoprenyl	H	H	OH	H
145	OH	H	H	H	Isoprenyl	OH	OH
146	OCH_3	H	H	H	Isoprenyl	OH	OH
147	H	Isoprenyl	Isoprenyl	OH	H	OH	H
148	H	H	Isoprenyl	H	Isoprenyl	OH	H
149	OH	H	H	H	H	OCH_3	Isoprenyl
150	OH	Isoprenyl	Isoprenyl	H	OH	OH	H
151	OH	Isoprenyl	Isoprenyl	H	OCH_3	OH	H

Fig. 8 Structures of isoflavones **140–156**

Flavanones

Flavanones (**103–139**) were found to possess significant PTP1B inhibitory effects (Na et al. 2006b; Cui et al. 2007, 2008, 2010; Nguyen et al. 2011, 2012; Sasaki et al. 2014; Quang et al. 2015; Wu et al. 2015; Jung et al. 2017). In this group, the most potent compounds were found as compounds **116**, **119**, and **122** with IC_{50} values of 5.7, 5.5, and 5.3 μM, respectively. Some conclusions were revealed based on the investigation of their SAR. Compounds **112** (IC_{50}: 26.3 μM) and **114** (IC_{50}: 39.7 μM), with one more OH group attached at C-5, were less active than the same skeleton of each **113** (IC_{50}: 21.2 μM) and **115** (IC_{50}: 16.0 μM), without OH group substituent at C-5. These data indicated that the OH group to C-5 of the A-ring was the most important for PTP1B inhibitory activity (Na et al. 2006b). In addition, Cui et al. (2008) suggested that compounds having isoprenyl group (**126**, **130**, **132**, and **133**) exhibited strong PTP1B inhibitory. This is indicative of the important role of the isoprenyl moiety in the inhibitory activity of flavonoids. The same argument as that of Cui et al. (2007) is also found in other studies. Furthermore, eleven flavanones containing isoprenyl group (**103–109**, **124**, **128**, **134**, and **135**) showed high inhibitory activity against PTP1B, with the range of IC_{50} values 14.2 ∼ 35.8 μM (Cui et al. 2007; Nguyen et al. 2011) (Table S6; Fig. 7).

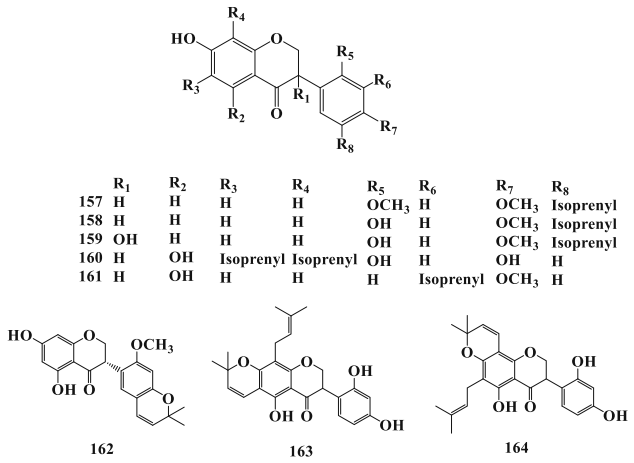


Fig. 9 Structures of isoflavanones **157–164**

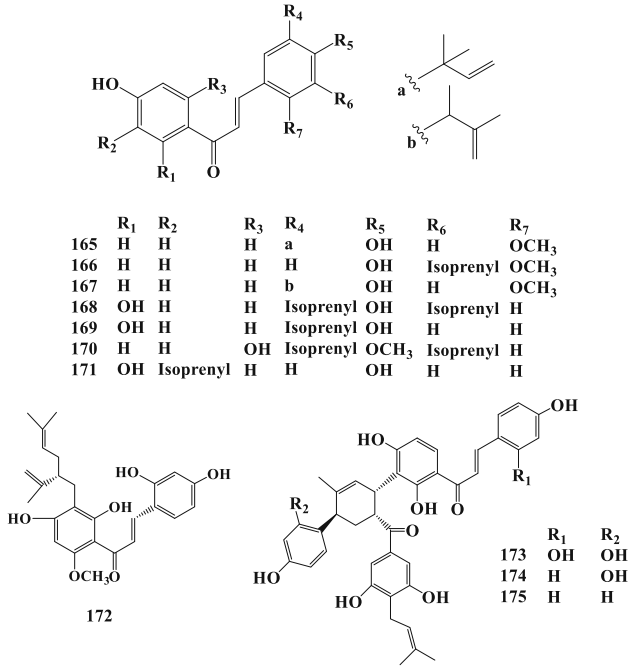


Fig. 10 Structures of chalcones **165–175**

Isoflavones and isoflavanones

Several isolavones (**140–156**) were found as PTP1B inhibitors (Na et al. 2006b; Li et al. 2010b; Nguyen et al. 2012; Wu et al. 2015; Ji et al. 2016; Wang et al. 2016b). Tables S7 and S8 list activity data for isolavone and isoflavanone PTP1B inhibitors, while Figs. 8 and 9 show their structures. Notably, four compounds **140**, **143**, **150**, and **155** displayed the strongest inhibitory effects, with IC_{50} values of 0.4, 3.0, 2.4, and 3.6 μM, respectively (Ji et al. 2016; Wang et al. 2016b). Nguyen et al. (2012) isolated three isoflavones (**147**, **148**, and **156**) and two isoflavanones (**161**, and **162**) from the root barks of *E. addisoniae*. All the isolates exhibited strong PTP1B inhibitory activity. Finally, the authors suggested that the isoprenyl group on flavonoids plays an important role for PTP1B inhibitory activity. In addition, most of the isoflavone (**140–146**, **149–151**, **153**, and **155**) and isoflavanone (**157–161**, **163**, and **164**) compounds containing isoprenyl group were found as PTP1B inhibitors (Bae et al. 2006; Na et al. 2006b; Li et al. 2010b; Wu et al. 2015; Ji et al. 2016; Wang et al. 2016b).

Chalcones

Chalcones (**165–175**) were isolated from the plants of the Fabaceae and Moraceae family. All chalcones showed significant PTP1B inhibitory activity, with IC_{50} values ranging from 2.7 to 30.9 μM (Na et al. 2006b; Cui et al. 2007; Hoang et al. 2009; Yoon et al. 2009; Li et al. 2013; Sasaki et al. 2014). Figure 10 shows the PTP1B inhibitors as chalcones, while Table S9 lists their activity information. Most of the chalcones containing isoprenyl group (**166**, and **168–175**) were found as PTP1B inhibitors. These studies futher illustrated the importance of isoprenyl group in flavonoids for PTP1B inhibitory activity. Moreover, Hoang et al. (2009) suggested that the number of hydroxy groups afforded different inhibitory effects, which was deduced by comparing the IC_{50} values between three compounds (**173–175**) with the same basic skeleton. Kuwanon V (**175**; $\mathbf{IC_{50}}$: 13.8 μM) displayed potent inhibitory activity, but was less potent than kuwanon R (**174**; $\mathbf{IC_{50}}$: 8.2 μM) with one more OH group at C-16′. In addition, kuwanon J (**173**; $\mathbf{IC_{50}}$: 2.7 μM) with additional OH group at C-2 compared to the structure of kuwanon R, showed more potent inhibitory effect than kuwanon R (**174**; $\mathbf{IC_{50}}$: 8.2 μM). The increase of the number of hydroxy groups in chalcone-derived Diels–Alder-type compound gave an increase of PTP1B inhibitory effects.

Biflavonoids and other flavonoids

Biflavonoids and licorice flavonoids (**176–184**) were isolated from the aerial parts of *Selaginella tamariscina* and the roots of *Glycyrrhiza* sp. (Table S10; Fig. 11). All the biflavonoids from *S. tamariscina* displayed potent inhibitory activity against PTP1B, with IC_{50} values ranging from 4.5 to 9.8 μM. The SAR of these biflavonoids was also deduced. The linkage between two apigenin moieties through C-3 position may lead to an increase of both PTP1B enzyme and 2-NBDG uptake in these biflavones (Nguyen et al. 2015b). Flavonoid dimers **182** and **183** showed strong PTP1B inhibitory activity, with IC_{50} values 6.0 and 11.5 μM, respectively. A prenylated aurone **184** (IC_{50} 23.9 μM) showed moderate effect (Li et al. 2013).

