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Review

Natural products possessing protein tyrosine phosphatase 1B (PTP1B) inhibitory activity found in the last decades

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This article provides an overview of approximately 300 secondary metabolites with inhibitory activity against protein tyrosine phosphatase 1B (PTP1B), which were isolated from various natural sources or derived from synthetic process in the last decades. The structure-activity relationship and the selectivity of some compounds against other protein phosphatases were also discussed. Potential pharmaceutical applications of several PTP1B inhibitors were presented.

Keywords: natural products; phytochemistry; protein tyrosine phosphatase 1B (PTP1B); inhibitor; structure-activity relationship (SAR); type 2 diabetes; obesity

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Introduction

Type 2 diabetes is a chronic disorder characterized by hyperglycemia associated with a gradual decline in insulin sensitivity and/or insulin secretion. Long-term complications from hyperglycemia can lead to an increased risk of heart attack, stroke, amputation, and kidney failure. According to statistics, more than 220 million people worldwide have diabetes. In 2004, an estimated 3.4 million people died from consequences of hyperglycemia, and this rate continues to increase each year. The WHO projected that diabetes death rates would double between 2005 and 2030. There are four main types of diabetes, including type 1, type 2, gestational diabetes, and drug-induced or chronic pancreatitis-induced diabetes. Type 2 diabetes accounts for 90% the cases of diabetes around the world[1], with obesity contributing to approximately 55% of the cases of type 2 diabetes[2]. It has been suggested that replacing saturated fats and trans fatty acids with unsaturated fats has beneficial effects on insulin sensitivity and may reduce the risk of type 2 diabetes[3]. Thus, it is not surprising that considerable efforts have been made to find drug targets or candidates to treat or cure type 2 diabetes and obesity. Natural products have proved to be an important source of new drugs[4]. An article written by Jung *et al* reviewed medicinal plants that have shown experimental or clinical anti-diabetic activity and that have been used in traditional systems of medicine[5].

Reversible protein tyrosine phosphorylation catalyzed by the coordinated actions of protein tyrosine kinases (PTKs) and phosphatases (PTPs) is important for the regulation of signaling events. Consequently, cellular pathways regulated by tyrosine phosphorylation offer many drug targets for developing novel therapeutics[6]. PTPs are enzymes that catalyze protein tyrosine dephosphorylation. In humans, more than one hundred PTPs exist and function as either negative or positive modulators in various signal transduction pathways[7]. Among the various members of the PTP superfamily, PTP1B is considered to be a negative regulator of insulin receptor (IR) signaling. PTP1B is a promising drug target for the treatment of type 2 diabetes and obesity and is also involved in cancer[8, 9].

A systematic literature search revealed that various natural compounds were reported to exhibit PTP1B inhibitory activity. There are several reviews regarding the development of PTP1B inhibitors but most of them focused on synthetic PTP1B inhibitors[6, 9–15]. Only one review, written by Thareja *et al*, briefly reviewed approximately 50 natural PTP1B inhibitors[15]. According to our literature search, sulfircin **236**, a sesterterpene sulfate isolated as its *N,N*-dimethylguanidinium salt from a deep-water sponge *Ircinia* (unknown species) collected from Andros, Bahamas, appears to be the first reported

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natural product with PTP1B inhibitory activity[16]. In 2002, five natural flavonoids were reported as PTP1B inhibitors[17]. Since then, approximately 300 new or known natural products, which possess PTP1B inhibitory activity, have been isolated and identified from various natural resources. Many of the products identified are characterized by remarkable structural diversity with rare carbon and heterocyclic skeletons. Because of the rapid development of natural PTP1B inhibitors and the lack of a comprehensive review regarding natural PTP1B inhibitors until now, it appears a comprehensive review is urgently needed on this topic. This review first gives a brief introduction on the definition and function of PTP1B, and then focuses on the isolation, bioactivities, and synthetic progress of the natural PTP1B inhibitors reported. The structure-activity-relationship (SAR) and the selectivity of some compounds against other protein phosphatases (PPs) are mentioned as well. (In the interest of space, if the activity or inhibitory activity below is not specified, it means PTP1B inhibitory activity.)

Structural biology, mechanism of PTP1B, and its validation as a drug target for diabetes and obesity

The structural biology, mechanism of PTP1B, and its validation as a drug target for diabetes and obesity have been discussed in detail in several reviews[6, 12, 15, 18, 19]. Nevertheless, a brief introduction on PTP1B is presented below.

PTP1B was the first PTP to be isolated in its pure form. The structure of PTP1B was elucidated by X-ray crystallography in 1994, and it has served as a model to illustrate several of the properties of PTPs[20]. The structure consists of 435 amino acids with the catalytic domain comprised of residues 30 to 278 and the 35 COOH-terminal residues target the enzyme to the cytoplasmic face of the endoplamic reticulum. The active site of PTP1B is approximately 8 to 9 Å deep and is defined by residues 214 to 221 (P-loop, phosphate binding loop, His-Cys-Ser-Ala-Gly-Ile-Gly-Arg). The phosphate group of the substrate forms a series of hydrogen bonds with the backbone amide protons of the P-loop and Arg-221. Upon binding of the substrate, the WPD loop (residues 79–187) shifts 10 Å to cover the phenyl phosphate group. This results in Asp-181 being in position to act as a general acid and protonate the ester oxygen. Cys-215 attacks the phosphorous atom resulting in cleavage of the P-O bond and formation of a phosphocysteine intermediate that is then hydrolyzed to give the final products. A number of other residues contribute significantly to peptide substrate recognition, such as Phe182, Tyr46, Lys120, Gln262, Val49, Arg47, and Asp181, by a mixture of hydrophobic, electrostatic and hydrogen-bonding interactions. Studies with phosphotyrosine (pTyr or pY)-bearing peptides indicate that PTP1B has a preference for acidic residues at several positions N-terminal to the pTyr residue[21].

Substantial evidence indicates that PTP1B, as a negative regulator in both insulin and leptin signaling, is a promising drug target for type 2 diabetes and obesity. In the insulin signaling pathway, PTP1B can associate with and dephosphorylate activated IRs or insulin receptor substrates (IRSs). In the leptin pathway, it binds and dephosphorylates JAK2, which is downstream of the receptor. Overexpression of PTP1B in cell cultures decreases insulin-stimulated phosphorylaton of IR and/or IRS-1, whereas a reduction in the level of PTP1B augments insulin-initiated signaling[6]. The genetic analysis of the PTPN1 gene, coding for PTP1B in humans, revealed a significant association with metabolic traits consistent with the proposed *in vivo* role of PTP1B[22]. In murine models, disruption of the PTPN1 gene resulted in resistance to diet-induced obesity and increased insulin sensitivity. The *PTP1B*$^{-}$/$^{-}$ mice had significantly lower triglyceride levels even at feeding on a high-fat diet, and showed an enhanced response toward leptin-mediated weight loss and suppression of feeding[23–25]. In addition, small molecule PTP1B inhibitors can act as both insulin mimetics and insulin sensitizers[26]. Consequently, it has been suggested that the PTP1B inhibitors might have a role in the treatment of type 2 diabetes and obesity.

Natural PTP1B inhibitors

Phenolics

Phenolics are characterized by having at least one aromatic ring with one or more hydroxyl groups attached[27]. According to their structural characteristics, the phenolics discussed below are classified into seven groups, including flavonoids, bromophenol, phenolic acid, phenolics containing furan or pyran rings, coumarins, lignans and miscellaneous phenolics.

Flavonoids

Flavonoids are polyphenolic compounds comprised of 15 carbons, with two aromatic rings connected by a three-carbon bridge. They are the most numerous natural products and exist extensively in nature. Flavonoids include flavonols, flavones, flavanones, isoflavones, catechins, anthocyanidins and chalcones. Their potential beneficial effects, such as antiviral, antitumor, antiplatelet, anti-inflammatory and antioxidant activities, greatly interest chemists and pharmacologists. For example, just between January 2007 and December 2009, 796 new naturally occurring flavonoids were isolated from various natural resources[28].

In 2002, five natural flavonoids, including 8-(1,1-dimethylallyl)-5′-(3-methylbut-2-enyl)-3′,4′,5,7-tetrahydroxyflanvonol **1**, 3′-(3-methylbut-2-enyl)-3′,4′,7-trihydroxyflavane **2**, quercetin **3**, uralenol **4**, and broussochalcone A **5** were isolated from the roots of the plant *Broussonetia papyrifera* collected from Zhibo, Anhui province, China[17]. Flavonoids **1–5** showed inhibitory activity against PTP1B with IC_{50} values ranging from 4.3 to 36.8 μmol/L. The preliminary SAR study indicated that less polar substituents at the 3′,4′,5,7-tetrahydroxyflanvonol skeleton produced stronger inhibitory activities.

Licochalcones A **6**, C **7**, and E **8** were isolated from the CH_2Cl_2 extract of plant *Glycyrrhiza inflate*[29]. Evaluation of the inhibitory activity of licochalcones **6–8**, together with their 4- and/or 4′-hydroxyl group methylated and/or acetylated derivatives indicated that the presence of the allyl group in ring B might increase inhibitory activity. However, the degree of activation varied depending on the configuration and substitution position of the allyl group in ring B and the inhibitory

activity was strongest when 4′-hydroxyl group in **6** was methylated. Licochalcone A **6** was concisely synthesized through water-accelerated [3,3]-sigmatropic rearrangement of an aryl isoprenyl ether as a key step[30]. Licochalcones C **7** was synthesized by a simple, inexpensive high yield method starting from 3-(3-methyl-2-butenyl)-2,4-dihydroxybenzaldehyde[31]. Licochalcone E **8** was first synthesized by employing Claisen rearrangement for synthesis of the key intermediate[32].

Three PTP1B inhibitors, glycyrrhisoflavone **9**, glisoflavone **10**, and licoflavone A **11**, were isolated from the roots of plant *G uralensis*[33]. Of these isolates, glisoflavone **10** showed the strongest inhibitory activity with an IC_{50} of 27.9 μmol/L, and kinetic analysis indicated that it inhibited PTP1B in a mixed-type manner. The presence of an isoprenyl group and an *ortho*-hydroxyl group was considered to be important for exhibiting the activity.

Bioassay-guided fractionation of the $CHCl_3$-soluble fraction of plant *Morus bombycis* led to the isolation of three chalcone-derived Diels-Alder products: kuwanons J **12**, R **13**, and V **14**[34]. All of these kuwanons showed remarkable inhibitory activity with IC_{50} values ranging from 4.3 to 13.8 μmol/L. The order of inhibitory activity of kuwanons was **12>13>14**, suggesting that increasing the number of hydroxyl groups improved the inhibitory effect. Additionally, a kinetics analysis suggested that these kuwanons inhibited PTP1B in a mixed-type manner, indicating that they might displace at both the active site and an additional binding site of the PTP1B.

The plant *Cyclocarya paliurus* has been used as a traditional tonic, and its leaves have been processed as tea products. Quercetin-3-*O*-β-*D*-glucuronide **15** and myricetin-3-*O*-β-*D*-glucuronide **16** were isolated from the leaves of *C paliurus*[35]. Compound **16** (IC_{50}=9.47±3.31 μg/mL) was slightly less active than **15** (IC_{50}=7.39±1.15 μg/mL), indicating that the decrease in activity is attributed to the addition of one hydroxyl group to C-5′ in ring B. As an epimer of **15**, quercetin-3-*O*-α-*D*-glucuronide was inactive, implying that sugar configuration played a key role in *in vitro* inhibitory activity. The synthesis of **15** was achieved in 1970 by coupling 7,4′-dibenzylquercetin with methyl(tri-*O*-acetyl-α-*D*-glucopyranosyl bromide)-uronate followed by total acetylation of the product and subsequent removal of the protecting groups[36].

The herb *Scutellaria indica*, known as 'Han-Xin-Cao' distributed widely in Asia, is traditionally used for hemoptysis, hematemesis, antitumor activity, and the treatment of other diseases in China. From the extract of *S indica*, wogonin **17** and (2*S*)-5,7-dihydroxy-8,2′-dimethoxyflavanone **18** were isolated with weak inhibitory activity[37]. In 2003, Huang *et al* synthesized **17** in 3 steps by a concise and efficient method[38].

Flavonoids **19–23** were isolated from an EtOAc-soluble partition of the MeOH extract of the plant *Tetracera scandens*, a traditional Vietnamese medicinal plant showing some therapeutic activities in inflammation, hepatitis and gout[39]. Flavonoids **19**, **21–23** exhibited stronger inhibitory activity (IC_{50} values ranging from 20.63±0.17 to 37.52±0.31 μmol/L) than **20** (IC_{50}>80 μmol/L). Moreover, compounds **19** and **21–23** exhibited significant glucose-uptake activity in basal and insulin-stimulated L6 myotubes, stimulated AMPK, phosphorylation, and inhibited GLUT4 and GLUT1 mRNA expressions. Furthermore, compounds **19**, **22**, and **23** showed no muscle cell toxicity at levels up to 60 μmol/L, indicating that they could be possible lead candidates for the treatment of type 2 diabetes. Compound **23** had been synthesized by Rao *et al* in 1987[40] (Figure 1).