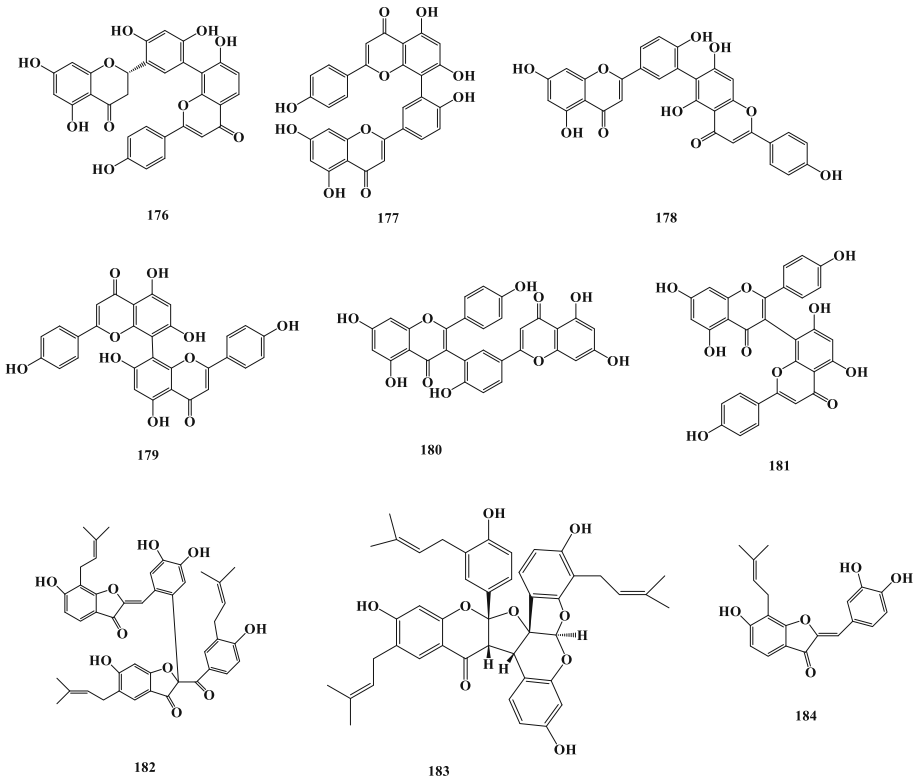


Fig. 11 Structures of biflavonoids and others **176–184**

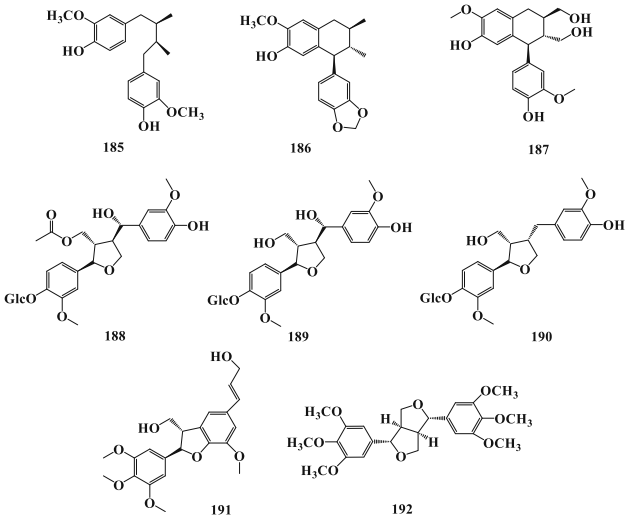


Fig. 12 Structures of lignans **185–192**

Lignans

Lignans belong to phenolic compounds with a backbone of two phenylpropanoids (C6–C3) units. These group compounds showed biological diversity, such as anti-cancer, anti-oxidative, anti-diabetes, and anti-inflammatory activities (Pimentel et al. 2011; Jung et al. 2015; Worawalai et al. 2016). Eight lignans were found as PTP1B inhibitors, and Table S11 and Fig. 12 show their structures and activity data. Two Non-competitive PTP1B inhibitors, **185** and **186**, were found from the semen of *Myristica fragrans,* with IC_{50} values of 19.6, and 48.9 μM, respectively. In the mechanism study, the result indicated a dose-dependent increase in the tyrosine phosphorylation of insulin receptor on 32D cell, after treatment with compound **185** (Yang et al. 2006). Five lignans obtained from *Coptis chinensis* were investigated, including their PTP1B inhibitory activity. Five lignans **187–191** inhibited PTP1B in a concentration-dependent manner, with IC_{50} values of 58, 57, 49, 51, and 71 μM, respectively (Chen et al. 2016). Compound **192** isolated from *Tinospora sinensis* was considered as a weak PTP1B inhibitor by Gupta et al. (2012).

Phenolic acids

Phenolic acids (or phenolcarboxylic acids) are plant metabolites that are widely distributed in nature, and are biosynthesized from the shikimate pathway from L-phelalanine or L-tyrosine. Chemically, these class compounds have at least one phenol skeleton, and one hydroxyl group (Heleno et al. 2015). In this review, about 30 compounds were found to have PTP1B inhibitory activity (Table S12; Fig. 13). Compounds **193**, **194**, and **206** were purified from the corks of *E. alatus*, exhibiting strong inhibition for PTP1B, with IC_{50} values of 29.9, 14.8, and 18.4 μM, respectively. In the kinetic assay, compound **194** (*Ki*: 13.6 μM) showed mixed-competitive type for the PTP1B enzyme, while compound **206** (*Ki*: 18.5 μM) displayed

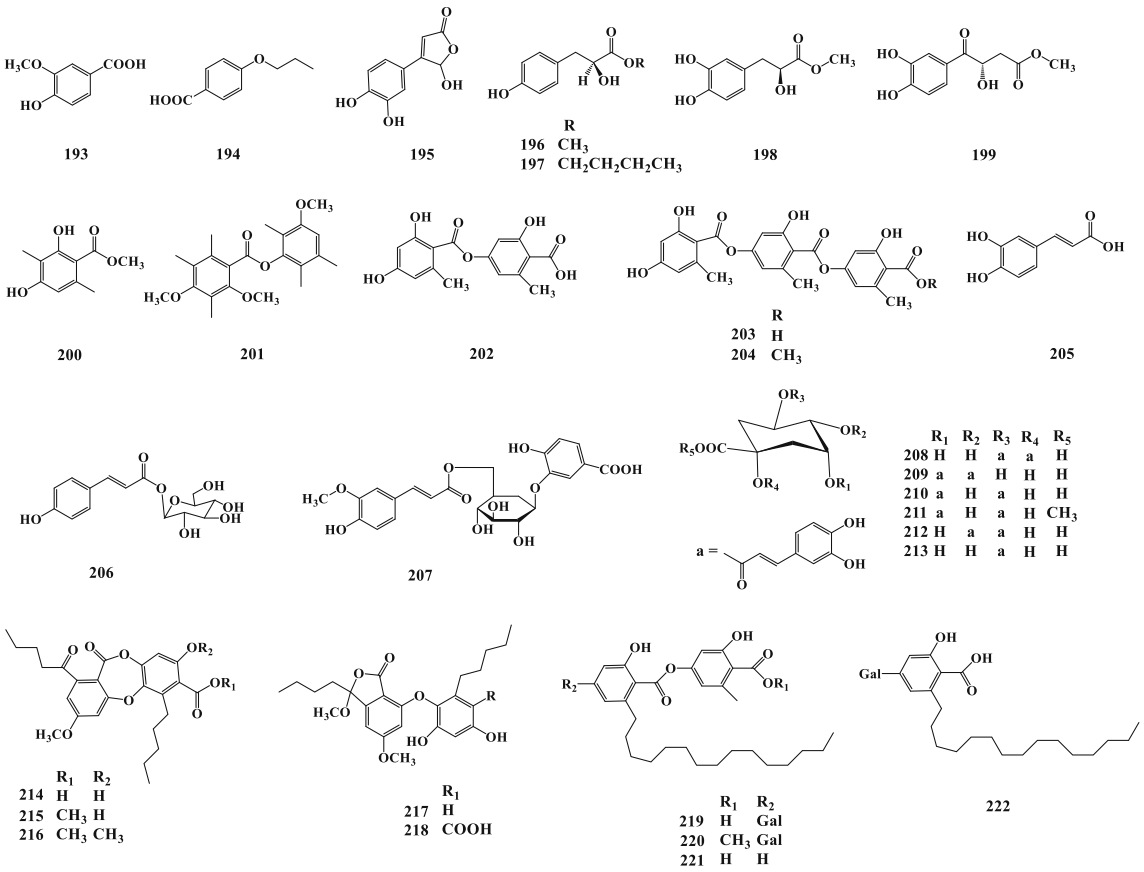


Fig. 13 Structures of phenolic acids **193–222**

non-competitive type. Among these single benzene molecules, compound **194** also exhibited other strong anti-diabetes effects against α-glucosidase (Jeong et al. 2015). Six PTP1B inhibitors (**195–199**, and **207**) were obtained from the aerial parts of *Tradescantia spathacea* Sw. by in vitro assay. Four single benzene compounds (**195–198**) possessed strong inhibitory activity for PTP1B (IC_{50}: 7.8, 6.8, 4.6, and 6.4 μM, respectively). But the kinetics of PTP1B action for each compound was different. **195** was a competitive type, and **196** and **197** were the mixed type, whereas **198** was a noncompetitive type inhibitor. Furthermore, compounds **199** (IC_{50}: 17.6 μM) and **207** (IC_{50}: 10.8 μM) showed good PTP1B inhibitory activity (Vo et al. 2015). Compounds **200** and **201** were isolated from the Antarctic lichen *Lecidella carpathica*. Compounds **200** (IC_{50}: 51.5 μM) and **201** (IC_{50}: 14.0 μM) inhibited PTP1B activity in a dose-dependent manner (Seo et al. 2011). In the same place of the Antarctic pole, the lichen of *Umbilicaria antarctica* MeOH extract was found to exhibit significant inhibitory effect with PTP1B. In the investigation for this plant, compounds **202–204** showed PTP1B inhibitory activity, with IC_{50} values of 31.0, 3.6, and 14.1 μM, respectively. Moreover, these distinctive types of lichen metabolites have also been shown to inhibit 5-lipoxygenase and prostaglandin biosynthesis (Seo et al. 2009a). Compound **205** was identified in *Artemisia minor,* and investigated as a potent PTP1B inhibitor (IC_{50}: 3.1 μM) (He et al. 2009). Six caffeoylquinic compounds (**208–213**) were isolated from *A. capillaris*, and showed strong PTP1B inhibitory activity (IC_{50}: 16.1, 2.6, 2.0, 3.0, 3.2, and 17.1 μM, respectively). This result indicated that the caffeoyl group at the C-3 position of the quinic acid moiety was an attribute for improving PTP1B activity (Nurul-Islam et al. 2013). Chen et al. (2014a) isolated eleven caffeoylquinic acid derivatives from *Gynura divaricate*. Among isolates, compounds **209**, **210**, and **213** had considerable inhibitory activity against PTP1B enzyme (Inhibition %: 58.2, 41.6, and 27.3%, respectively). All these active compounds have C-3 positions of quinic acid linked to caffeoyl group. In this result, it was also not difficult to prove that the C-3 position is important for PTP1B inhibitory effect on caffeoylquinic acid derivatives. Seven phenolic metabolites were obtained from the Antarctic lichen of *S. alpinum*. Among them, five compounds **214–218** showed strong PTP1B inhibitory activity, with IC_{50} values of 0.9, 3.0, 7.4, 6.9, and 2.5 μM, respectively; compounds **214** and **217** were determined by PTP1B kinetic analyses as non-competitive inhibitors. This

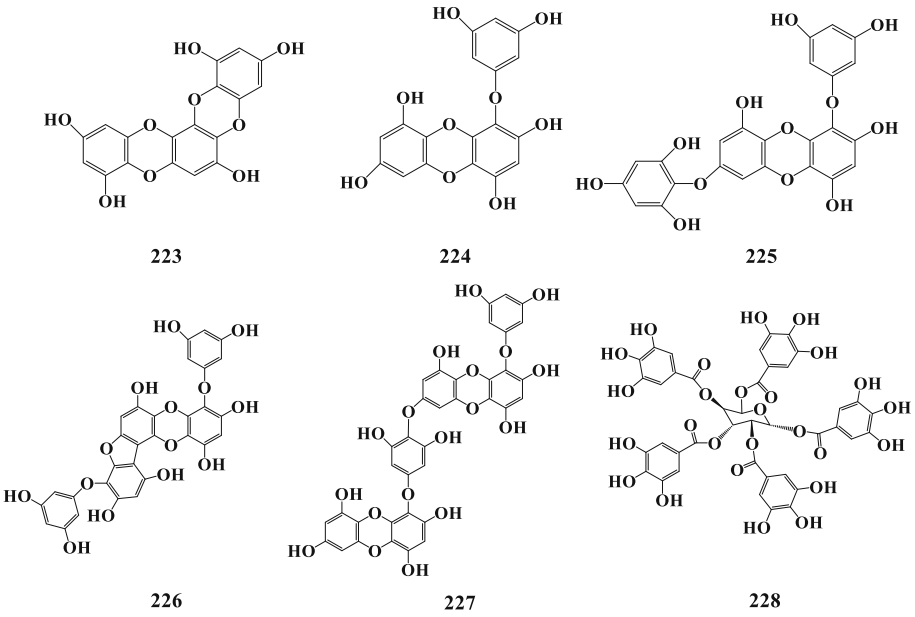


Fig. 14 Structures of tannins **223–228**

research indicated that as the number of methoxy group increases, the PTP1B inhibitory activity (**216** < **215** < **214**) decreases (Seo et al. 2009b). From the marine-derived fungus of *Cosmospora* sp. SF-5060, four orcinol *p*-depsides were isolated, and investigated for their PTP1B inhibitory activity. Compounds **219**, **221**, and **222** considerably inhibited PTP1B enzyme, with IC_{50} values of 0.2, 0.2, and 0.6 μM, respectively. Meanwhile, the positive control as ursolic acid showed the IC_{50} value of 2.5 μM. Compound **220** (IC_{50}: 17.0 μM) displayed moderate inhibitory activity for PTP1B (Seo et al. 2009c).