From fruits of the plant *Pongamia pinnata*, the flowers of which were found to have anti-hyperglycemic and antilipidperoxidative activities[41], pongamol **24** and karanjin **25** were obtained. Both flavonoids exhibited inhibitory activity with IC_{50} values of 75.0 μmol/L and 84.5 μmol/L, and with K_i values of 58 μmol/L and 76 μmol/L, respectively[42]. In Streptozotocin (STZ)-induced diabetic rats, single-dose treatment with **24** and **25** lowered the blood glucose level by 12.8% (P<0.05) and 11.7% (P<0.05) at a 50 mg/kg dose and 22.0% (P<0.01) and 20.7% (P<0.01) at a 100 mg/kg dose, respectively, 6 h post-oral administration. Additionally, they significantly lowered the blood glucose level in db/db mice, which is well characterized as a mode of type 2 diabetes, with percent activities of 35.7% (P<0.01) and 30.6% (P<0.01), respectively, at a 100 mg/kg dose after consecutive treatment for 10 d. Therefore, the anti-hyperglycemic activity of *P pinnata* for STZ-induced diabetic rats and type 2 diabetic db/db mice is likely due to the PTP1B inhibitory effect of **24** and **25**. Pongamol **24** was synthesized by Goel *et al* in 2004 and Yadav *et al* in 2005[43, 44]. Karanjin **25** was synthesized by Hossain *et al* in 2003[45].

The plants in genus *Erythrina* of the Leguminosae family are distributed in tropical and subtropical zones of the world and have been used to treat many ailments. During a study to search for PTP1B inhibitors, Oh *et al* isolated and characterized a series of flavonoids (**26–114**) described below from the extract of the species *Erythrina*. Most of the flavonoids isolated showed significant inhibitory activity against PTP1B[46–54].

Six prenylated isoflavonoids **26–31** were isolated from the EtOAc extract of the stem bark of *E addisoniae*[46]. The bioassay results indicated that **30** (IC_{50}=2.6±0.5 μmol/L) and **31** (IC_{50}=4.1±0.2 μmol/L), both bearing an isoprenyl group and a dimethylpyran moiety in the ring A, exhibited stronger inhibitory activity than **26** (IC_{50}=10.1±0.3 μmol/L), suggesting that cyclization between a hydroxy group at C-7 and one of the isoprenyl groups at C-6 or C-8 in ring A may be important for activity. Moreover, the 2′,4′-dihydroxy group in ring B of isoflavanoids appears to correlate with the inhibitory activity, and a double bond between C-2 and C-3 of the ring might be responsible for a loss of activity.

Bioassay-guided fractionation of an EtOAc-soluble extract of the root bark of *E mildbraedii* yielded flavonoids **19** and **32–39**, which show significant inhibitory activity (IC_{50} ranging from 14.8±1.1 to 39.7±2.5 μmol/L)[47]. Flavonoid **35** (IC_{50}=39.7±2.5 μmol/L), with one more hydroxyl group at C-5, was less active than **36**. A similar observation was made for flavonoids **32** and **33**, indicating that addition of a hydroxyl group to C-5 in ring A may be responsible for the loss of *in vitro* activity. Flavonoid **34** (IC_{50}>60 μmol/L), in which an additional

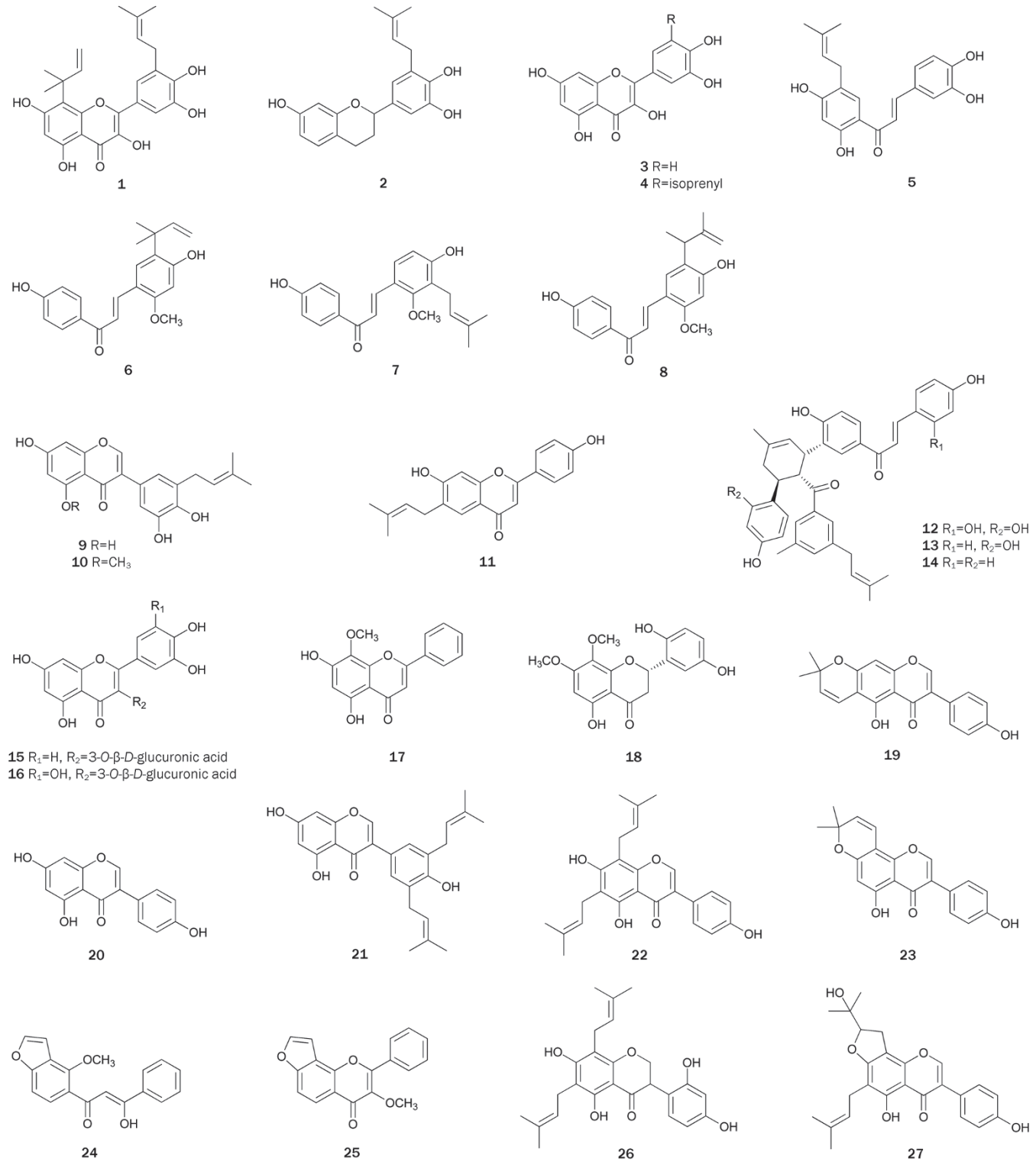


Figure 1. Structures of flavonoids **1–27**.

hydroxyl group is present at C-3″ of the isoprenyl group, exhibited a significantly lower inhibitory activity than **33**. The inhibitory activity of **38** was similar to that of **35**, suggesting that cyclization between a hydroxyl group and one of the isoprenyl groups in ring B may not affect the resultant activity. A group of related flavonoids, commercially available or isolated from other plants[55], was assayed to evaluate the role of the isoprenyl group in ring B in the bioactivity. The

results indicated that substitution of isoprenyl groups in the ring B might be important for inhibitory activity *in vitro*, and introduction of one more hydroxyl group to C-5 of ring A or one of the isoprenyl groups in ring B may be responsible for the loss of activity. Likewise, the presence of isoprenyl groups in ring A seems to be essential for the activity of chalcones[47]. Further studies on the EtOAc-soluble extract of the root bark of *E mildbraedii* led to the isolation of flavonoids **40–45**[48]. With the exception of **43**, which has an isoprenyl group in ring A, the other flavonoids inhibited PTP1B *in vitro* with IC_{50} values ranging from 5.5±0.3 to 42.6±2.4 μmol/L, thus demonstrating that the isoprenyl group in the ring B played an important role in suppressing PTP1B. Recently, flavonoid **33** was synthesized as an inhibitor of prostate cancer and MMP-2 expression[56]. The first synthesis of other flavonoids, such as **35**, **39**, **40**, and **45**, has also been reported[40, 57–59] (Figure 2).

Abyssinoflavanones V–VII **46–48**, together with sigmoidins A-C **49–51**, F **52**, abyssinins I **53**, II **44**, 5-deoxyabyssinin II **54**, 3′-prenylnarringenin **55**, abyssinone-VI **56**, licoagrochalcone A **57**[49], flavonoids **58–73**[50], flavanones **74-79** with a dihydrofuran moiety, erylatissin C **80**, abyssinin III **81**[51], and flavanones **82–93**[52] were isolated from the stem bark of *E abyssinica*. Among the isolates **46–57**, compounds **47–50** and **52–57** strongly inhibited PTP1B in *in vitro* assays with IC_{50} values ranging from 14.2±1.7 to 26.7±1.2 μmol/L. Flavonoids **58**, **60**, **62**, **63**, **65**, and **66** exhibited inhibitory effects on PTP1B in *in vitro* assays with IC_{50} values ranging from 13.9±2.1 to 19.0±1.8 μmol/L. Additionally, compounds **59**, **61**, **64**, and **67–71** with 2,2-dimethylpyrano ring(s), in which isoprenyl and/or methoxyl groups are absent, showed very weak inhibitory effects. Flavonoids **74**, **75**, **77**, and **79–81** inhibited PTP1B in a dose-dependent manner, with IC_{50} values ranging from 15.2±1.2 to 19.6±2.3 μmol/L. Flavonoids **74** and **77** with the isoprenyl group at C-3′, and **75** with methoxyl group at C-3′ exhibited stronger inhibitory activity (IC_{50} 15.2±1.2, 17.9±2.6 μmol/L, respectively) than **76** and **78** (IC_{50}>60 μmol/L, respectively) without an isoprenyl or a methoxyl group. Among flavonoids **82–93**, most flavanones exhibited potent inhibitory effects on PTP1B (IC_{50} ranging from 14.9 to 35.8 μmol/L) except for **83**, **86**, **90**, and **92** (IC_{50}>72 μmol/L). All of these results indicated that the significant inhibitory activity of these flavonoids could be attributed to the isoprenyl or methoxyl groups in the ring B, while the presence of a polar functionality (*eg*, hydroxyl group) caused the activity to decrease. However, the 2,2-dimethylpyrano or dihydrofurano residue was considered to have almost no effect on the inhibitory activity when the isoprenyl or methoxy groups exist in the ring B. Treatment of CHO/*h*IR cells with **75** resulted in a time-dependent increase of the insulin-induced tyrosine phosphorylation of IR and IRS, and cytotoxicity was not observed in cells treated with over 20 μmol/L of **75** for 48 h. These results indicated that **75** might also act in the cells as an insulin-sensitizing agent. Given that those

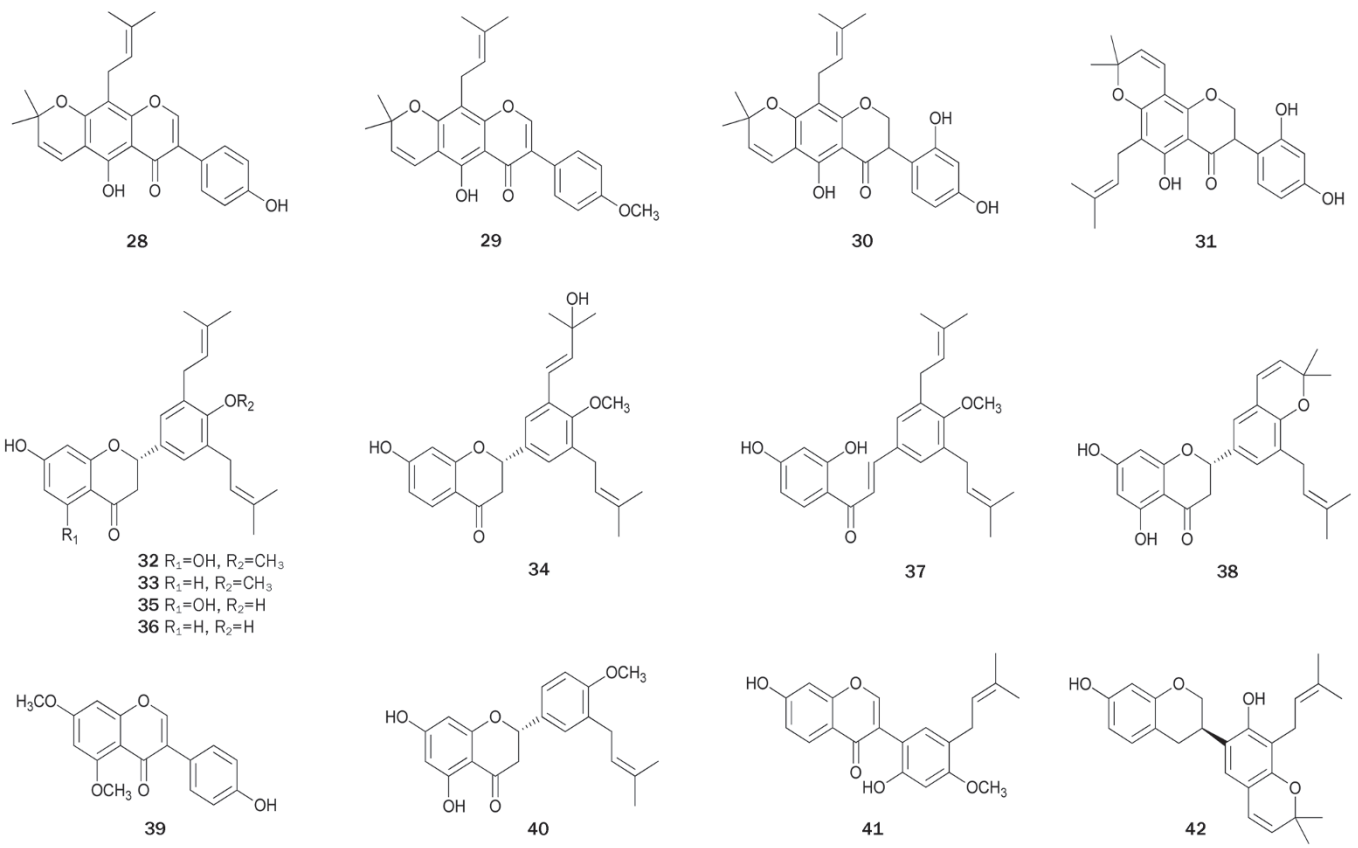


Figure 2. Structures of flavonoids **28–42**.

flavonoids showed promising bioactivity, some have been synthesized. The complete synthesis of **46** was first achieved through C-prenylation, selective protection of the phenolic hydroxyl group, aldol condensation, cyclization and deprotection starting from the inexpensive materials 4-hydroxybenzaldehyde and 2,4,6-trihydroxyacetophenone with a total yield of 24%[60]. Rao *et al* prepared **83** by condensing 2,2-dimethyl chrom-3-6-carboxaldehyde with protected resacetophenone under phase transfer conditions followed by deprotection and cyclization[61]. In 2006, abyssinone II **84** was synthesized via condensation of the aldehyde with an *o*-hydroxyacetophenone under Claisen-Schmidt conditions followed by cyclization and deprotection[62]. Using a synthetic procedure similar to the one described above, Maiti *et al* synthesized **87**, an analog of **84**[63] (Figure 3).

Bioassay-guided fractionation of the EtOAc extract of the stem bark of *E abyssinica* resulted in the isolation of nine pterocarpan derivatives **94–102**, which showed inhibitory activity[53]. Compounds **94**, **96**, **98**, **99**, and **101** exhibited inhibitory activity with IC_{50} values ranging from 4.2±0.2 to 19.3±0.3 μmol/L, and showed strong cytotoxic activities against MCF7, MCF7/TAMR, MCF7/ADR and MDA-MB-231 breast cancer cell lines with IC_{50} values from 5.6±0.7 to 28.0±0.2 μmol/L. Additionally, the other pterocarpan derivatives were weakly active or not active against PTP1B and cancer cell lines. Thus, the antitumor activity of **94**, **96**, **98**, **99**, and **101** was possibly attributed to their PTP1B inhibitory effects. From the MeOH extract of the stem bark of *E lysistemon*, other pterocarpan derivatives **103–114** were isolated[54]. All of the isolates, with the exception of **105**, **108**, and **113**, inhibited PTP1B activity with IC_{50} values ranging from 1.01±0.3 to 18.1±0.9 μg/mL. The diisoprenylated **114** (IC_{50}=1.01±0.3 μg/mL) had the strongest activity. Compounds **104**, **111**, **112**, and **114** were highly active compared to the weak **103**, **106**, and **107** compounds, which only have a pyran ring. These results suggested that isoprenylation of ring A and/or ring D played an important role in PTP1B inhibitory properties. Phaseollin **107** was synthesized by Mohamed *et al* in 1987[64] (Figure 4).

From the MeOH extract of plant *Selaginella tamariscina*, used to treat infectious disease and malignant tumors, amentoflavone **115** was obtained and characterized as a noncompetitive PTP1B inhibitor (IC_{50} value of 7.3±0.5 μmol/L and K_i value of 5.2 μmol/L)[65]. Treatment with **115** of 32D cells overexpressing the IR resulted in a dose-dependent increase in tyrosine phosphorylation of IR, possibly through inhibition of PTP1B to enhance insulin-induced intracellular signaling.

The leaf of *Morus* sp has been used in traditional Chinese medicinal to treat diabetes mellitus, and 'Sang-Bai-Pi', the root bark of the same plant, is also well known as a Chinese crude drug. From the extract of 'Sang-Bai-Pi', sanggenons C **116**, G **117**, and kuwanon L **118** were isolated[66]. Compounds **116–118** inhibited PTP1B (IC_{50} values ranging from 1.6±0.3 to 16.9±1.1 μmol/L) with good selectivity over other PPs, expecially **116** and **118**, which showed no inhibitory effects toward VHR and PP1 at levels up to 50 μmol/L. In addition, sanggenons **116** and **117** inhibited PTP1B in the mixed-type manner (Figure 5).

Bromophenols

The marine environment is a rich source of bromophenols, which exhibit interesting and useful biological activities, including feeding deterrent, antimicrobial, and radical-scavenging activities[67]. Several species of marine algae are found to contain bromophenols with PTP1B inhibitory activity.

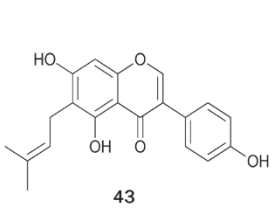
Bromophenol **119**, isolated from the red alga *Polysiphonia urceolata* collected at the coast of Weihai, China, showed potent inhibition against PTP1B with an IC_{50} value of 4.9 μg/mL[68].

Isolation of the ethanol extract from the red alga *Rhodomela confervoides* collected at the coast of Qingdao, China, which displayed anti-hyperglycemic effects of on STZ-induced diabetes in male Wistar rats fed with high fat diet, produced four bromophenols **120–123**. All four bromophenols **120–123** showed significant inhibitory activity with IC_{50} values ranging from 0.84 to 2.4 μmol/L, which might be responsible for the *in vivo* anti-hyperglycemic activity of the extract[69]. Bromophenols **124–126**, isolated from algae *R confervoides* collected at the coast of Qingdao, China, and *Leathesia nan* collected at the coast of Weihai, China, showed significant inhibitory activity with IC_{50} values ranging from 2.8 to 4.5 μmol/L[70]. Additional studies on chemical constituents of *R confervoides* and *P urceolata* produced two more PTP1B inhibitors with bromophenol structures **127** and **128**[67]. Bromophenol **120** was synthesized in four steps with an overall yield of 14.7%[71]. Bromophenol **122** and its related analogs were synthesized to test for their antifungal activity[72]. Bromophenols **123**, **127** and **128** were synthesized in eight steps with overall yields of 14.4%, 14.4%, and 18.2%, respectively, via a practical approach using bromination, Wolff-Kishner-Huang reduction and a Friedel-Crafts reaction as key steps[67]. Bromophenol **123** exhibited better inhibitory activity than **127** and **128**, suggesting that the long side chain at the R_1 position and the bromine atom at the R_2 position enhanced the biological inhibitory activity.

Bromophenols **129** and **130**, isolated from the Hainan red alga *Laurencia similis*, showed strong inhibitory activity with IC_{50} of 2.97 and 2.66 μmol/L, respectively[73]. Bromophenols **131–135**, together with **124**, were isolated from the red alga *Symphyocladia latiuscula,* collected from the Weihai coastline of Shandong Province. Bromophenols **132–134** showed potent activity with IC_{50} values of 3.9, 4.3, and 3.5 μmol/L, respectively[74]. The first synthesis of **133** was reported by Balaydin *et al*[75] (Figure 6).

Phenolic acids

Caffeic acid **136** is a widespread phenolic acid that occurs naturally in many agriculture products such as fruits, vegetables, wine, olive oil, and coffee[76]. Isolated from the aerial parts of *Artemisia minor*, phenolic acid **136** was found to be a PTP1B inhibitor with an IC_{50} value of 3.06 μmol/L[77]. Together with **136**, another three phenolic acids **137**[35], **138** and **139**[78] were isolated from the leaves of the plant *Cyclocarya paliurus* and the fruiting body of the fungus *Phellinus linteus*, respectively. Compounds **137-139** had inhibitory activity with IC_{50} values of 16.64±0.04[35], 52.9±3.6 and 26.2±1.9 μmol/L[78], respectively. 2-Acetylaminogentisic acid **140**, isolated from fungus *Strepto-*



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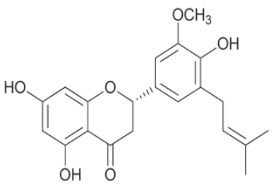

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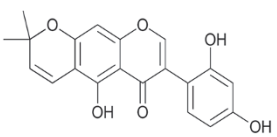

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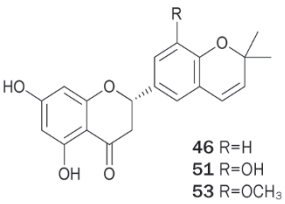
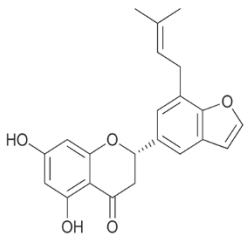


46 R=H
51 R=OH
53 R=OCH_3



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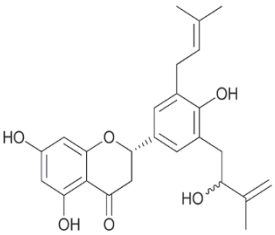

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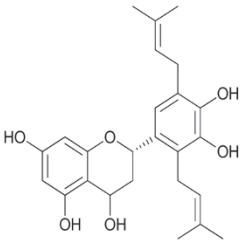

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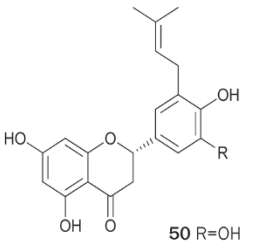
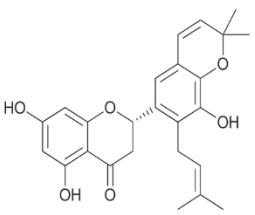


50 R=OH
55 R=H



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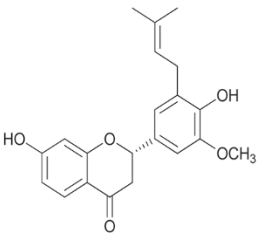

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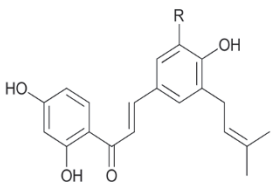
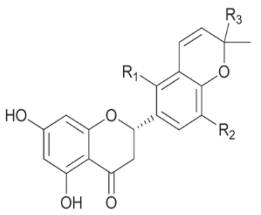
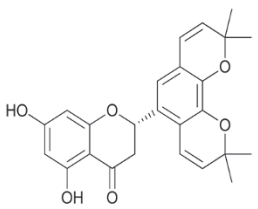


56 R=isoprenyl
57 R=H



58 R_1=isoprenyl, R_2=OH, R_3=CH_3
59 R_1=H, R_2=OH, R_3=CH_2OH
60 R_1=H, R_2=OCH_3, R_3=CH_2OH



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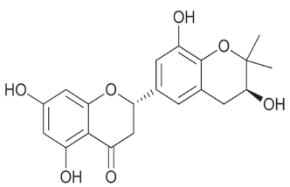

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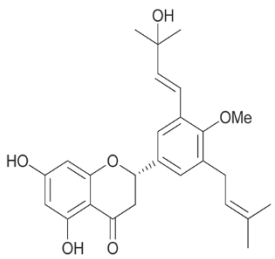

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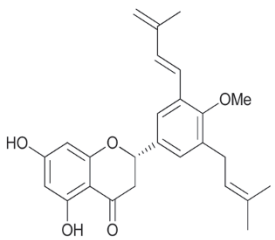

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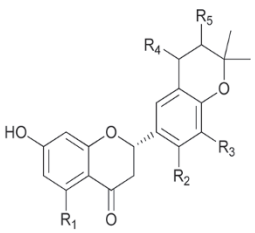
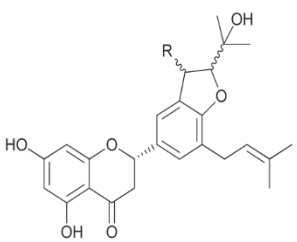
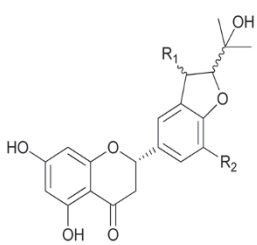


62 R_1=R_5=OH, R_2=R_4=H, R_3=isoprenyl
63 R_1=R_5=OH, R_2=R_4=H, R_3=OCH_3
64 R_1=R_4=R_5=OH, R_2=R_3=H
65 R_1=R_4=R_5=OH, R_2=H, R_3=isoprenyl
66 R_1=R_4=R_5=OH, R_2=isoprenyl, R_3=H
67 R_1=R_3=OH, R_2=R_5=H, R_4=(=O)
68 R_1=R_2=R_4=H, R_3=R_5=OH
69 R_1=R_2=H, R_3=R_4=R_5=OH
71 R_1=R_3=R_4=R_5=OH, R_2=H



74 R_1=H
77 R_1=OH



75 R_1=H, R_2=OCH_3
76 R_1=H, R_2=OH
78 R_1=OH, R_2=OH

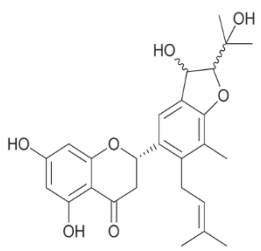


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Figure 3. Structures of flavonoids **43**–**79**.