Tannins

Tannins, with sufficient hydroxyls and other suitable groups, possess heterogeneous polyphenolic groups, which are able to precipitate proteins, and are soluble in water or polar organic solvents. Many reports have been published highlighting the variety of biological activities of tannins, including anti-microbial and the inhibition of various enzyme activities (Chao et al. 2017). Six PTP1B inhibitors of phlorotannins were isolated from two edible brown algaes of *Ecklonia stolonifera* and *Eisenia bicyclis*. Compounds **224–227** were confirmed as potent noncompetitive inhibitors against PTP1B (IC_{50}: 2.6, 2.1, 0.6, and 1.2 μM, respectively). Compound **223** showed moderate activity for PTP1B inhibition. Additionally, compounds **225–227** showed the strongest α-glucosidase inhibitory activity. The authors indicated that these sea-weeds and their tannin compounds are of value as anti-diabetic agents (Moon et al. 2011). Compound **228** obtained from the roots of *Paeonia lactiflora* as a strong PTP1B inhibitor (IC_{50}: 4.8 μM) displayed insulin sensitization activity on human hepatoma cells (HCC-1.2) (Baumgartner et al. 2010). In tannin derivatives, only six compounds were found in previous reports, but these components all showed potent activity (IC_{50} < 10 μM) (Table S13; Fig. 14).

Other phenolics

Compounds **229–231**, **253**, and **254** were found from the stems of *Acanthopanax senticosus*, and demonstrated PTP1B inhibitory activity, with IC_{50} values of 9.2, 12.6, 26.4, 23.1, and 17.5 μM, respectively. Li et al. (2015b) reported that the propenal moiety in diphenyl ethers (**229–231**) plays an important role in increasing PTP1B inhibitory activity. Compound **232** is a famous bioactive component from *Curcuma longa*. In the in vivo assay, Li et al. (2010a) reported that curcumin protected against fructose-induced hypertriglyceridemia, and inhibited hepatic steatosis via inhibiting PTP1B. Ai et al. (2014) isolated six spirodioxynaphthalens from the cultures of endophytic fungus *Guignardia* sp. In this report, compound **233** exhibited significant inhibitory activity against both PTP1B (IC_{50}: 25.7 μM) and SIRT1 (IC_{50}: 43.9 μM) enzymes. SIRT1 (Silent information regulator T1) is an NAD^+-dependent deacetylase, and produces beneficial effects on glucose homeostasis and insulin sensitivity. The authors indicated that **233** could treat diabetes by double-side enzyme targets. Sixteen phloroglucinol derivatives (**234–249**) were isolated from the seed of *Eugenia jambolana*. Compounds **234–242**, **244**, **245**, and **247–249** exhibited potent PTP1B activity, with IC_{50} values ranging from 0.4–3.2 μM. Because of the limited quantities, compounds

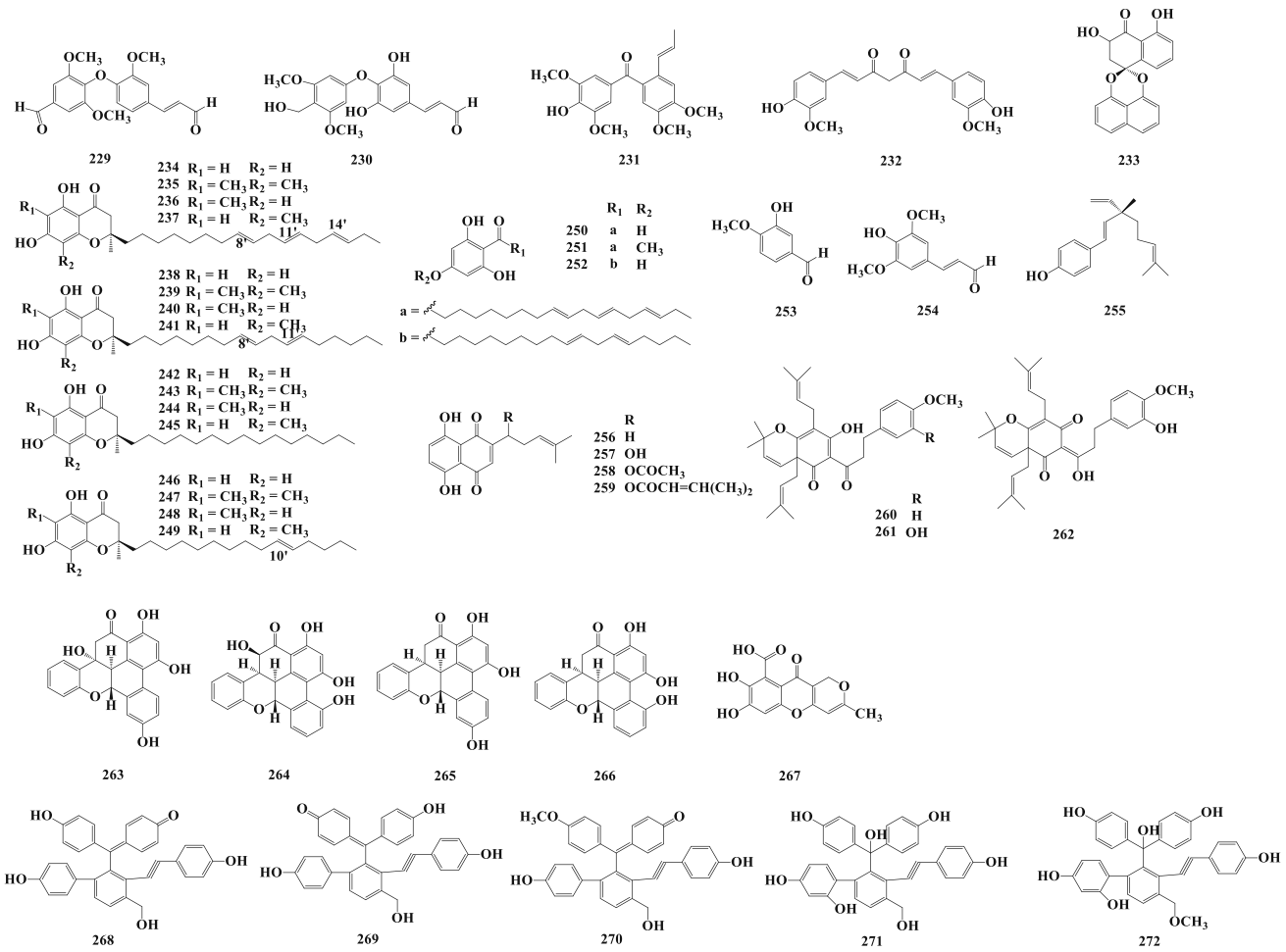


Fig. 15 Structures of other phenolics **229–272**

243 and **246** were not evaluated in the report. All these strong active compounds have the common feature of long alkyl side chain (Liu et al. 2017). Another three phenolic compounds (**250–252**) with long alkyl side chain obtained from the brown algae of *Protorhus thouvenotii* also showed considerable inhibition effect for PTP1B, with IC_{50} values of 8.1, 16.2, and 3.8 μM, respectively (Xiong et al. 2015). Compound **255** was acquired from the seeds of *P. corylifolia*. In the PTP1B study, **255** (IC_{50}: 20.8 μM; *Ki*: 8.9 μM) was determined as a moderate competitive-type inhibitor (Kim et al. 2005). Four naphthoquinones **256–259** from the aerial parts of *Arnebia euchroma* exhibited strong PTP1B inhibitory activity, with IC_{50} values of 0.8, 4.4, 1.0, and 0.4 μM, respectively. In the SAR study, Wang et al. (2016a) suggested that the ring of naphthoquinone and long lipo-chain might be the key skeleton structure for inhibitory activity on PTP1B. Three chromenedione derivatives **260–262** displayed PTP1B inhibitory activity, which was obtained from *Flemingia philippinensis* (Wang et al. 2016b). From the Antarctic moss of *Polytrichastrum alpinum*, four benzonaphthoxanthenones **263–266** were found by various chromatographic methods. These derivatives showed potent inhibitory activity against PTP1B (IC_{50}: 3.5, 5.6, 4.3, and 7.6 μM, respectively). Moreover, Seo et al. (2008a) reported that these four benzonaphthoxanthenones functioned as non-competitive inhibitors of PTP1B enzyme. Compound **267**, obtained from the marine-derived fungus *Penicillum* sp. JF-55, showed PTP1B inhibitory activity in a dose-dependent manner, and the kinetic analysis results suggested that this compound inhibited PTP1B activity (IC_{50}: 1.90 μM) in a competitive manner (Lee et al. 2013). Nguyen et al. (2015a) isolated five selaginellin derivatives (**268–272**) from the *S. tamariscina*. All the isolates **268–272** exhibited potent PTP1B inhibitory activity on 3T3-L1 adipocyte cell, along with IC_{50} values of 15.9, 4.6, 11.5, 21.6, and 19.4 μM, respectively. In the enzyme kinetic assay, the result indicated that compounds **268–270** acted as mixed type inhibitors with PTP1B (*Ki*: 13.9, 3.0, and 8.9 μM, respectively). Compound **271** (*Ki*: 10.3 μM) was proved to