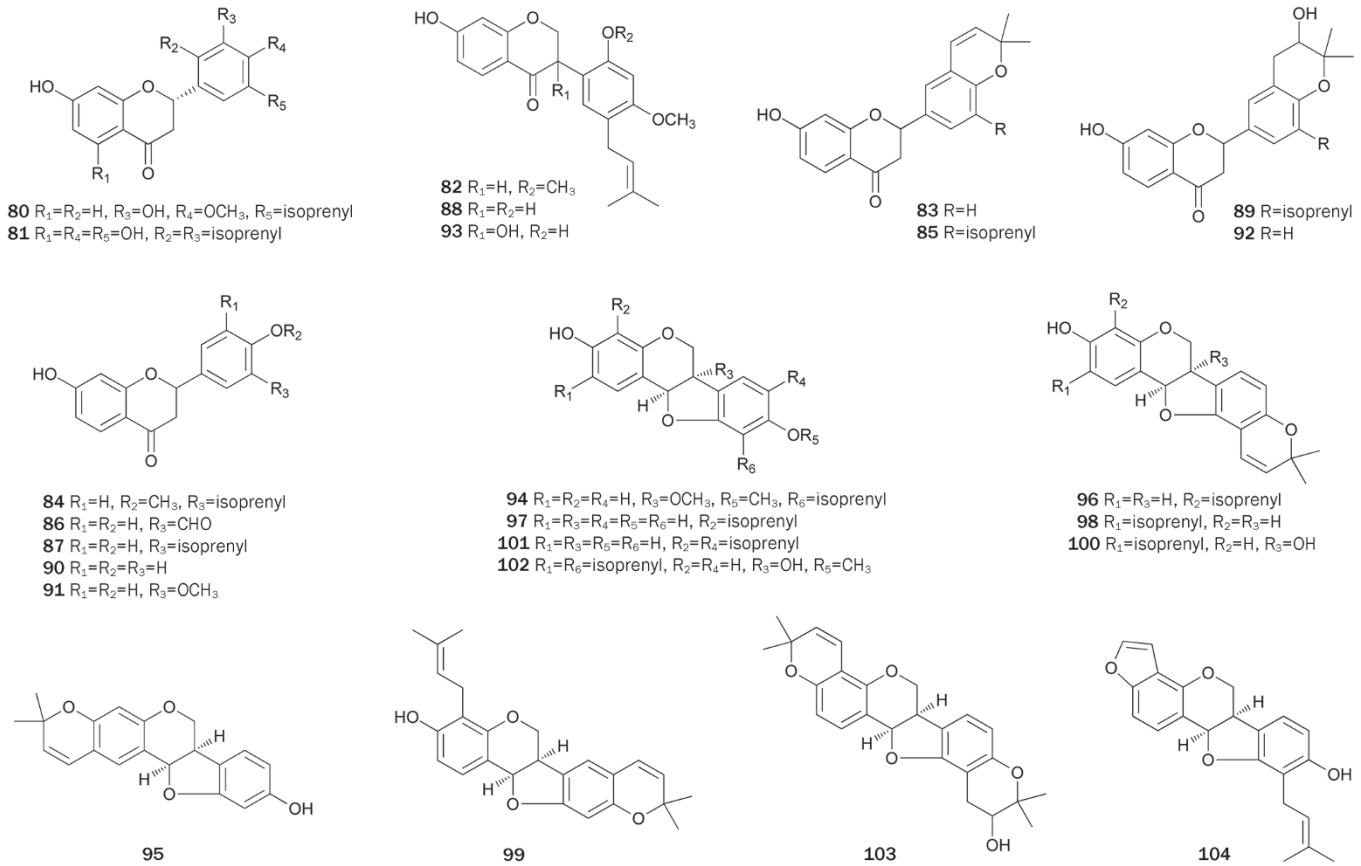

Figure 4. Structures of flavonoids **80–104**.

myces (unknown species), exhibited inhibitory activity with an IC value of 20.4±1.9 μmol/L[79].

PTP1B inhibitors **141** and **142**[80], **143–145**[81], and **146–148**[82], respectively, were isolated from the MeOH extracts of the Antarctic lichens *Lecidella carpathica, Umbilicaria antarctica*, and *Stereocaulon alpinum* by Seo *et al*. Although phenolic acids **143-145** share a similar structural pattern with the monomeric hydroxylbenzoic acid, compound **143** showed the strongest inhibitory effect (IC_{50}=3.6±0.04 μmol/L)[81], suggesting that the molecular size could be an important factor for the activity among these compounds. The fact that the activity of methyl ester derivative of **143** was four-fold weaker than that of **143**, suggests that the acid functionality in **143** was crucial to exhibiting the inhibitory activity. Phenol acids **146–148** exhibited potent inhibitory activity with IC_{50} values of 0.87, 6.86, and 2.48 μmol/L, respectively[82]. The preliminary SAR from **146–148** indicated that the presence of acidic protons was, at least in part, required in the inhibition mechanism, presumably to provide hydrogen-bonding sites that were relevant to the interaction with PTP1B. Kinetic analysis suggested that **142** inhibited PTP1B activity in a competitive manner[80], while **143**, **146**, and **147** inhibited PTP1B activity in non-competitive manner[81, 82].

KS-506a **149** and KS-506m **150**, both containing sulfur atoms, were PTP1B inhibitors both isolated from the culture of the fungus *Mortierella vinacea*[83]. KS-506a **149** showed potent inhibitory activity with an IC_{50} value of 4.9 μmol/L, while KS-506m **150** showed moderate inhibitory activity (IC_{50}=69.9 μmol/L). Kinetic analysis suggested that 149 was a competitive inhibitor with a K_i value of 2.7 μmol/L. Additionally, both compounds showed no inhibitory effects toward other PPs, such as VHR and PP1, at levels up to 200 μmol/L.

Caloporoside **151**, originally found as a phospholipase C inhibitor isolated from the fungus *Caloporus dichrous*, was totally synthesized in 1998[84]. Later, compound **151** was found to inhibit PTP1B with an IC_{50} value of 1.6±0.8 μmol/L, approximately three-fold in inhibitory activity against Cdc25A[85]. During a bioassay-guided study on the EtOAc extract of a culture broth of the marine-derived fungus *Cosmospora* (unknown species), aquastatin A **152** was isolated as a PTP1B inhibitor with an IC_{50} value of 0.19 μmol/L[86]. Kinetic analyses suggested that **152** competitively inhibited PTP1B and showed modest but selective inhibitory activity against PTP1B over other PTPs, such as TCPTP, SHP-2, LAR, and CD45.

1,2,3,4,6-penta-*O*-galloyl-*D*-glucopyranose **153**, a PTP1B inhibitor (IC_{50}=4.8 μmol/L) isolated from the roots of plant *Paeonia lactiflora*, was shown to act as an insulin sensitizer in human hepatoma cells (HCC-1.2) at 10 μmol/L[87, 88]. Additionally, **153** inhibited TCPTP with an IC_{50} value of 0.07 μmol/L, but did not inhibit LAR and SHP-2 at concentrations below 50

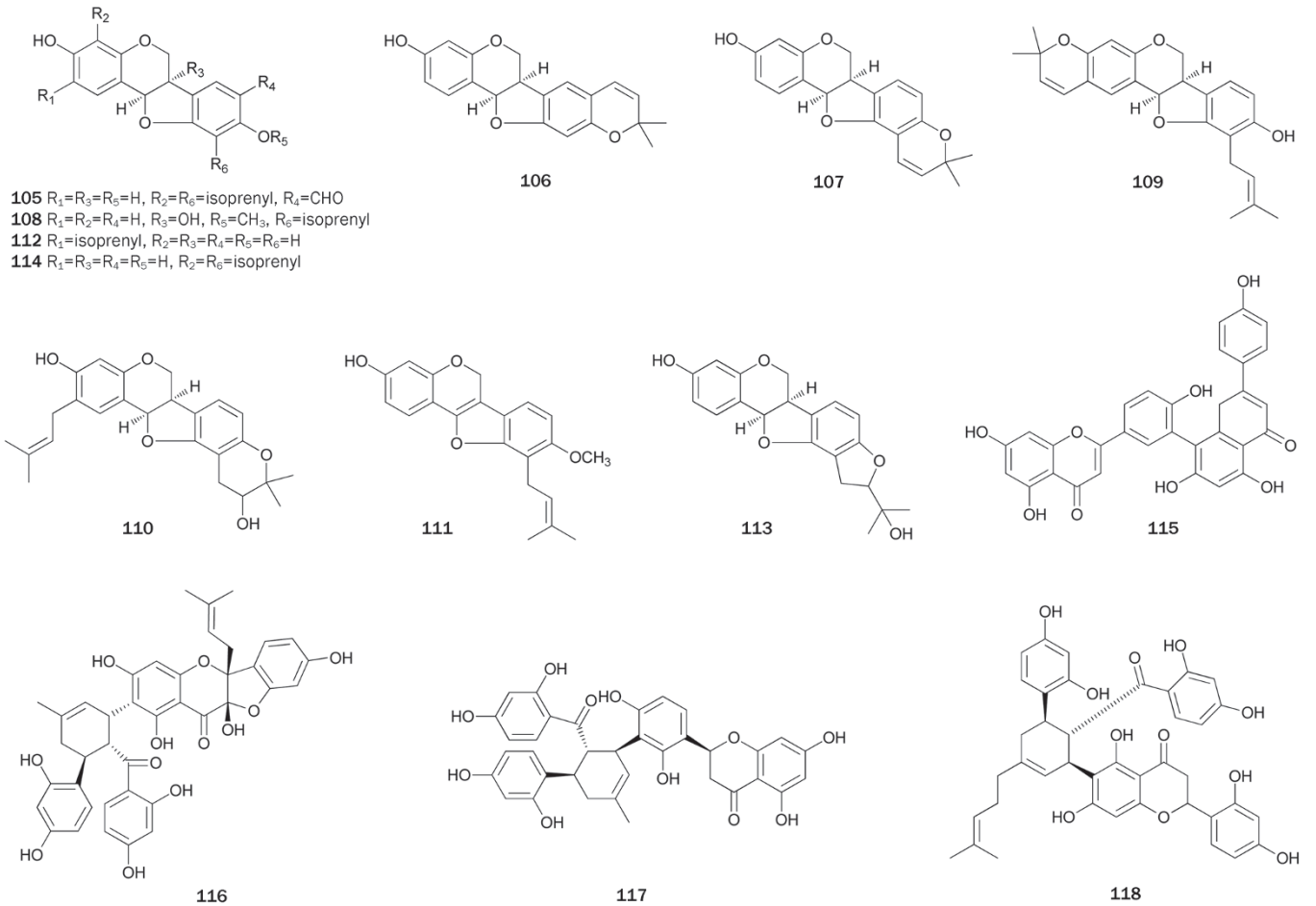

Figure 5. Structures of flavonoids **105–118**.

μmol/L (Figure 7).

Phenolics containing furan or pyran rings

Two 2-arylbenzofuran PTP1B inhibitors, glycybenzofuran **154** and licocoumarone **155**, were isolated from the roots of the plant *Glycyrrhiza uralensis*[33]. Compound **154** showed stronger inhibitory activity *in vitro* with an IC_{50} value of 25.5 μmol/L by a competitive manner.

The bioassay-guided fractionation of 'Sang-Bai-Pi' mentioned above also resulted in isolation of mulberrofuran C **156**, which inhibited PTP1B with an IC_{50} of 4.9±0.2 μmol/L in a mixed-type manner[66]. The bioassay for the inhibitory effects on other PPs showed that **156** had no inhibitory effects toward VHR and PP1 at levels up to 50 μmol/L. Albafuran A **157**, mulberrofurans W **158** and D **159** were isolated from the chloroform-soluble fraction of the plant *Morus bombycis*[34]. An analysis of the inhibition kinetics suggested **157–159** inhibited PTP1B in a mixed-type manner (IC_{50} values ranging from 2.7 to 9.2 μmol/L). The respective lipophilic and hydroxyl groups of **157–159** are considered to play an important role in inhibition of PTP1B.