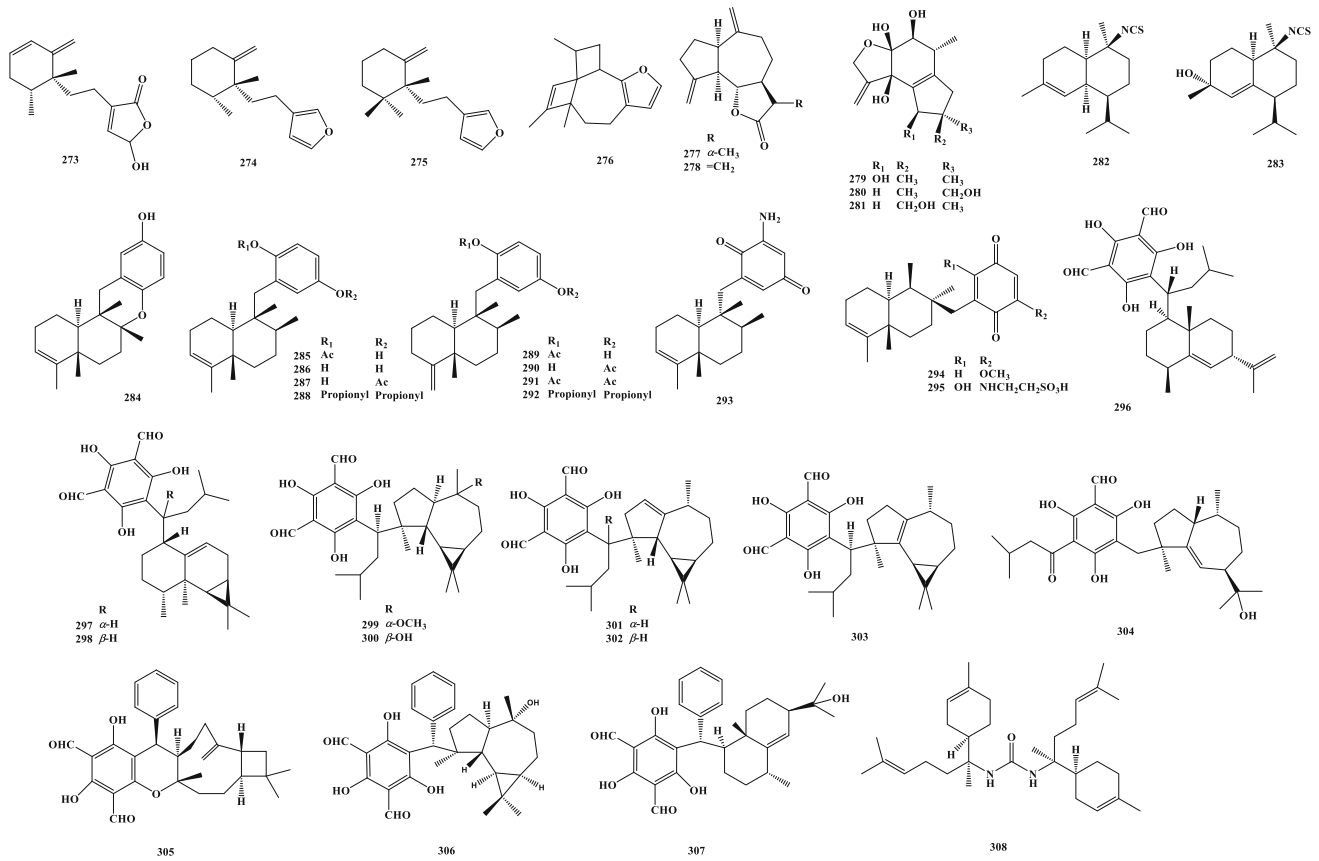


Fig. 16 Structures of sesquiterpenoids **273–308**

be a noncompetitive inhibitor, whereas compound **272** (*Ki*: 15.1 μM) was determined as an uncompetitive inhibitor (Table S14; Fig. 15).

Terpenoids

Sesquiterpenoids

Sesquiterpenoids have been considered as therapeutic target compounds for inhibiting PTP1B activity. Many scientists worldwide discovered interesting PTP1B inhibitors of sesquiterpenoid compounds (Table S15; Fig. 16). Huang et al. (2008) reported strong PTP1B inhibitors, hydroxybetenolide (**273**), microcionin-4 (**274**), dihydropallescensin-2 (**275**), and nakafuran (**276**), from the sponge *Desydea* sp., with IC_{50} values of 8.8, 11.6, 6.8, and 1.9 μg/mL, respectively. PTP1B inhibitors from the roots of *Saussurea lappa* were investigated, including guaiane sesquiterpenoids of mokko lactone (**277**) and dehydrocostuslatone (**278**), which contained low IC_{50} values of 1.4 and 6.5 μM, respectively (Choi et al. 2009). Yang Yu and his group found potent sesquiterpenoids, eucarobustols A–I (**296–304**), with IC_{50} values ranging from 1.3 to 5.6 μM, respectively (2016b). Drimane-type sesquiterpene hydroquinones (**284–293**) from marine sponge that was collected in Okinawa displayed strong PTP1B inhibitory effects, with IC_{50} values ranging from 6.5 to 14.0 μM. The results demonstrated the favorable activity of avarol-type bicyclic sesquiterpene moiety (Abdjul et al. 2016b). Other sesquiterpene quinone, 21-dehydroxybolinaquinone (**294**) and dysidine (**295**) isolated from sponge *Dysidea villosa,* showed potent PTP1B inhibitory activity, with IC_{50} values of 39.5 and 6.7 μM, respectively (Li et al. 2009). Tao et al. (2016) reported that clitocybulol G (**279**), clitocybulol L (**280**) and clitocybulol C (**281**) exhibited moderated inhibition on PTP1B, with IC_{50} values of 49.5, 38.1 and 36.0 μM, respectively. Meanwhile, Abdjul et al. (2016a) investigated PTP1B inhibitors (**282**, **283**, and **308**), with IC_{50} values of 17.0, 36.0, and 1.9 μM, respectively. Three unusual meroterpenoids, psidials A-C (**305–307**), were identified from the leaves of *Psidium guajava* L., and showed PTP1B activity, with inhibition rates of 1.7, 61.7, and 38.8% at the same tested concentration of 10 μM (Fu et al. 2010).

Diterpenoids

Diterpenoids have also been known as a major sub-group in the terpenes group, and have shown abundant activities, with a large number of compounds being patented. From the roots of *Aralia continentalis*, ten diterpenoids (**309**–**313** and **317**–**322**) were identified as strong PTP1B inhibitors, with IC_{50} values ranging from 0.1 to 11.0 μM (Jung et al. 2012). These results strongly suggest that the molecular type of the diterpenoids, and the kinds of substituents present in the molecules, are important to the strong interactions with enzyme molecules, as well as consequent inhibition of the enzyme. The kaurane-type diterpenoids containing an isovaleryloxy moiety at C-17 inhibited PTP1B, whereas either a hydroxyl group or reduction of a carboxyl group at C-19 in pimarane type diterpenoids to alcohol abolished the inhibitory effects on PTP1B. Kaurane diterpenoids showed the significant PTP1B inhibitory effects contained by *Siegesbeckia glabrescens,* including *ent*-16*β*H,17-isobutylryloxy-kauran-19-oic acid (**314**) and *ent*-16*β*H,17-acetoxy-18-isobutylryloxy-kauran-19-oic acid (**315**), with IC_{50} values of 8.7 and 30.6 μM, respectively. The result suggested the isobutyryloxy moiety at C-17 in this kaurane-type possessing the activity. Meanwhile, compound **315** substituted with an acetoxy and an isobutyryloxy group at C-17 and C-18 was less effective than **314** (Kim et al. 2006). Acanthoic acid (**310**), 16*α*H,17-isovaleryloxy-*ent*-kauran-19-oic acid (**316**), and *ent*-kaur-16-en-19-oic acid (**319**) displayed moderate inhibition on PTP1B with IC_{50} values of 23.5, 7.1, and 20.2 μM, respectively. The result indicated the isovaleryloxy group possessing the PTP1B activity, as well as the carboxyl group at C-19 in primarane-type diterpenoid, was essential for PTP1B activity (Na et al. 2006c). From the stem roots of *A. senticosus*, Li et al. (2014e) reported other diterpenoid PTP1B inhibitors (**314**–**316** and **319**, **320**) that contained strong PTP1B

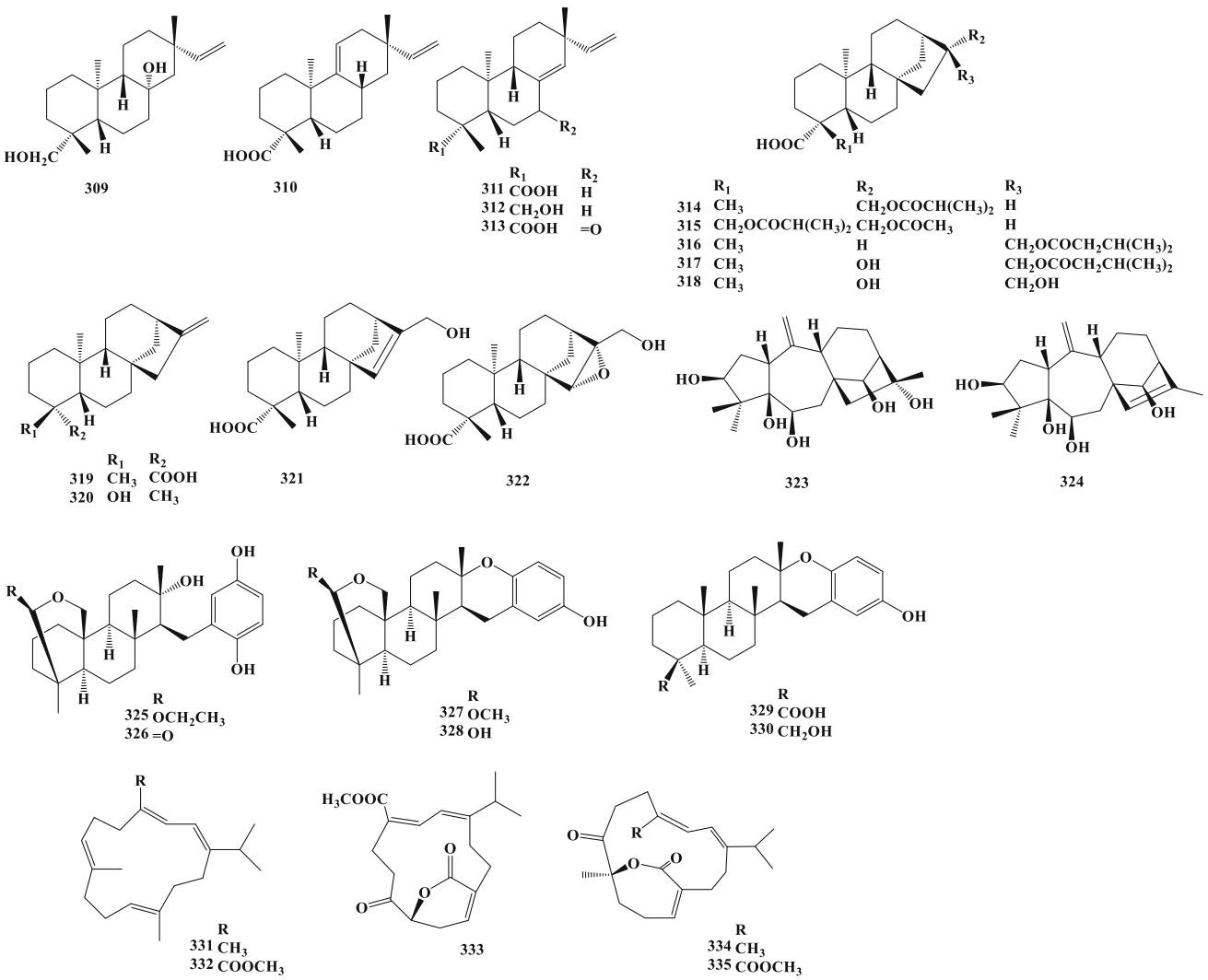


Fig. 17 Structures of diterpenoids (**309**–**335**)