2-Arylbenzofurans **160–165** were isolated from the plant *Erythrina addisoniae* by Na *et al*[89]. Compounds **160-162** inhibited PTP1B (IC_{50} values ranging from 13.6±1.1 to 17.5±1.2 μmol/L *in vitro* assay) much more strongly than **163–165** (IC_{50} values ranging from 62.7±2.0 to 74.1±1.9 μmol/L), indicating that cyclization between an isoprenyl group and one of the phenolic hydroxyl group in ring B or loss of the isoprenyl group might be responsible for the loss of *in vitro* activity.

Dibenzofuran derivatives 166 and its sulfate adduct **167** were isolated from the green alga *Cladophora socialis*, which was supplied by the Queensland Museum[90]. Both dibenzofurans showed potent inhibitory activity against PTP1B, with IC_{50} values of 3.7 and 1.7 μmol/L. It was speculated that the dibenzofuran and phenyl ring systems at each end of **166** acted as two binding sites with PTP1B, and the phenyl ring in the middle of **166** acted as the linker. The carboxyl group at C-3 and the phenolic hydroxyl group at C-4″ may contribute to the binding, while the presence of more highly acidic sulfate functionality at C-4″ in **167** may enhance its activity (Figure 8).

Usimines A-C **168–170** and usnic acid **171**, were isolated from a MeOH extract of the Antarctic lichen *Stereocaulon alpinum*[91]. The absolute configurations of the chiral centers in **168–170** were determined by comparison of optical rotations and Marfey's derivatization of the mixture from acid hydrolysis. Compounds **168–171** showed inhibitory activity with

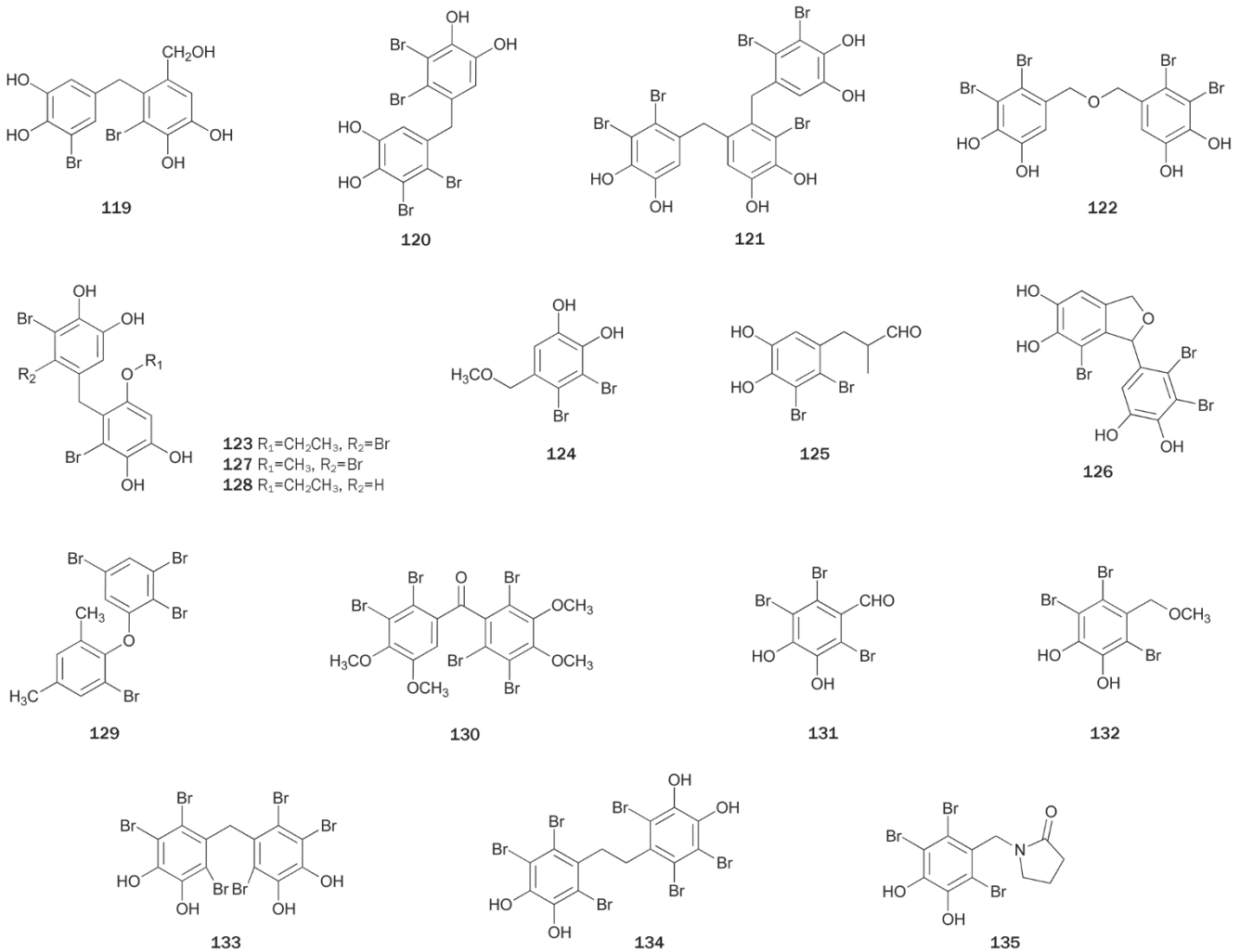

Figure 6. Structures of bromophenols **119–135**.

IC_{50} values ranging from 15.0±0.1 to 27.7±2.1 μmol/L. Synthesis of **171** from commercially available starting material was achieved in two steps, the methylation of phloracetophenone followed by oxidation with horseradish peroxidase[92].

A tricyclic polyketide ortho-quinone, nocardione A **172**, was produced by the fungus *Nocardiam* (unknown species)[93]. Compound **172** showed inhibition of intracellular PTP1B with a similar potency to Cdc25b (IC_{50}=17 μmol/L) and showed weaker inhibition of FAP-1 (IC_{50}=89 μmol/L). Additionally, it showed moderated *in vitro* antifungal and cytotoxic activities. In 2001, two routes for total synthesis of **172** were achieved by starting from a propylene oxide and a 5-benzyloxy-1-tetralone, chloropropene and 5-methoxyl-1-naphthol, respectively[94, 95]. Clive *et al* reported another route based on a method for achieving formal cyclization of a radical onto a benzene ring to synthesized (+)-**172**[96, 97]

Ohioensins A **173**, C **174**, F **175**, and G **176** were isolated from the MeOH extract of the Antarctic moss *Polytrichastrum alpinum*[98]. All these compounds showed inhibitory activity with IC_{50} values ranging from 3.5±0.2 to 7.6±0.7 μmol/L. Kinetic analysis of PTP1B inhibition by **175** suggested that these benzopyrans inhibited PTP1B activity in a non-competitive manner.

Chemical investigation of the species of fungus *Phelliuns* resulted in the isolation of several α-pyrone PTP1B inhibitors, such as pyrano[4,3-c]isochromen-4-one derivatives, phelligridins H **177** and I **178** from *P igniarius*[99], and hispidin derivatives, phelligridimer A **179**, davallialactone **180**, hypholomine B **181**, interfungins A **182** and inoscavin A **183** from *P linteus*[78]. Phelligridins **180** and **181** inhibited PTP1B with IC_{50} values of 3.1 and 3.0 μmol/L, respectively, and also exhibited antioxidant activity against rat liver microsomal lipid peroxidation. Compounds **180** and **181** with a hispidin moiety exhibited higher inhibitory activity than **179**, **182**, and **183** (Figure 9).

Coumarins and lignans

Coumarin is a fragrant chemical compound of benzopyrone found in many plants. It has a distinctive odor which has led to its use as a food additive and ingredient in perfume. Natural coumarin displays extensively interesting bioactivities,

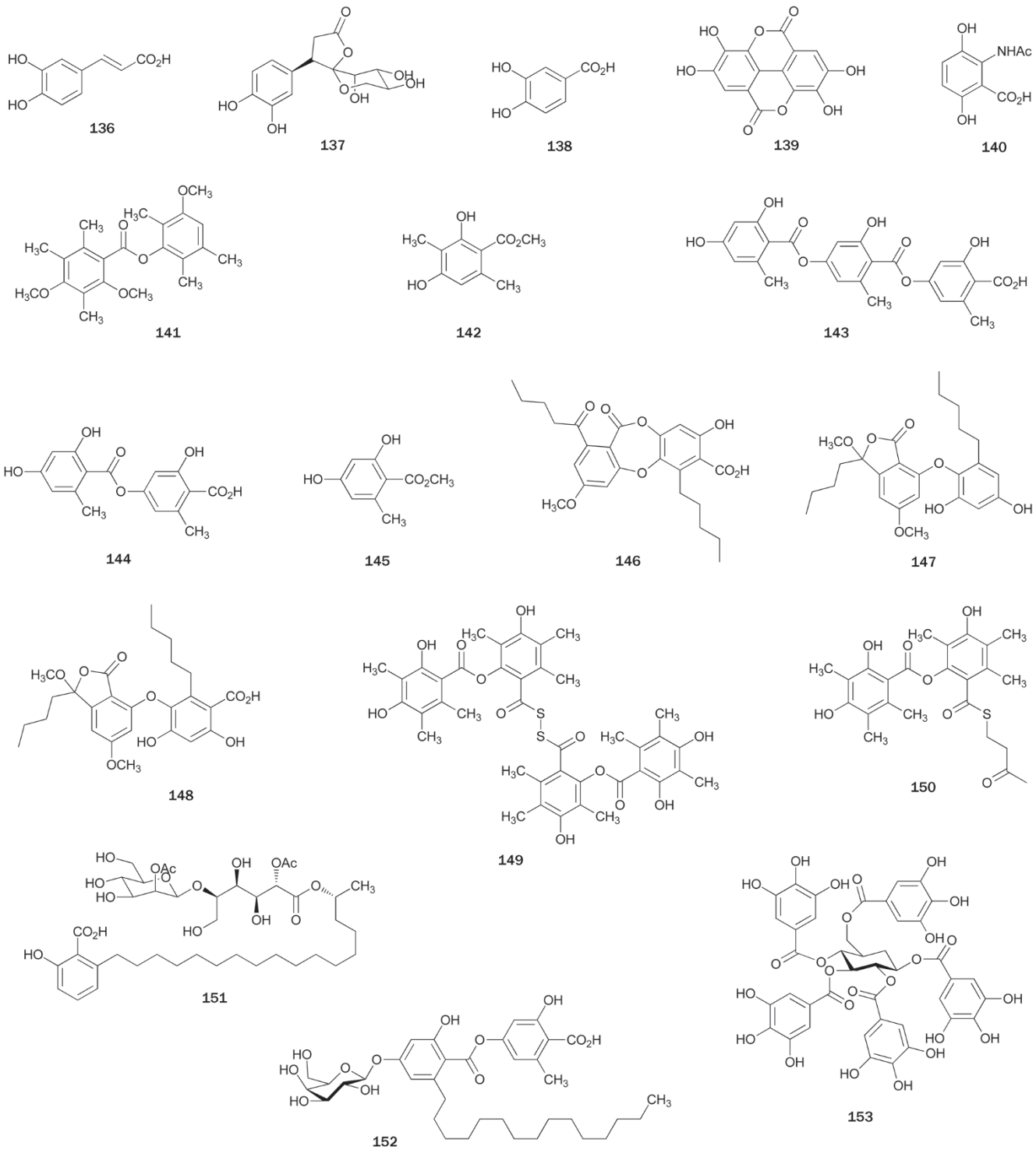

Figure 7. Structures of phenolic acids **136–153**.

intriguing chemists and medicinal chemists for decades to explore their applicability as drugs[100–102]. Lignans are phenylpropanoid demers, where the phenylpropane units are linked by the central carbon (C8) of their side chains. Lignans also have a number of medically important biological activities, *eg*, antitumor, antimitotic and antiviral properties[103]. However, there are only a few reports about natural coumarins or lignans with PTP1B inhibitory activity.