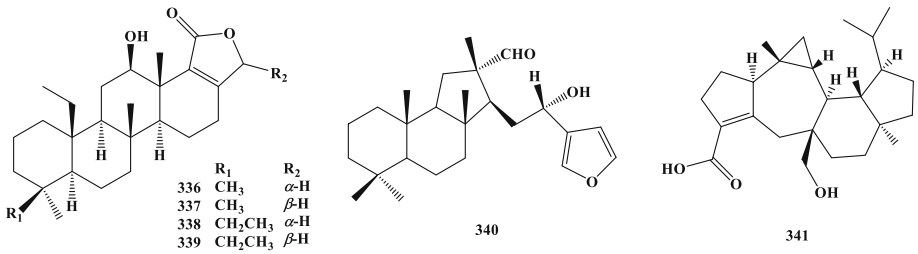


Fig. 18 Structures of sesterterpenoids **336–341**

inhibition, with IC_{50} values of 12.6, 21.3, 8.5 and 5.6, 12.6 μM, respectively. Similar results from the study of Kim et al. (2006) also showed significant PTP1B inhibition of *ent*-16α*H*,17-isobutylryloxy-kauran-19-oic acid (**314**) and *ent*-16α*H*,17-acetoxy-18-isobutylryloxy-kauran-19-oic acid (**315**) from the aerial parts of *S. glabrescens,* with IC_{50} values of 8.7 and 30.6 μM, respectively. Novel grayanane diterpenoids, such as principinol D (**323**) and principinol E (**324**) from *Rhododendron principis,* exhibited moderate to strong PTP1B inhibitory effect, with IC_{50} values of 24.5 to 3.1 μM, respectively. Thus, the Δ^{15} double bond may increase the activity (Zhang et al. 2015). Lee et al. (2015) identified strongylophorine diterpenoids (**325–330**) as PTP1B inhibitors, with IC_{50} values ranging from 8.7 to 21.2 μM. The inhibitory effects of strongylophorines possessing the acetal moiety at C-26 were stronger than those of the lactone derivatives. Other diterpenoids (**331–335**) were contained in *Sarcophyton trocheliophorum* corals exhibiting moderate to strong inhibition on PTP1B, with IC_{50} values of 26.6, 6.0, 27.2, 15.4, and 6.3 μM, respectively (Liang et al. 2013a). The active compounds showed the presence of a dienoate moiety at C-1 through C-18, while α,*β*-unsaturated *ε*-lactone should not be essential for the activity. In addition, the methyl ester group at C-18 significantly increases the enzyme inhibitory activity. The presence of the conjugated diene/ester moiety should not complete the description of the pharmacophore, as indicated by the inactivity of sarcophytonolide N (**333**), and the moderate potency of ketoemblide (**334**) for PTP1B inhibitory activity. Table S16 and Fig. 17 show all PTP1B inhibitors as diterpenoids.

Sesterterpenoids

Six sesterterpenoids (**409–416)** were found to possess PTP1B inhibitory activity (Table S17; Fig. 18). Abdjul et al. (2015b) reported that scalarane sesterterpenoids from marine sponge *Hyatterlla* sp. displayed strong inhibitory effects of hyattellactone A (**336**) and phyllofolactone F (**338**), with IC_{50} values of 7.45 and 7.47 μM, respectively. Meanwhile, hyattellactone B (**337**) showed an inhibition rate of 42% on PTP1B at a concentration of 24.2 μM, and phyllofolactone G (**339**) was inactive at the tested condition. A structure–activity relationship revealed that the stereochemistry at the C-24 position was very important for this activity. On the other hand, 24*S*-isomers (**337** and **339**) showed much more PTP1B inhibitory activity than the 24*R*-isomers (**336** and **338**). Sun et al. (2007) reported hyrtiosal (**340**) from *Hyrtios erectus* sponge containing moderate PTP1B inhibitory effects, with an IC_{50} value of 42.0 μM. Insulin receptor phosphorylates insulin receptor substrates (IRSs), and stimulates their downstream signaling, such as in the phosphatidylinositol 3-kinase (PI3K)/AKT pathway (Pessin and Saltiel 2000). The results suggested that hyrtiosal displayed potent activity in abolishing the retardation of AKT membrane translocation caused by PTP1B overexpression in Chinese hamster ovary cells. Moreover, it was found that this newly identified PTP1B inhibitor could dramatically enhance the membrane translocation of the key glucose transporter Glut4 in PTP1B-overexpressed Chinese hamster ovary cells. From the *Aspergillus* sp., asperterpenoid A (**341**) was found to inhibit PTP1B with a low IC_{50} value of 2.2 μM (Huang et al. 2013).

Triterpenoids

Triterpenes are among the most abundant natural products, containing about 30,000 compounds to date (Muffler et al. 2011). These compounds could be found in medicinal plants, such as vegetable or fruits, which contained benefit health effects, and were consumed every day (Siddique and Saleem 2011). The biological activities of these compounds were discovered to include anti-inflammatory, antioxidation, anti-viral, anti-cancer, and anti-hyperglycemic activities (Zhong et al. 2016; Zhang et al. 2017). In this study, we focus on the triterpenoid inhibitors from natural sources. Dammarane-type triterpenoids from *G. pentaphyllum*, including 3*β*-hydroxyetio-17*β*-dammaranic acid (**342**), (20*S*)-dammarane-24(25)-ene-3*β*,20,21-tetrol (**343**), 20(*S*)-protopanaxadiol (**353**), gypensapogenin E (**362**), gypensapogenin F (**363**), gypensapogenin G (**364**), (20*S*,23*S*)-3*β*,20-dihydroxyldammarane-24-ene-21-oic acid-21,23-lactone (**365**), (20*R*,23*R*)-3*β*,20-dihydroxyldammarane -24-ene-21-oic acid-21,23-lactone (**366**), gypensapogenin A (**370**), and gypensapogenin B (**371**) seem to be interesting compounds for inhibiting PTP1B, with IC_{50} values ranging from 8.4 to 49 μM (Zhang et al. 2013). The results revealed that the hydroxyl group at C-3 may reduce the inhibitory

effect on PTP1B. The double bond $\Delta^{20(22)}$ played a significant role in decreasing the PTP1B inhibition. In addition, the carboxyl group was also important toward inhibitory activity against PTP1B. From the roots of *Panax ginseng*, Yang et al. (2016) found ginsenosides **344**, **353**, **356**, **357,** and **381** to inhibit PTP1B, with IC_{50} values of 21.3, 18.0, 16.5, 10.1, and 21.0 μM, respectively. The result indicated that the protopanaxatriol-type is more effective than the protopanaxadiol-type. In addition, the 25-OH-protopanaxatriol-type exerted stronger inhibitory activity than the protopanaxatriol-type. Study on the structures and biological activities of constituent from *Russula lepida* revealed the first report for PTP1B inhibitory activity of *seco*-cucurbitane triterpenoids, (24*E*)-3,4-*seco*-cucurbita-4,24-diene-3-hydroxy-26,29-dioic acid (**347**) and (24*E*)-3,4-*seco*-cucurbita-4,24-diene-3,26,29-trioic acid (**348**), exhibiting moderate and strong inhibitory effects, with IC_{50} values of 20.3 and 0.4 μM, respectively (Lee et al. 2016). The existence of carboxyl group at C-2 may possess potent activity against PTP1B. From the fruits of *Momordica charantia*, cucubitane-type triterpenoids were isolated, and evaluated for PTP1B inhibitory activity at concentration of 10 μM (Zeng et al. 2014). A structure–activity relationship indicated that the PTP1B inhibitory activity of these triterpenes may associate with the presence of OH groups at the side chain, as well as the number of OH groups. Dammarane-type triterpenoids from the leaves of *Panax notoginseng* displayed the significant PTP1B inhibition of 20(*R*)-protopanaxadiol (**349**, IC_{50}: 21.3 μM), 20(*S*)-proptopanaxadiol (**350**, IC_{50}: 57.1 μM), 20(*R*)-ginsenoside-Rh2 (**351**, IC_{50}: 28.1 μM), 20(*S*)-ginsenoside-Mc (**352**, IC_{50}: 26.6 μM), notoginsenoside-LX (**360**, IC_{50}: 77.2 μM), and notoginsenoside-LY (**361**, IC_{50}: 29.1 μM) (Li et al. 2014b). The difference in absolute configuration of 20(*R*)- and 20(*S*)-forms in protopanaxadiol skeleton resulted in different inhibition effects. These results suggest that *P. notoginseng* leaves can be used in folk medicine for their anti-diabetic property, and that dammarane-type triterpenes enable this plant to be utilized for the treatment of diabetes. On the other hand, other PTP1B inhibitors were also identified from the roots (Li et al. 2014c), and leaves (Hung et al. 2009), of this plant containing dammarane-type triterpenoids (**345**, **346**, **354**, **365**, **382**, **383**, **358**, **359**, and **366–369**), with IC_{50} values ranging from 5.3 to 29.1 μM. Other triterpenoid inhibitors (**384**, **386**, **387**, and **400–403**) against PTP1B were found in the roots of *Potentilla discolor,* with IC_{50} values of 11.8, 22.7, 11.5, 15.7, 10.1, 16.3, and 7.5 μM, respectively (Tuo et al. 2016). The results revealed that carboxyl group or α-configuration of hydroxyl group at C-3, as well as hydroxyl group at C-23, might affect PTP1B inhibitory activity. Isolated triterpenoids from *Astilbe koreana* resulted in the finding of strong inhibitory PTP1B effects of 3-oxoolean-12-en-27-oic acid (**386**, IC_{50}: 6.8 μM), 3*β*-hydroxuolean-12-en-27-oic acid (**387**, IC_{50}: 5.2 μM), 3*β*-hydroxyurs-12-en-27-oic acid (**388**, IC_{50}: 4.9 μM), 3*β*,24-dihydroxyolean-12-en-27-oic acid (**390**, IC_{50}: 11.7 μM), and 3*β*,6*β*-dihydroxyolean-12-en-27-oic acid (**389**, IC_{50}: 12.8 μM). The results revealed that the hydroxyl group at C-3 and carboxyl group at C-27 played an important role in this activity. In contrast, the hydroxyl groups at C-6 and C-24 may reduce the PTP1B inhibitory activity in this skeleton (Na et al. 2006a). Cui et al. (2012) discovered the PTP1B inhibitors from *Aceriphyllum rossii*, in which aceriphyllic acid derivatives, including aceriphyllic acid C (**391**), aceriphyllic acid D (**392**), aceriphyllic acid E (**393**), and aceriphyllic acid F (**394**), exhibited potent inhibitory effects, with IC_{50} values of 2.7, 2.1, 11.2, and 6.3, μM, respectively. These compounds might be considered as the inhibitor agents for the treatment of PTP1B-related diseases. These results showed an inhibition rate of around 85% on PTP1B of MeOH extract of the stem barks of *A. rossii* at the level of 30 μg/mL, and the PTP1B inhibitory activity of triterpene constituents might be related to the anti-diabetic effect of this plant. From the stem-bark of *Styrax japonica*, three triterpenoid PTP1B inhibitors of 3*β*-acetoxy-28-hydroxyolean-12-ene (**396**, IC_{50}: 44.4 μM), 3*β*-acetoxyolean-12-en-28-acid (**397**, IC_{50}: 7.8 μM), and 3*β*-acetoxyolean-12-en-28-aldehyde (**398**:IC_{50} 9.3 μM) were discovered, with moderate to strong inhibitory effects, respectively (Kwon et al. 2008). The results indicated that the carbonyl groups in oleanane-type triterpenoids play an important role of possessing the PTP1B inhibitory activity. Meanwhile, ursolic acid (**385**) and its derivatives from *A. pilosa*, tormentic acid (**399**), exhibited a novel inhibitory effect, with IC_{50} values of 2.3 and 0.5 μM, respectively (Na et al. 2016; Xu et al. 2009). Furthermore, Zhao et al. (2017) isolated twelve triterpenoids from the same plant of *A. pilosa*. Among them, ten triterpenoids (**384**, **404**, and **409–416**) showed the inhibitory effects against PTP1B, with IC_{50} range of 0.5–74.7 μM. However, the structures with sugar moiety showed PTP1B activity as inactive, indicating that the sugar-based triterpenoids may not favor PTP1B inhibitory activity. Two ursane-type compounds, **411** (IC_{50}: 0.5 μM) and **412** (IC_{50}: 5.88 μM), which have three hydroxyl groups at C-2, C-3 and C-19, exhibited potent inhibitory activity against PTP1B. However, compound **404** (IC_{50}: 27.8 μM), without a hydroxyl group at C-19, showed weak inhibitory activity. In the molecular docking analysis, the authors suggested that Lys116 and Gln262 play important roles for PTP1B inhibitory effects in triterpenoid derivatives. Uddin et al. (2014) studied the fruit peel of *Camellia japonica,* which contained potent inhibitory oleanane triterpenes (**384**, **406–408**, **425–427**) against PTP1B. Among them, oleanolic acid (**384**), 3*β*,16α,17*β*–trihydroxy-olean-12-ene (**406**), 3*β*-acetoxyolean-12-ene-28-oic acid (**407**), camellenodiol (**408**), 3*β*-hydroxy-olean-11,13(18)-diene-28-oic acid (**426**), and 3*β*-hydroxy-16-oxo-olean-11,13(18)-diene (**427**) exhibited strong inhibitory effects, with low IC_{50} values of 5.3, 3.9, 4.8, 3.8, 6.4, and

4.7 μM, respectively. The important role of A ring may possess PTP1B inhibitory activity, and the replacement of 3-OH by a ketone group may considerably reduce the activity in PTP1B assay. The functional groups of 3-OH and 28-COOH significantly inhibited the PTP1B enzyme. Therefore, the critical roles of 3-OH and 28-COOH were beneficial for the pharmacological activities of pentacyclic triterpenes. Ursane type triterpenoids were also known to possess PTP1B inhibitory effects, with low IC_{50} values, such as ursolic acid (**385**, IC_{50}: 3.8 μM) and corosolic acid (**404**, IC_{50}: 7.2 μM), which were isolated from *Symplocos paniculata* (Na et al. 2006d). Euphyperin A (**424**) isolated from *Euphorbia hypericifolia* significantly inhibited PTP1B, with IC_{50} value of 17.05 μg/mL (Zhao et al. 2015). From the roots of *Saussurea lappa*, Choi et al. (2009) reported that betulinic acid (**428**) and betulinic acid methyl ester (**429**) contained strong inhibitory effects, with IC_{50} of 0.7 and 0.9 μM, respectively. Therefore, these compounds could be beneficial for development as PTP1B inhibitors from nature. According to the inhibitory result, the hydroxyl groups at C-28 may increase inhibitory activity. Moreover, lupane-type triterpenoids from the roots of *Euphorbia micractina* and *Sorbus commixta* were also found to inhibit PTP1B with significant effects, such as lupeone (**430**), lupeol (**431**), and betulin (**433**), with IC_{50} of 13.7, 5.6, and 15.3 μM, respectively (Na et al. 2009; Xu et al. 2009). Those findings indicated that lupeol and lupenone were capable of modulating signaling cascades in cells, and offered promise for developing new PTP1B inhibitors. Jeong et al. (2015) reported the PTP1B inhibitory activity of constituents from *E. alatus* (Thunb.) Sieb., which contained active triterpenoids, taraxerol (**423**), lupeol (**431**), and *epi*-lupeol (**432**), with interesting IC_{50} values of 21.9, 5.6, and 28.4 μM, respectively. The results suggested the different roles of 3α-hydroxyl and 3*β*-hydroxyl groups in possessing the PTP1B inhibitory effect. Meanwhile, compound **431** containing hydroxyl group in *β*-form expressed stronger inhibitory effect than compound **432** with hydroxyl group in α-form. Therefore, 3*β*-hydroxyl group increased the inhibitory effect. Cai et al. (2015) reported that 2α,3*β*-dihydroxyolean-12-en-23,28,30-trioic acid (**395**), friedelin (**417**), epifriedelanol (**418**), friedelane (**419**), and sorghumol (**437**) from *Anoectochilus chapaensis* showed novel PTP1B inhibitory effects, with IC_{50} values of 2.6, 6.21, 3.7, 4.6, and 3.5 μM, respectively. The carboxylic group at C-23 and hydroxyl group at C-3 of oleanolic acid may cause some effects against PTP1B. Oleanolic acid (**384**), moronic acid (**421**), and morolic acid (**422**) were known as famous PTP1B inhibitors, with interesting IC_{50} values of 9.5, 13.2, and 9.1 μM, respectively (Ramírez-Espinosa et al. 2011). Moreover, the selectivity of each inhibitor towards other non-structurally related PTPases, such as the IF1, IF2 isoenzymes of human LMW-PTP, the yeast LMW-PTP (LTP1), and human LAR, were also discovered. The results indicated that the IC_{50} values for other PTPases were higher than those for PTP1B. Thus, all compounds are selective towards PTP1B, with respect to the other PTPases tested. Li et al. (2014c) reported seven lupane type triterpenoids (**428**, **430**, **431**, and **433**–**436**) from the seeds of *Betula platyphylla* with strong inhibitory effects against PTP1B, having low IC_{50} values ranging from 4.1 to 13.6 μM. With the above information, triterpenoids from natural sources may be good candidates for PTP1B inhibitors (Table S18; Figs. 19, 20).

Steroids

Steroids, isoprenoid derivatives, are structural components of biological membranes. The steroid is one of the largest groups in nature, and were identified from plants, marine sources, and other natural sources. Among them, steroids as PTP1B inhibitors have emerged. Steroid compounds were derived into different analogs, and expressed their activation according to their functional groups. In particular, pregnane steroids, (*Z*)-aglawone (**439**), exhibited moderate PTP1B inhibitory effect, with an IC_{50} value of 1.45 g/mL, among seven isolated compounds from *Toona ciliata var. pubescens* (Wang et al. 2011). This compound was considered as a potential drug target for the treatment of type-II diabetes and obesity. Liang et al. (2013b) found the significant inhibition of polyhydroxylated steroids, (3*β*,4α,5α)-4-methylergost-24(28)-ene-3-ol (**440**) and ergost-4,24(28)-diene-3-one (**452**), expressing on PTP1B enzyme with IC_{50} values of 19.5, and 15.3 μM, respectively. In this steroids analog, the observation suggested the crucial role of α,*β*-unsaturated carbonyl group in ring A. The substitution of 8-OH may be inactive function group for PTP1B inhibitory activity, while the acetylation of 3-OH may contribute to increase this activity. From *E. alatus*, Jeong et al. (2015) found a moderate PTP1B inhibitor, 24*R*-methyllophenol (**441**), with IC_{50} value of 15.4 μM. Also, a PTP1B inhibitor **442** was found in the research of Chen et al. (2014a), and exhibited a moderate PTP1B inhibitory effect, with IC_{50} value of 33.05 μM. Marine animals are known as abundant sources of steroids. In these, *Axinyssa* sp. and *X. testudinaria* sponges contained many interesting active steroids against PTP1B, including axinysterol (**443**, IC_{50}: 24.0 μM) (Abdjul et al. 2016a), and 9-hydroperoxystigmasta-5,24(28)-dien-3-ol (**450**, IC_{50}: 5.8 μg/mL) (Zhou et al. 2014). Yang et al. (2015) reported the PTP1B inhibitory effects of steroids (**444**–**447**) isolated from the green alga of *C. racemosa,* with significant IC_{50} values of 3.8, 10.34, 41.7, and 49.9 μM, respectively. The results indicated that the *R*-form of C-24 may be important for PTP1B effect in this skeleton. One of our studies from the aerial parts of *A. pilosa* also contained moderated inhibitory effect of *β*-sitosterol (**448**) against PTP1B, with an IC_{50} value of

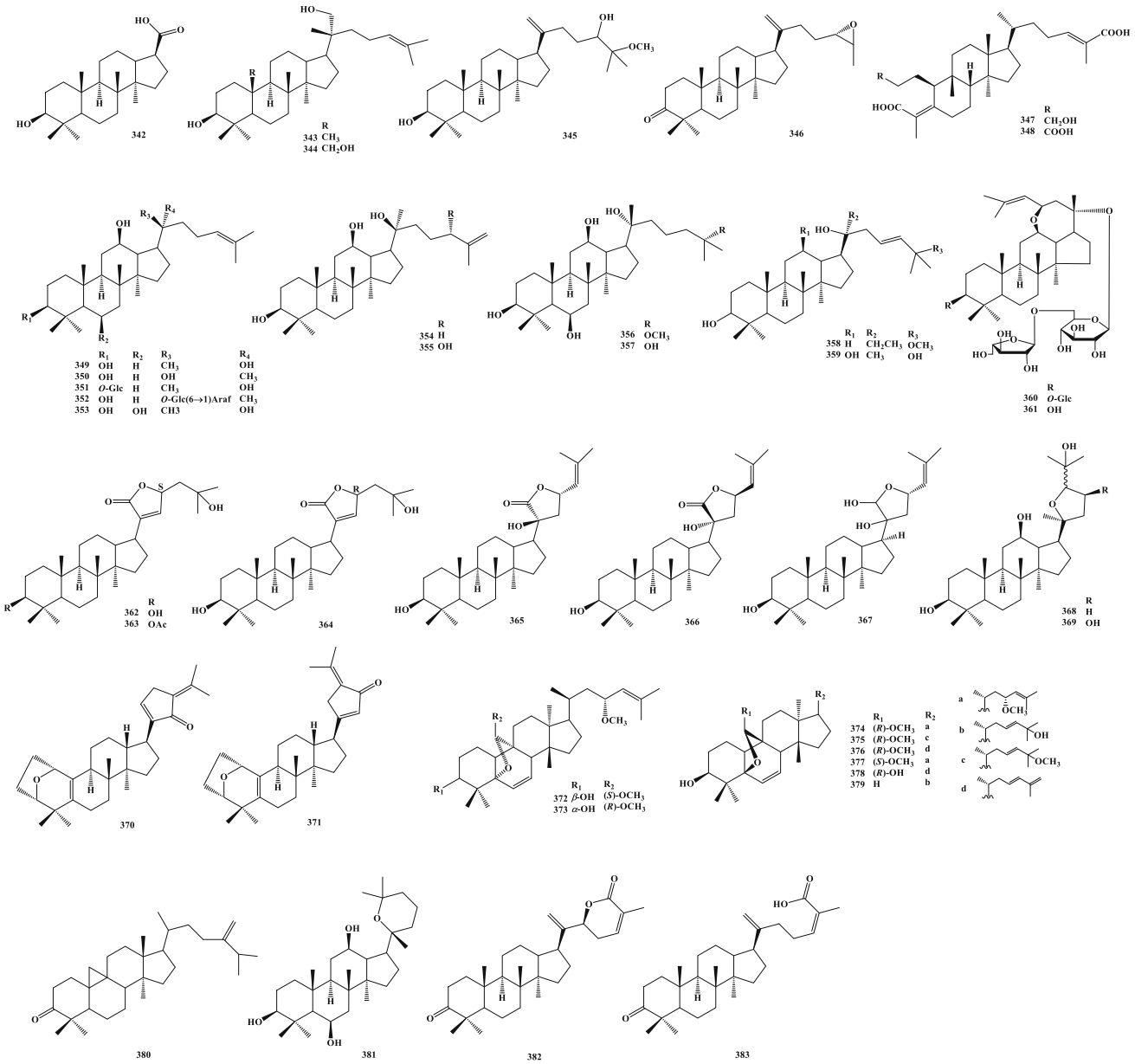
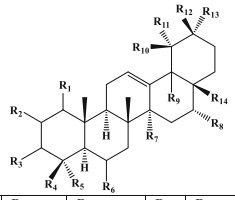