The seed of the plant *Psoralea corylifolia* is a commonly used traditional Chinese medicine against gynecological bleeding, vitiligo and psoriasis. Bioassay-guided fractionation of the EtOAc-soluble extract of *P corylifolia* produced psoralidin **184**,

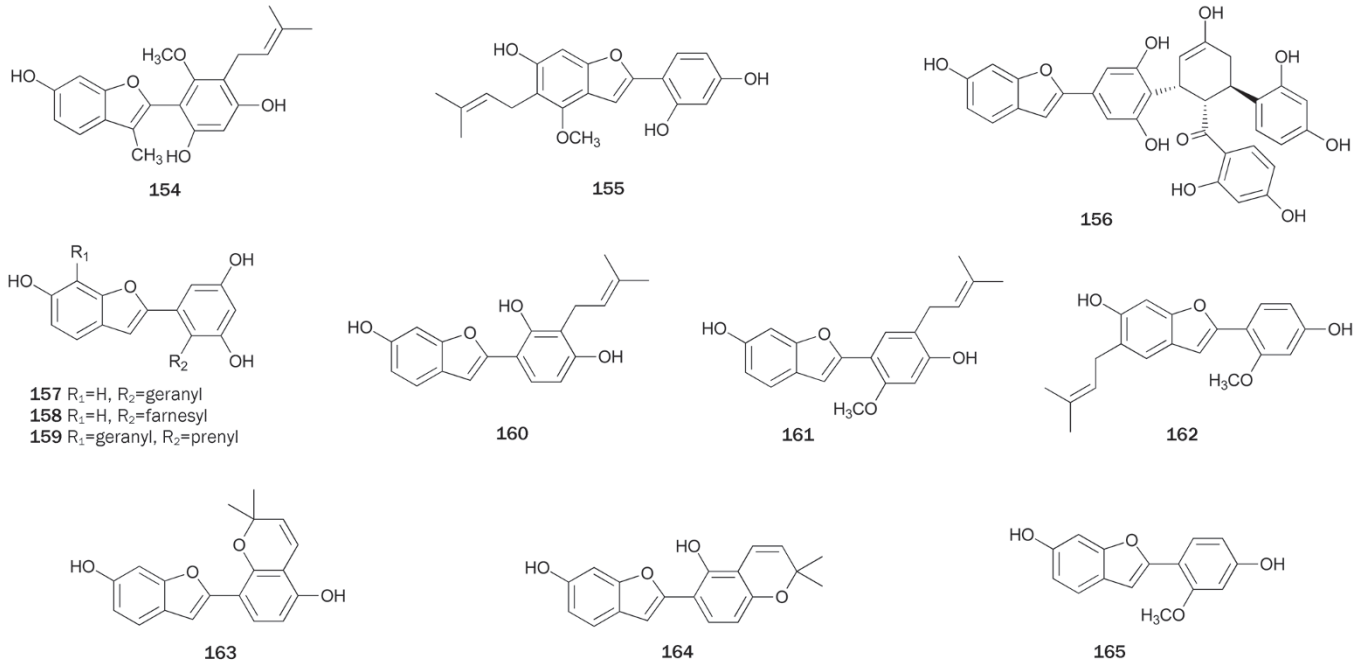

Figure 8. Structures of phenolics containing furan or pyran ring **154–165**.

which is a non-competitive PTP1B inhibitor with an IC_{50} value of 9.4±0.5 μmol/L that showed no inhibitory effects toward VHR and PP1 at levels up to 100 μmol/L[104]. Chemical studies on the roots of plant *Fraxinus rhynchophylla* (Qinpi), a traditional Chinese herbal drug used as anti-inflammatory agent, led to the isolation of a coumarin-secoiridoid hybrid glycoside, fraxisecoside **185**. Compound **185** exhibited moderate inhibitory activity (IC_{50}=21 μmol/L) and inhibited the proliferation of the lymphocyte T and B cells[105]. Glycycoumarin **186**, isolated from the roots of the plant *G uralensis*, showed weak inhibitory activity with an IC_{50} value of 183.9±4.5 μmol/L[33]. A based-catalyzed condensation of phenyl acetate with acid chloride, followed by intramolecular cyclization and microwave-assisted cross-metathesis reaction, led to the first total synthesis of **184**[106].

Bioassay-guided fractionation of the MeOH extract of plant *Myristica fragrans* Houtt (Myristicaceae) afforded *meso*-dihydroguaiaretic acid **187** and otobaphenol **188**[107]. Both compounds inhibited PTP1B with IC_{50} values of 19.6±0.3 and 48.9±0.5 μmol/L, respectively, in a non-competitive manner. Compound **187** was reported to increase the tyrosine phosphorylation of 32D cells overexpressing the IR in a dose-dependent manner, possibly through the inhibition of PTP1B activity. 1,4-Benzodioxane lignan **189**, isolated from the MeOH extract of the plant *Artemisia minor* collected from Tibet, inhibited PTP1B with an IC_{50} of 1.62 μg/mL[108] (Figure 10).

Miscellaneous

Bakuchiol **190**, isolated from the extract of the seeds of the plant *Psoralea corylifolia*, was found to inhibit PTP1B in a dose-dependent manner with an IC_{50} value of 20.8±1.9 μmol/L and with good selectivity against other PPs, such as VHR and PP1 (IC_{50}>100 μmol/L)[104]. The first enantiocontrolled synthesis of **190** was completed by starting from (S)-*O*-benzylglycidol[109]. Later, several simple and convenient methods were reported for the total synthesis of **190**[110-114].

A study on the constituents of the mangrove plant *Lumnitzera racemosa* produced two alkylphenols **191** and **192**[115]. Both alkylphenols showed inhibitory activity with IC_{50} values of 13.38±1.98 and 10.40±0.88 μmol/L, respectively. Alkylphenol **192** had been synthesized in 1989 to test for cytotoxicity against the KB cell lines (ED_{50}=2.4 μmol/mL)[116].

Curcumin **193**, the principal constituent of the rhizomes of the plant *Curucma longa*[117], was found to inhibit PTP1B and subsequently improve insulin and leptin sensitivity in the liver of rats, which protects against fructose-induced hypertriglyceridemia and hepatic steatosis[118]. Compound **193** was prepared by condensing dimethyl malonate with vanillin in the presence of B_2O_3 and $(BuO)_3B$ to prevent Knoevenagel condensation[119, 120].

4-Di-*O*-β-*D*-glucopyranoside **194**, isolated from the leaves of the plant *Cyclocarya paliurus*, showed inhibitory activity against PTP1B with an IC_{50} value of 10.50±2.67 μmol/L[35].

Physcion **195**, isolated from the ethanol extract of the plant *Ardisia japonica*, showed weak inhibitory activity[121]. The total synthesis of **195** was completed in two steps by the regioselective two-fold Diels-Alder reaction[122].

From the EtOH extract of the roots of the plant *Saussurea lappa*, Li *et al* also obtained three PTP1B inhibitors, including chrysophanol **196** and its glucopyranoside derivatives **197** and **198**[123]. The first total synthesis of **196** was achieved by the

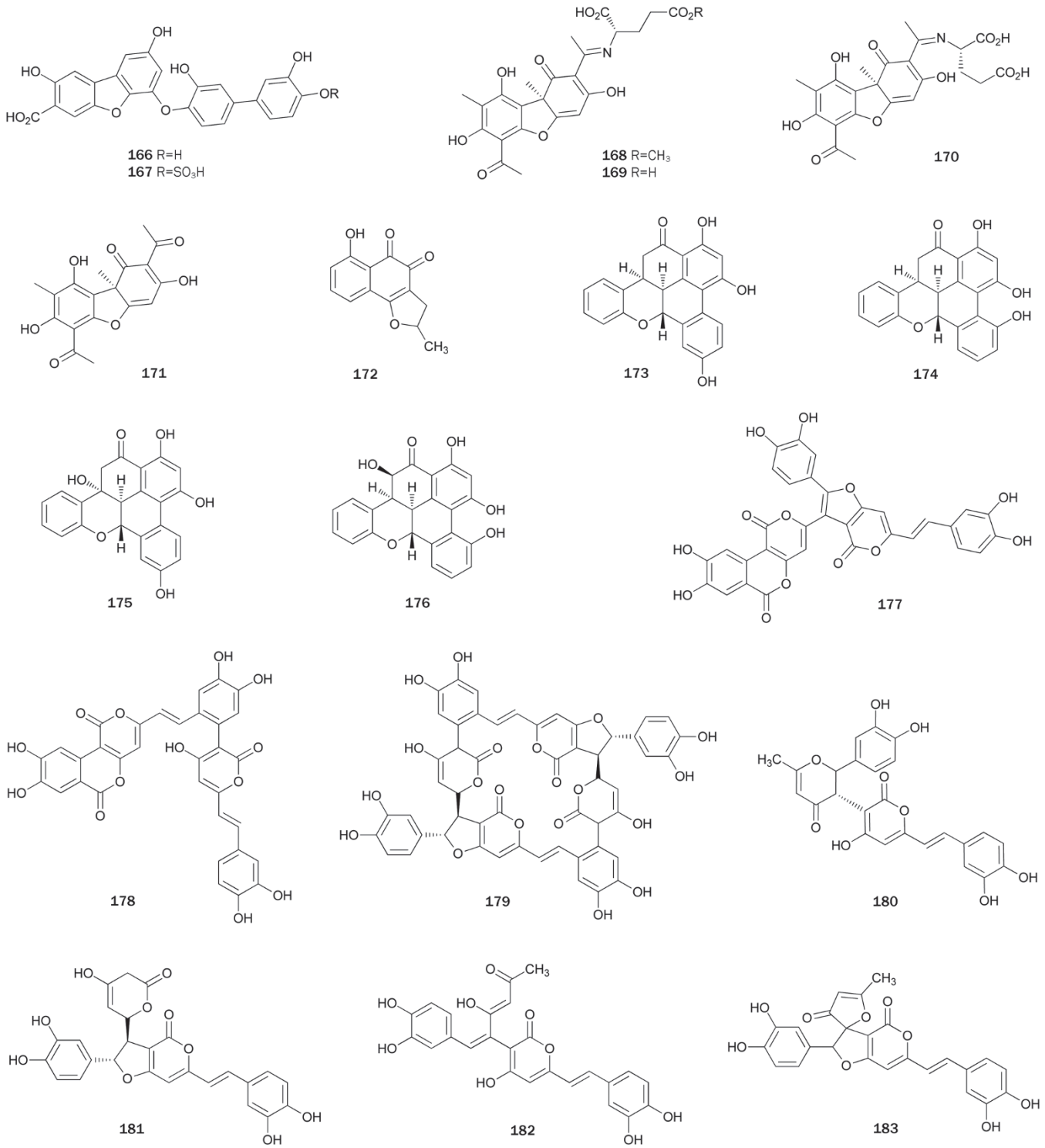

Figure 9. Structures of phenolics containing furan or pyran ring **166–183**.

cycloaddition reaction of 6-methoxy-3-methyl-2-pyrone with naphthoquinone as the key step[124]. In 1990, another synthetic route for **196** using dihydro-oxazoles and Grignard reagents from Mg(Anthracene)$(THF)_3$ was reported[125].

A phenanthraquinone-type metabolite **199**, with inhibitory activity with an IC_{50} value of 38.0±1.5 μmol/L, was isolated from the EtOAc-soluble extract of the plant *Dendrobium moniliforme*[126]. Compound **199** showed no inhibition against PP1 at levels up to 200 μmol/L, but lacked selectivity against PTP1B over VHR (IC_{50}=3.0±1.5 μmol/L).

Grecocycline B **200**, an angucycline with a thiol substitution at C-6a, was isolated from fungus *Streptomyces* (unknown spe-

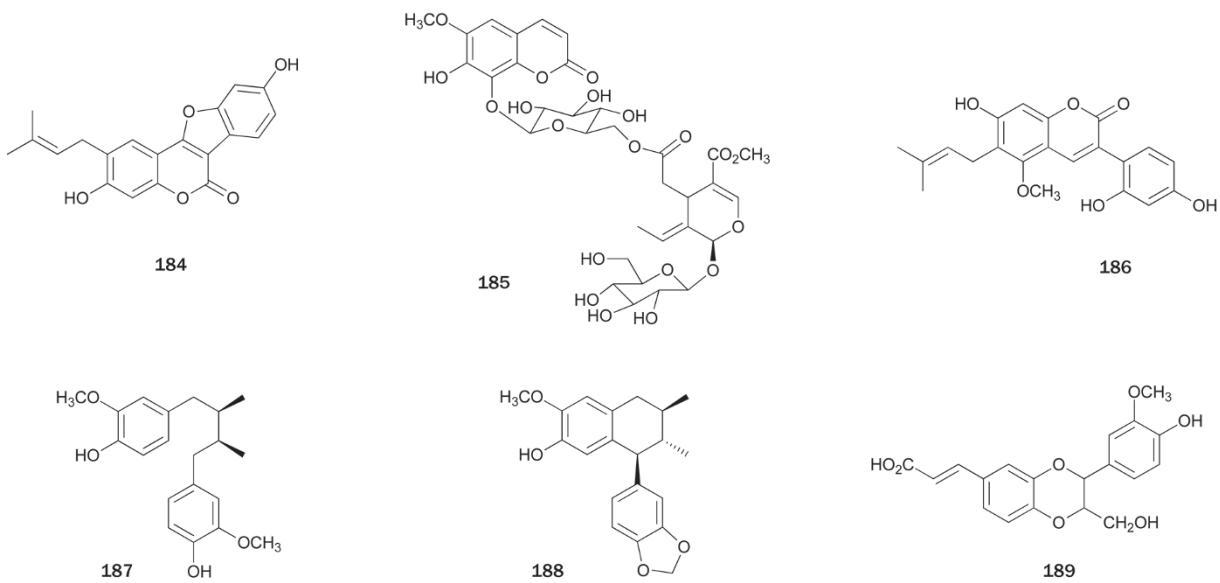

Figure 10. Structures of coumarins and lignans **184–189**.

cies)[127]. Compound **200** was reported to exhibit strong inhibitory activity with an IC_{50} value of 0.52±0.17 μmol/L. The free SH group in the C-6a position is proposed to be responsible for the irreversible inhibition of PTP1B (Figure 11).

Terpenes

Terpenes are a large and varied class of organic compounds produced by a wide variety of plants, animals, and marine organisms. Terpenes, which are derived biosynthetically from units of isoprene (C_5H_8), are classified sequentially by size as hemiterpenes, monoterpenes, sesquiterpenes, diterpenes, sesterterpenes, triterpenes, tetraterpenes, and polyterpenes. Naturally occurring terpenes usually display remarkable pharmacological activities, including antitumor, antimicrobial, antifungal, antiviral, anti-hyperglycemic, anti-inflammatory, and antiparasitic activities as well as a skin permeability effect[128, 129]. There are also many terpenes, primarily sesquiterpenes, diterpenes, sesterterpenes, triterpenes, that are found

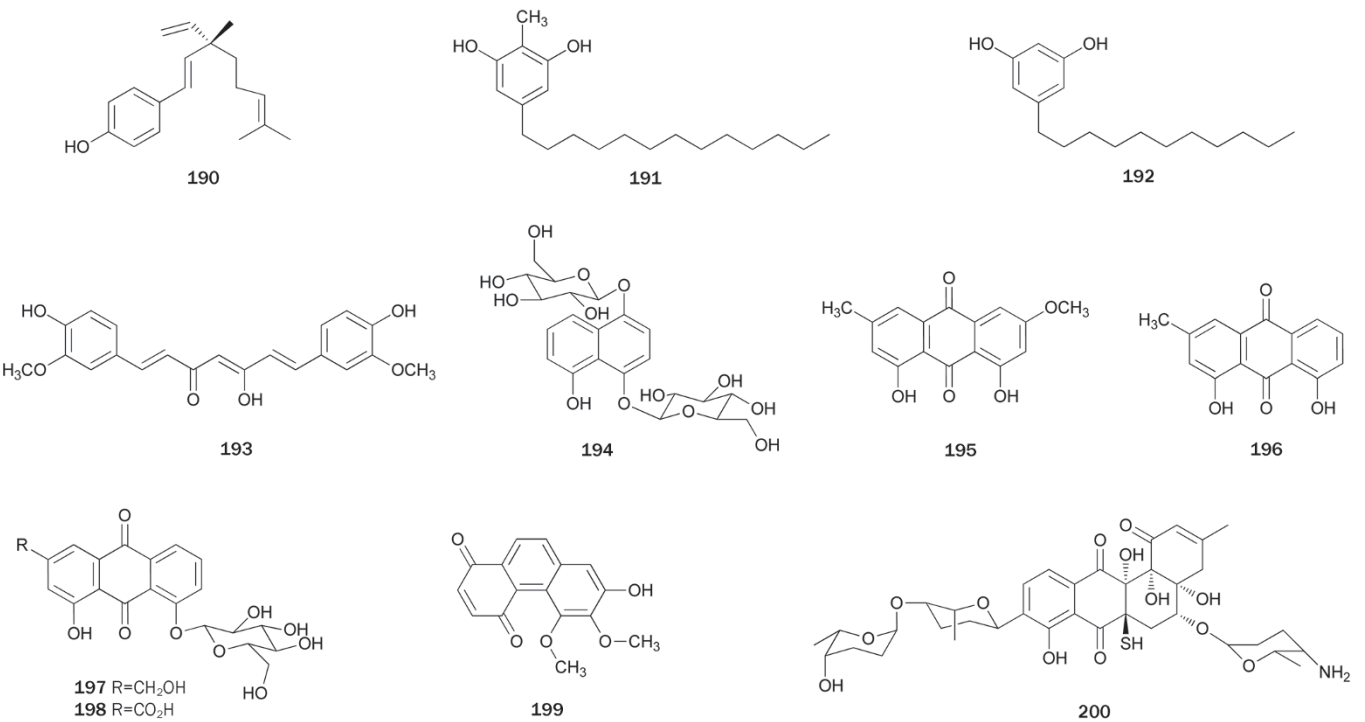

Figure 11. Structures of coumarins and lignans **190–200**.

to act as PTP1B inhibiters.

Sesquiterpenes

The plant *Ligularia fischeri* is common in southwestern China and has been used as a traditional Chinese medicine since ancient time. From the roots of *L fischeri*, an eremophilane sesquiterpene **201** was isolated[130]. Its structure was elucidated by spectroscopic methods including 1D and 2D NMR spectra and was further confirmed by a single-crystal X-ray diffraction analysis. Sesquiterpene **201** exhibited *in vivo* inhibitory activity with an IC_{50} value of 1.34 μmol/L.

O-Methyl nakafuran-8 lactone **202** was isolated from a Hainan sponge *Dysidea* (unknown species) and its structure proposed by spectral data was confirmed by X-ray diffraction analysis[131]. Lactone **202** showed strong inhibitory activity with an IC_{50} value of 1.58 μmol/L. Further studies on several species of *Dysidea* from Hainan produced other sesquiterpene PTP1B inhibitors, such as **203–206** from *D septosa*[132], and **207** and **208** from *D villosa*[133]. Sesquiterpene **203** had the strongest inhibitory effect among **203–206**[132]. Compound **207**, a member of the family of sesquiterpene quinine derivatives with a further rearranged drimane skeketon characterized by the abnormal position of the quinine moiety, showed moderate inhibitory activity and moderate cytotoxicity against HeLa cell lines. Moreover, **208** showed much stronger inhibitory activity with an IC_{50} value of 6.70 μmol/L. More-in-depth pharmacology studies revealed that **208** is a novel slow-binding PTP1B inhibitor with moderate inhibitory selectivity over other PTPs. Further cell based evaluation indicated that **208** could strongly activate the insulin signaling pathway and promote membrane translocation of the glucose transporter 4 (GLUT4) in CHO-K1 and 3T3-L1 cells. Additionally, **208** could significantly increase glucose uptake in 3T3-L1 cells by 2.3 fold[133]. The total synthesis of **204** was accomplished starting from 1-methoxy-4,5,8-endo-trimethylbicyclo[2.2.2]oct-5-en-2-one by a rearrangement strategy[134, 135]. The absolute configuration of **207** was confirmed by total synthesis with the key reaction being a Chiron-mediated asymmetric Aza-Claisen rearrangement[136].

Lactucin **209**, isolated from the root of the plant *Cichorium glandulosum*, was reported to inhibit PTP1B with an IC_{50} value of ≈1 μmol/L[137]. Activity-guided fractionation of a MeOH extract of the roots of the plant *Saussurea lappa* led to the isolation of guaiane sesquiterpenoids, mokko lactone **210** and dehydrocostuslactone **211** with inhibitory activity (IC_{50}=1.41±0.02 and 6.51±0.64 μg/mL, respectively)[138]. The lactones **210** and **211** were first synthesized in 1984[139]. Later, they were synthesized with their related guaianolides, starting from 1-α-santonin, in an effort to examine their SAR as inhibitors as the killing function of cytotoxic T lymphocytes (CTL) and the induction of intercellular adhesion molecule-1 (ICAM-1)[140].

Psidials B **212** and C **213** are sesquiterpenoid-based meroterpenoids representing the new skeleton of the 3,5-diformylbenzyl phloroglucinol-coupled sesquiterpenoid. Compounds **212** and **213** were isolated from the leaves of the plant *Psidium guajava*, which is used in folk medicine as anti-inflammatory and hemostatic agents and for treating pulmonary disease, cough, vomiting, and diarrhea[141]. Their complete structures were elucidated by spectral and chemical methods. Both psidials showed inhibitory activity at the concentration of 10 μmol/L (Figure 12).

Diterpenes

Kaurane-type diterpenes **214–216** were isolated from a MeOH extract of the aerial part of the plant *Siegesbeckia glabrescens*[142]. Diterpene **214**, possesssing an isobutyryloxyl moiety at C-17 of the kaurane skeleton, exhibited the strongest inhibitory activity (IC_{50}=8.7±0.9 μmol/L) among these isolates. Compound **215**, with an acetoxy and an isobutyryloxy group at C-17 and C-18, respectively, inhibited PTP1B with an IC_{50} value of 30.6±2.1 μmol/L, which was less effective than **214**. However, compound **216** (IC_{50}>200 μmol/L), substituted with a hydroxyl group at C-17, exhibited significantly lower activity than **214**, suggesting that an ester moiety at C-17 of the kaurane diterpene is essential for activity. Additionally, **214** and **215** had no inhibitory effects on VHR and PP1 at levels up to 200 μmol/L and kinetic analyses suggested that both compounds are non-competitive inhibitors with K_i values of 9.1 and 31.8 μmol/L, respectively.

The roots and stem barks of the plant *Acanthopanax koreanum* have been traditionally used as a tonic and to treat rheumatism, hepatitis, and diabetes in Korea. Diterpenes **217–224** were isolated from a CH_2Cl_2-soluble extract of the roots of *A koreanum*[143]. Of the isolates tested, diterpene **223**, possessing an isovaleryloxy group at C-17 of kaurane-type, exhibited the most potent inhibitory activity (IC_{50}=7.1±0.9 μmol/L) by a non-competitive manner. Diterpene **224** (IC_{50}>30 μmol/L), with a hydroxyl group substituted at C-16 of **223**, exhibited significantly lower activity than **223**. A similar case was observed between **221** and **222**. These results indicate that substitution of a hydroxyl group at C-16 of kaurane-type diterpenes decreases the inhibitory activity. The pimarane-type diterpene **218** inhibited PTP1B in a dose-dependent manner (IC_{50}=23.5±1.8 μmol/L). However, **217**, with conversion of a carboxyl group at C-19 to a primary alcohol, did not exhibit PTP1B inhibitory activity up to 30 μmol/L, suggesting that a carboxyl group at C-19 of pimarane-type is essential for the activity. Other pimarane-type diterpenes **219** and **220**, with hydroxyl groups at C-7 and C-9, respectively, had no activity at levels up to 30 μmol/L. Another three kaurane-type PTP1B inhibitors **225–227** (IC_{50}=12.6, 200, 21.3 μmol/L, respectively) were isolated from the plant *S orientalis*[144]. Diterpene **218** was synthesized from stevioside via two skeletal rearrangements in nine steps, with a total yield of 9%[145]. An enantioselective synthesis of **221** is described by Ling *et al*[146].

Bioassay-guided fractionation and purification of the MeOH extract of the dried root of the plant *Salvia miltiorrhiza* called 'Dan-Shen' in China, produced three related abietane-type diterpene metabolites, namely isotanshinone IIA **228**, dihydroisotanshinone I **229**, and isocryptotanshinone **230**[147]. Diterpenes **228–230** non-competitively inhibited PTP1B with IC_{50} values of 11.4±0.6, 22.4±0.6, and 56.1±6.3 μmol/L,

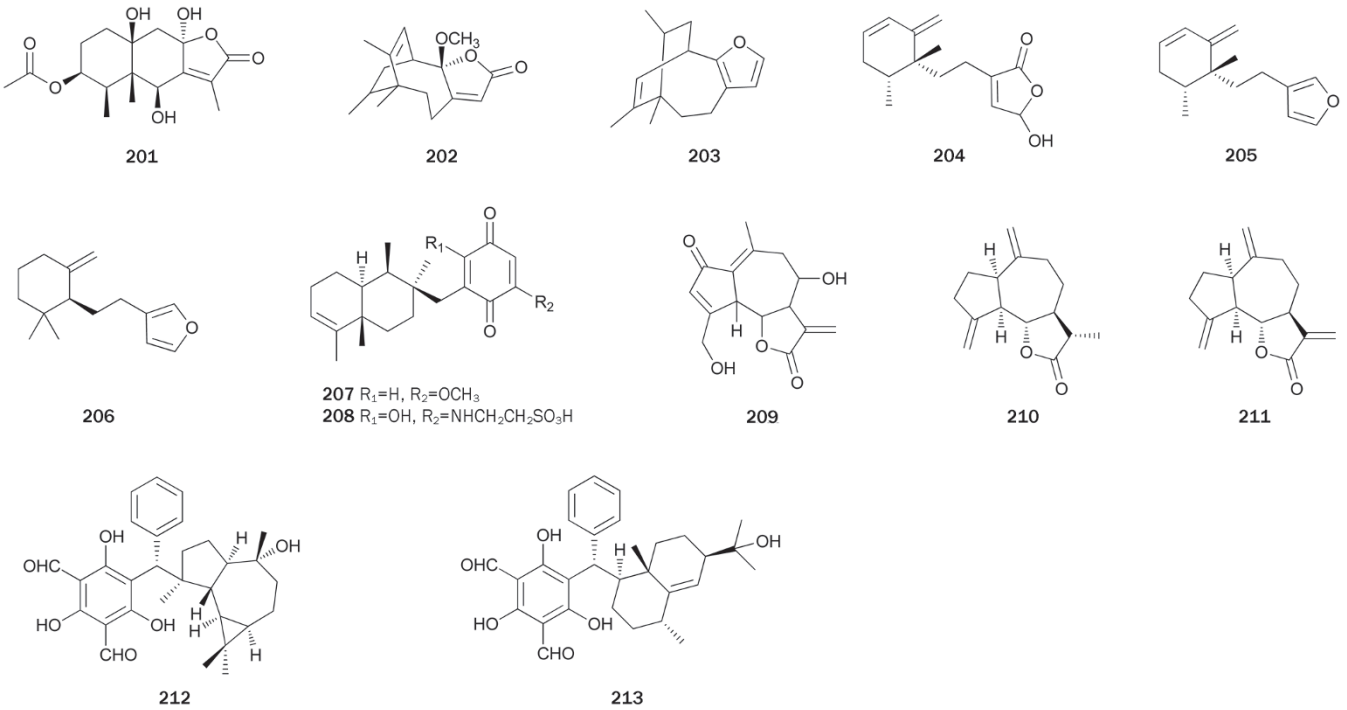

Figure 12. Structures of sesquiterpenes **201–213**.

respectively. Isotanshinone IIA **228** had been prepared as an intermediate to synthesize tanshinones[148], which were also obtained by partial synthesis from 16-hydroxycarnosol[149].