Fig. 19 Structures of triterpenes (four membered lactone rings) **342–383**

49.8 μM (Na et al. 2016). From the edible brown algae of *E. bicyclis* and *E. stolonifera*, fucosterol (**449**) moderately inhibited PTP1B enzyme (Jung et al. 2013). Thus, the inhibition mechanism of fucosterol on PTP1B was investigated using enzyme kinetic analysis. The result showed the inhibition constant (K_i) value of 77.13 μM, and a noncompetive inhibitor against PTP1B. The steroidal ketone from sponge *X. testudinaria* with an ergosta-22,25-dien side chain, (22*E*,24*S*)-24-methylcholesta-4,7,22,25-tetraene-3-one (**451**), exhibited potent PTP1P inhibitory activity, with an IC_{50} value of 4.27 μM, in the research of He et al. (2016). The result from this study revealed that the double bond $\Delta^{25(26)}$ was indicated as a reasonable possession of PTP1B inhibitory activity in these steroids. Chen et al. (2014d) reported that the degraded steroids from the cultures of *Antrodiella albocinnamomea*, albocisterols B and C (**453** and **454**), also displayed significant inhibition on PTP1B enzyme, with the same IC_{50} values of 1.1 μg/mL. The result suggested that the carbonyl group at C-27 plays a key role in mediating PTP1B inhibitory activities, and provides a vivid demonstration of how subtle differences in structure impact their biological activities. In a similar study from *Muricella Sinensis* sponge, Yan et al. (2008) identified calicoferol E (**455**) containing moderate PTP1B inhibitory effect, with an IC_{50} value of 27.3 μM. With the above collected information, steroid derivatives



No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	R_{11}	R_{12}	R_{13}	R_{14}
384	H	H	β-OH	CH_3	CH_3	H	CH_3	H	β-H	H	H	CH_3	CH_3	COOH
385	H	H	β-OH	CH_3	CH_3	H	CH_3	H	β-H	CH_3	H	H	CH_3	COOH
386	H	H	=O	CH_3	CH_3	H	COOH	H	β-H	H	H	CH_3	CH_3	CH_3
387	H	H	β-OH	CH_3	CH_3	H	COOH	H	β-H	H	H	CH_3	CH_3	CH_3
387	H	H	β-OH	CH_3	CH_3	H	COOH	H	β-H	CH_3	H	H	CH_3	CH_3
389	H	H	β-OH	CH_3	CH_3	β-OH	COOH	H	β-H	H	H	CH_3	CH_3	CH_3
390	H	H	α-OH	CH_2OH	CH_3	H	COOH	H	β-H	H	H	CH_3	CH_3	CH_3
391	H	H	α-OH	COOH	CH_3	H	CH_3	H	β-H	H	H	CH_3	COOH	CH_3
392	H	H	β-OH	COOH	CH_3	H	CH_3	H	β-H	H	H	CH_3	COOH	CH_3
393	H	H	β-OH	CH_2OH	CH_3	H	CH_3	H	β-H	H	H	CH_3	COOH	CH_3
394	H	H	α-$OCOCH_3$	COOH	CH_3	H	CH_3	H	β-H	H	H	CH_3	COOH	CH_3
395	H	α-OH	β-OH	CH_3	COOH	H	CH_3	H	β-H	H	H	COOH	CH_3	COOH
396	H	H	β-$OCOCH_3$	CH_3	CH_3	H	H	H	β-H	H	H	CH_3	CH_3	CH_2OH
397	H	H	β-$OCOCH_3$	CH_3	CH_3	H	H	H	β-H	H	H	CH_3	CH_3	COOH
398	H	H	β-$OCOCH_3$	CH_3	CH_3	H	H	H	β-H	H	H	CH_3	CH_3	CHO
399	H	β-OH	β-OH	CH_3	CH_3	H	CH_3	H	β-H	CH_3	OH	H	CH_3	COOH
400	H	H	β-OH	CH_3	COOH	H	CH_3	H	β-H	H	H	CH_3	CH_3	COOH
401	H	H	α-OH	CH_3	CH_3	H	COOH	H	β-H	H	H	CH_3	CH_3	CH_3
402	H	H	α-OH	CH_3	CH_2OH	H	COOH	H	β-H	H	H	CH_3	CH_3	CH_3
403	H	H	α-OH	CH_3	CH_2OH	H	$COOCH_3$	H	β-H	H	H	CH_3	CH_3	CH_3
404	H	α-OH	β-OH	CH_3	CH_3	H	CH_3	H	β-H	CH_3	H	H	CH_3	COOH
405	H	α-OH	α-OH	CH_3	CH_2OH	H	CH_3	H	β-H	CH_3	OH	H	CH_3	COOH
406	H	H	β-OH	CH_3	CH_3	H	CH_3	OH	β-H	H	H	CH_3	CH_3	OH
407	H	H	β-$OCOCH_3$	CH_3	CH_3	H	CH_3	H	β-H	H	H	CH_3	CH_3	COOH
408	H	H	β-OH	CH_3	CH_3	H	CH_3	=O	β-H	H	H	CH_3	CH_3	OH
409	β-OH	=O	β-OH	CH_3	CH_3	H	CH_3	H	β-H	CH_3	OH	H	CH_3	COOH
410	β-OH	α-OH	=O	CH_3	CH_3	H	CH_3	H	β-H	CH_3	OH	H	CH_3	COOH
411	H	α-OH	β-OH	CH_3	CH_3	H	CH_3	H	β-H	CH_3	OH	H	CH_3	COOH
412	H	β-OH	β-OH	CH_3	CH_3	H	CH_3	H	β-H	CH_3	H	H	CH_3	COOH
413	H	H	β-OH	CH_3	CH_3	H	CH_3	H	β-H	CH_3	OH	H	CH_3	COOH
414	H	H	β-$OCOCH_3$	CH_3	CH_3	H	CH_3	H	β-H	CH_3	H	H	CH_3	COOH
415	H	α-OH	β-OH	CH_3	CH_3	H	CH_3	H	β-H	CH_3	H	CH_3	CH_3	COOH
416	H	H	β-OH	CH_3	CH_3	H	CH_3	H	α-H	H	H	CH_3	H	COOH

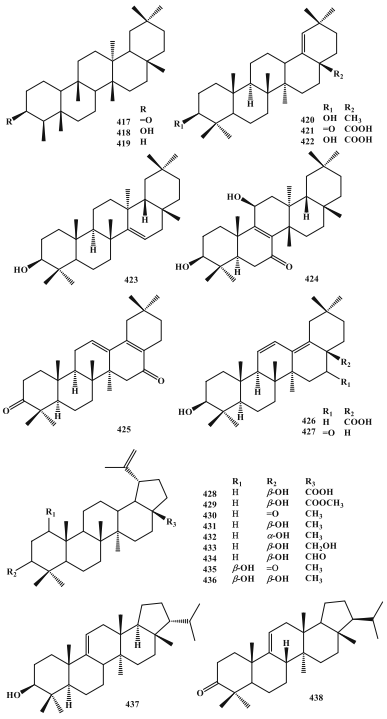


Fig. 20 Structures of triterpenes (five membered lactone rings) **417–438**

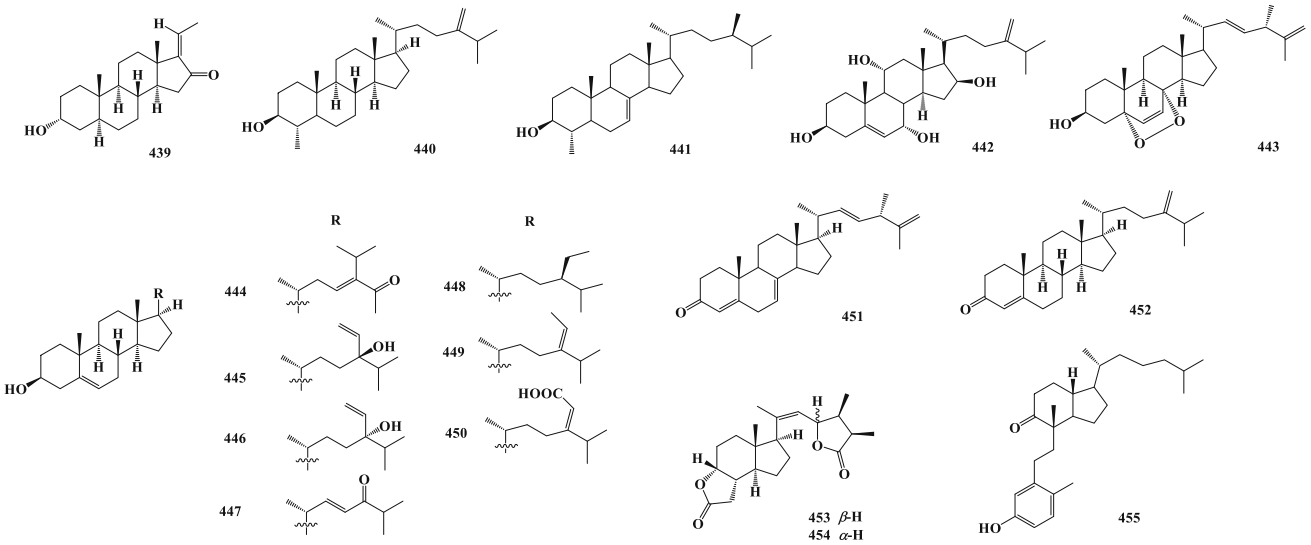


Fig. 21 Structures of steroids **439–455**

may be good candidates for developing natural PTP1B inhibitors from natural sources (Table S19; Fig. 21).

Alkaloids

Alkaloids are nitrogen-containing organic compounds that are considered to be involved in plant defenses against herbivores and pathogens. Several alkaloids were used as traditional and modern drugs (Schrittwieser and Resch 2013). Alkaloids from natural possess diverse bioactivities, such as anticancer, anti-inflammatory, and anti-diabetes (Dong et al. 2016; Zeng et al. 2017). However, few alkaloids showing potent PTP1B inhibitory activity have been reported to date. The aerial parts of *Houttuynia cordata* Thunb. have been traditionally used in Korea and China for the treatment of pyretic, detoxicant, and ulcer. Its constituents were reported to cure coughing, leucorrhea, nephrotic syndromes, ureteritis, and lung abscesses.

Several alkaloids were found from *H. cordata,* in which 3-hydroxy-1,2-dimethoxy-5-methyl-5*H*-dibenzoindol-4-one (**456**), 4-hydroxy-1,2,3-trimethoxy-7*H*-dibenzo-quiolin-7-one (**457**), 7-oxodehydroasimilobine (**458**), and cepharadione B (**459**) had potent PTP1B inhibitory activities, with IC_{50} values of 1.3, 2.0, 2.7, and 1.9 μM, respectively (Ma et al. 2017). The SARs of these PTP1B inhibitors were not revealed, due to their complex structures. The rhizome of *C. chinensis* Franch, a drug herba from China and Japan, has been prescribed for the treatment of anti-diabetic, anti-inflamatory, anti-hypertensive, anti-proliferative, and anti-Alzheimer diseases. Magnoflorine (**460**), berberine (**469**), epiberberine (**470**), and coptisine (**471**) isolated from the rhizomes of *C. chinensis* were reported to possess significant inhibitory effects against PTP1B enzyme, with IC_{50} values ranging from 16.4 to 51.0 μM (Choi et al. 2015). Raemosin (**461**) and caulersin (**462**), two alkaloids in the green alga *C. racemosa*, showed potent PTP1B inhibitory activity, with IC_{50} values of 5.9 and 7.01 μM, respectively (Yang et al. 2014). Sasaki et al. (2015) investigated seventy-six alkaloids, to find PTP1B inhibitors from *Picrasma quassioides*, *Picrasma javanica*, *Ailanthus altissima*, *Simarouba amara*, *Eurycoma longifolia*, *Simaba cuspidata*, and *Quassia amara*. Among them, six canthinone alkaloids, picrasidine L (**463**), 3,4-dimethyl-canthin-5,6-dione (**464**), 4-ethyl-3-methyl-canthin-5,6-dione (**465**), eurycomine E (**466**), 5-methoxy-canthin-6-one (**467**), and 5-acethoxy-canthin-6-one (**468**), exhibited significant PTP1B inhibitory activities, with IC_{50} values of 19.8, 24.7, 27.8, 19.2, 20.3, and 28.9 μM, respectively. In addition, compounds **464–478** displayed non-competitive types, and **463** showed competitive type against PTP1B by enzyme kinetic assay. Finally, the authors suggested that compound **463** may be useful for potential PTP1B inhibitor as lead compound in future anti-insulin-resistant drug developments. Chen et al. (2014b) reported that norditerpenoids (**472–474**) and a pyrroloquinoline (**475**), the skeletons with cross-ring conjugated systems, were isolated from the seeds of *Nigella glandulifera* Freyn. Compounds **472–475** showed potent inhibitory activity, with IC_{50} values of 10.0, 9.7, 16.9, and 6.4 μM, respectively. Compound **476** possessed potent PTP1B inhibitory activity, with an IC_{50} value of 3.7 μM (Chen et al. 2017). *Murray koenigii* (L.) Spreng., a medicinal plant, was used traditionally to treat piles, inflammation, dysentery, and vomiting. Ma et al. (2013) reported that three carbazole alkaloids, mahanine (**477**), mahanimbine (**478**), and 8,8′-biskoenigine (**779**), isolated from the whole plant of *M. koenigii,* showed potent inhibitory effects against PTP1B enzyme, with IC_{50} values of 1.8, 1.9, and 2.3, respectively. *Veratrum nigrum* was traditionally used as a treatment for hypertension, stroke, and excessive phlegm. Kang et al. (2015) reported that two steroidal alkaloids, jervine-3-yl formate (**480**) and veratramine-3-yl acetate (**481**), from the roots and rhizomes of *V. nigrum,* had potent inhibitory activities (IC_{50} = 11.3 for **480**, and 4.7 μM for **481**) against PTP1B. The Okinawan marine sponge *Agelas nakamurai* was reported to possess several alkaloids. However, only an agelasine alkaloid, agelasines G (**482**), displayed significant inhibitory activity, with an IC_{50} value of 15 μM (Abdjul et al. 2015a). Marine microorganisms, a rich source of structurally novel and pharmacologically active secondary metabolites, have been of interest to date (Molinski et al. 2009). In particular, the fungi from the marine environment have been shown to produce diverse secondary metabolites that are more or less similar to those produced by terrestrial fungi. Sohn et al. (2013) reported that four alkaloids, fructigenine A (**483**), cyclopenol (**484**), echinulin (**485**), and viridicatol (**486**), isolated from marine-derived fungal strains *Penicillium* spp. and *Eurotium* sp., had significant PTP1B inhibitory activity, with IC_{50} values of 10.7, 30.0, 29.4, and 64 μM, respectively. Several alkaloids were found from *Daphniphyllum himalense* (Benth.) Muell.-Arg, in which 17-epi-daphlongamine F (**487**) and himalenine E (**488**) showed moderate inhibitory effects on the concentrations of 40.4 and 38.0% at 20 μg/mL (Zhang et al. 2015). Daphniphyllum alkaloids, a class of natural products, were found in the Daphniphyllaceae to possess a variety of bioactivities. Zhang et al. (2016) reported that two alkaloids, himalensine A (**489**) and himalensine B (**490**), were isolated from the twigs and leaves of *D. himalense*. Compounds **489** and **490** exhibited moderate inhibitory activities against PTP1B, with inhibitory rates of 31.2% and 23.6% at the concentration of 20 μM, respectively. *Hericium erinaceus*, a medicinal mushroom in East Asian, was reported to contain several alkaloids. Indeed, Wang et al. (2015a, b, c) found the culture extract of *H. erinaceus* to contain eight new alkaloids. As a result, compounds erinacerin Q (**491**), erinacerin R (**492**), erinacerin S (**493**), and erinacerin T (**494**) displayed significant inhibitory activities against PTP1B enzyme, with IC_{50} values of 29.1, 42.1, 28.5, 24.9 μM, respectively. A 2-pyridone alkaloid, fumosorinone (**495**), displayed significant PTP1B inhibitory activity, with an IC_{50} value of 14.0 μM, which was isolated from the entomogenous fungus *Isaria fumosorosea* (Liu et al. 2015). Table S20 and Fig. 22 show the PTP1B inhibitors as alkaloids (**456–495**).

Conclusion

In this review, approximately 500 compounds (24 fatty acids, 248 phenolics, 159 terpenoids, 17 steroids and 40 alkaloids) from about 100 species of natural sources were investigated, but these are only a small part of the infinite

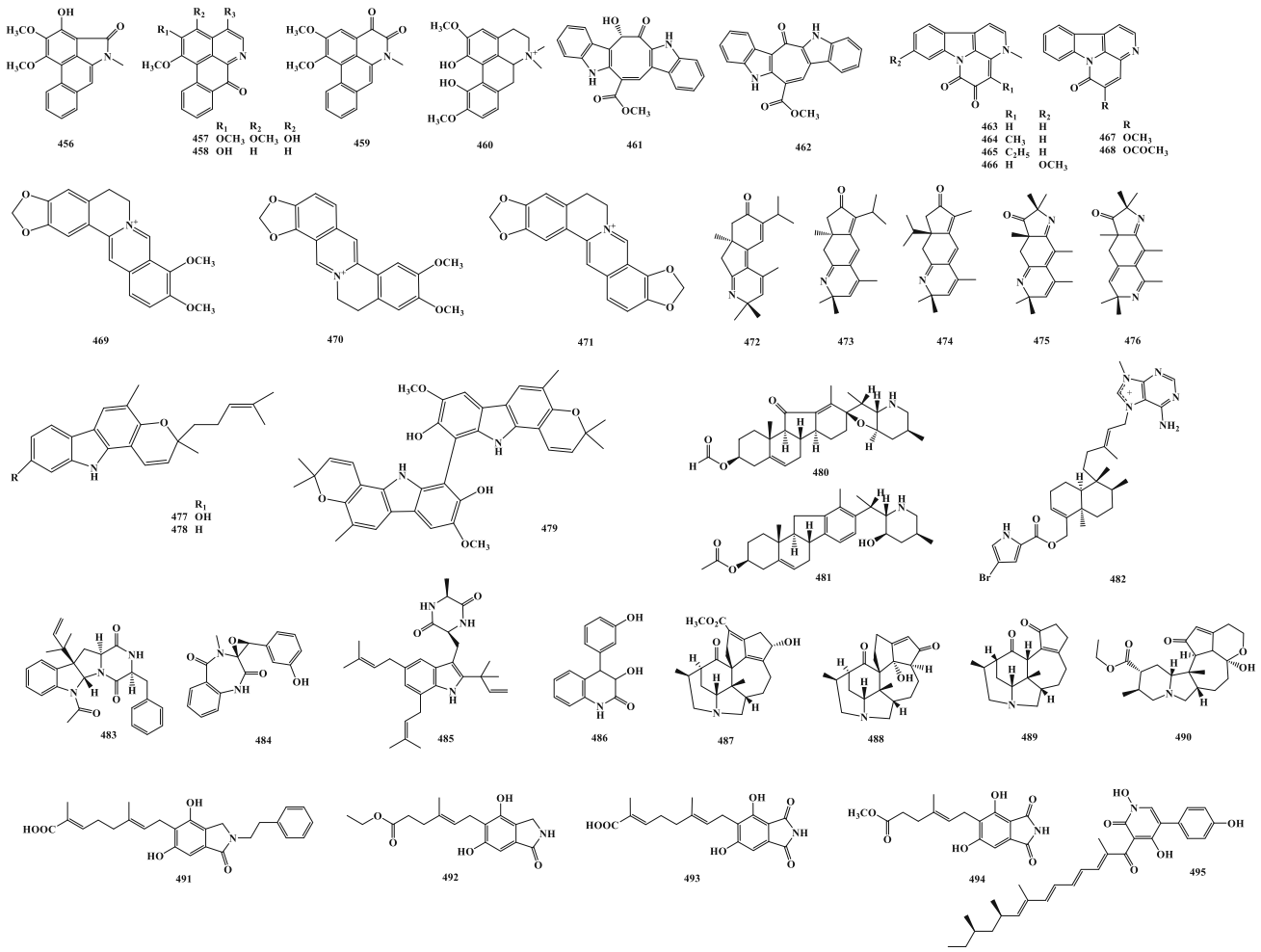


Fig. 22 Structures of alkaloids **456–495**

kingdom of nature. In fact, the majority of published studies have focused on phenolic and terpenoid inhibitors that are characterized by major PTP1B activity and selectivity. But in a wide variety of natural products, other kinds of compounds also can not be ignored. Forthermore, most of the PTP1B activities was determined on in vitro test. Therefore, this review majorly explores the structure of active compounds rather than the PTP1B mechanism for their action. The knowledge offered from this review should help to provide leads to the ultimate goal of developing new therapeutic drugs with more efficacy and safety for the treatment of PTP1B-related disease such as diabetes.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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