Lipidyl pseudopteranes A **231** and D **232** were isolated from the soft coral *Pseudopterogorgia acerosa* collected from the Bahamas[150]. Their structures represent the first report of a pseudopterane diterpene with a fatty acid moiety. Compounds **231** and **232** exhibited modest inhibitory activity, but were inactive against other PTPs, including LAR, SHP-1, and MKPX. Their lipidyl moiety appears to aid in their ability to diffuse into mammalian cells and inhibit PTP1B (Figure 13).

Sesterterpenes

Hyrtiosal **233**, a sesterterpenoid possessing a novel, rearranged tricarbocyclic skeleton, was isolated from the Okinawan sponge *Hyrtios erectus*[151]. A possible biosynthesis pathway of **233** was proposed in which the olefinic bond of the tricarbocyclic precursor containing a cheilanthane skeleton is oxidized to give an epoxy intermediate. The subsequent rearrangement produces a ring-contracted hyrtiosane skeleton. Sun *et al* found that **233** inhibited PTP1B activity in a dose-dependent, non-competitive manner with an IC_{50} value of 42 μmol/L[152]. Further research showed that **233** displayed potent activity for abolishing the retardation of AKT membrane translocation caused by PTP1B overexpression in CHO cells, dramatically enhanced the membrane translocation of the key glucose transporter Glut4 in PTP1B-overexpressed CHO cells, and effectively facilitated insulin inhibition of Smad2 activation. Moreover, hyrtiosal **233** was found to inhibit HIV-1 integrase from binding to viral DNA by a new inhibitor binding site[153]. The absolute configuration of natural (-)-**233** was confirmed by total synthesis, together with its C-16 epimer, starting from sclareol in moderate yield[154, 155]. Lunardi *et al* also completed the total synthesis of (-)-**233** along with its enantiomer (+)-**233** and their C-16 epimers starting from 30% ee copalic acid[156].

Bioassay-directed separation of the extract from the sponge *Thorectandra* (unknown species) collected in Papua New Guinea led to the isolation of luffariellolide-type sesterterpenoids, luffariellolide **234** and dehydroluffariellolide diacid 235[157]. Both compounds had no inhibitory activity against VHR at concentrations as high as 40 μg/mL and they lacked inhibitory selectivity against PTP1B over Cdc25B. The first synthesis of **234** was achieved by a convergent pathway involving sp^3–sp^3 cross-coupling and silyloxyfuran oxyfunctionalisation as key steps[158].

Sulfircin **236**, a sesterterpene sulfate mentioned at the beginning of this paper, was found to act as a nonspecific PPs inhibitor with moderate PTP1B inhibitory activity (IC_{50}=29.8 μmol/L) as well as activity against other PTPs (VHR, Cdc25A) with slightly better potencies[16, 159] (Figure 14).

Triterpenes

Five oleanane-type PTP1B inhibitors, including 3α,24-dihydroxyolean-12-en-27-oic acid **237**, 3-oxoolean-12-en-27-oic acid **238**, 3β-hydroxyolean-12-en-27-oic acid **239** (β-peltoboykinolic acid), 3β-hydroxyurs-12-en-27-oic acid **240**, and 3β,6β-dihydroxyolean-12-en-27-oic acid **241** (astilbic acid) were isolated from a MeOH extract of the rhizomes of the plant *Astilbe koreana*[160]. Of the isolates, **238** and **239** exhibited the strongest inhibitory activity with IC_{50} values of 4.9±0.4

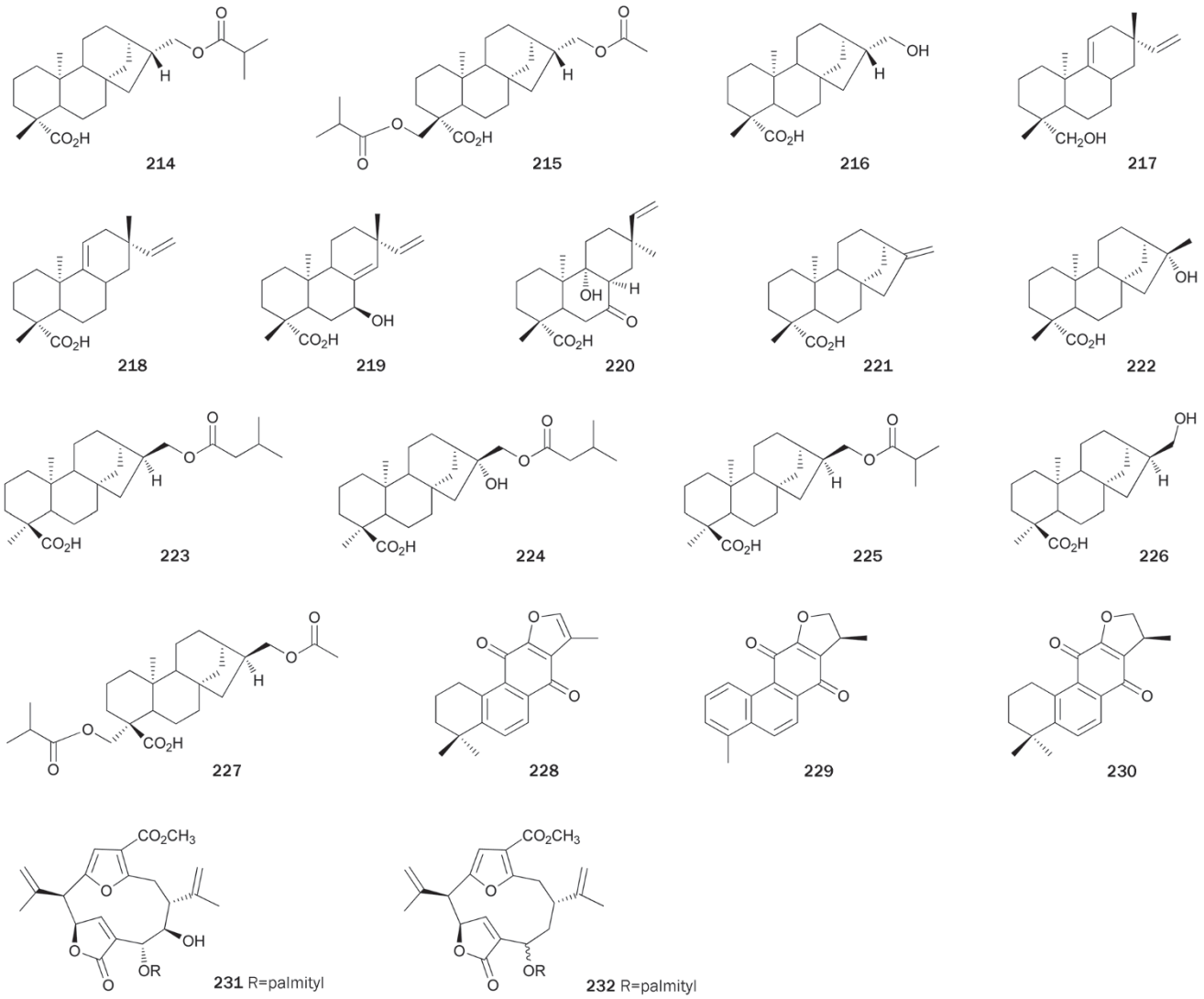

Figure 13. Structures of diterpenes **214–232**.

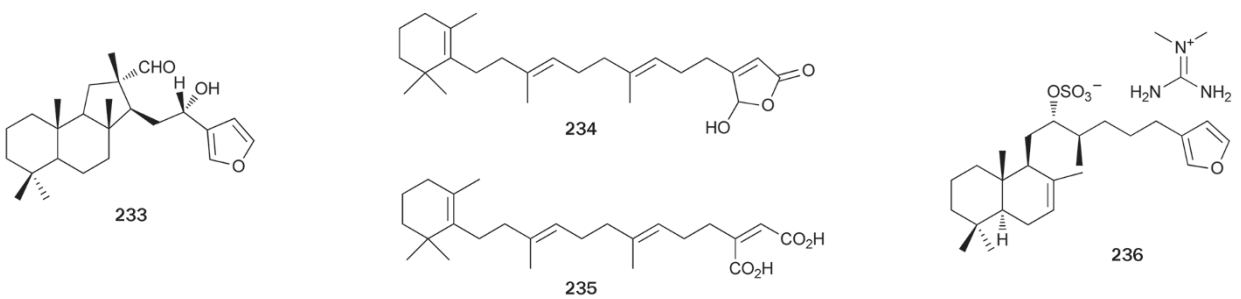

Figure 14. Structures of sesterterpenes **233–236**.

and 5.2±0.5 μmol/L, respectively. This result indicated that a positional change only of methyl groups at C-29 and C-30 might not affect the inhibitory activity. The preliminary SAR of **238** and **239** with their related synthetic analog indicated that a 3-hydroxyl group and a carboxyl group in this type of triterpenes might be required for activity. Moreover, addition of one more hydroxyl group at C-6 or C-24 may be responsible for a loss of activity.

Three ursane-type triterpenes, ursolic acid **242**, corosolic acid **243** and 2α,3α,19α,23-tetrahydroxyurs-12-en-28-oic acid

244, were isolated from a MeOH extract of the leaves and stems of the plant *Symplocos paniculata* using an *in vitro* PTP1B inhibitory assay[161]. Comparison of the activity of triterpenes **242–244** (IC_{50} values of 3.8±0.5, 7.2±0.8, and 42.1±1.5 μmol/L, respectively) indicated that the substitution of hydroxyl groups on the ursane-type triterpenes was responsible for the loss of activity. Kinetic studies suggest that **242** is a competitive inhibitor with a K_i value of 2.0 μmol/L, whereas **243** is a mixed-type PTP1B inhibitor. Furthermore, ursolic acid **242** was found to stimulate glucose uptake in L6 myotubes and facilitate glucose transporter isoform 4 translocation in CHO/hIR cells via enhancing IR phosphorylation. Additionally, **242** could inhibit other PTPs, including TCPTP, SHP1, and SHP2 (IC_{50} values ranging from 10.50±0.29 to 24.56±0.56 μmol/L)[162].

Triterpene metabolites with inhibitory activity, identified as oleanolic acid **245**, 3β,28-dihydroxy-12-en-olean **246**, maslinic acid **247** and 3β-O-acetyl aleuritolic acid 248, were obtained from the plant *Macaranga adenantha*[163]. Triterpenes **245–248** showed inhibitory activity with IC_{50} values ranging from 6.2±0.9 to 12.4±5.5 μg/mL. Qian *et al* designed and synthesized a variety of oleanolic acid **245** derivatives with modified C-17 moieties and rings A and C. These compounds were PTP1B inhibitors and the bioassay results suggested that the integrity of ring A and the 12-ene moieties was important in the retention of PTP1B enzyme inhibitory activities. Additionally, hydrophilic and acidic groups as well as the distance between the oleanene and acid moieties were associated with inhibitory activities[164]. Preparing a series of derivatives of **247** by introducing various fused heterocyclic rings at the C-2 and C-3 positions, Qiu *et al* found some derivatives with improved inhibitory activity and selectivity against PTP1B over related PTPs, such as TCPTP, LAR, SHP-1, and SHP-2[165]. The first enantioselective total synthesis of **245** and **246** from 7-methoxy-1-tetraline was reported by Corey *et al*[166].

Two more PTP1B inhibitors, moronic acid **249** and **250**, together with **242** and **245**, were purified and characterized from the acetone extract of the leaves and stems of the plant *Phoradendron reichenbachianum*[167]. All isolates were docked with a crystal structure of PTP1B and completely inhibited PTP1B at 50 μmol/L. Docking results suggested the potential binding of the triterpenic acids in a binding pocket next to the catalytic site. An extensive hydrogen bond network with the carboxyl group along with Van der Waals interactions stabilized the protein-ligand complexes. The efficient syntheses of **249** and **250** were accomplished starting from betulin **251**[168, 169]. Compound **251** from an ethanolic extract of the roots of the plant *Euphorbia micractina* showed inhibitory activity with an IC_{50} value of 15.3 μmol/L, and a selective cytotoxicity against A2780 ovarian cells[170].

Triterpenes **252–256** were isolated from the stem-bark of the plant *Styrax japonica*, whose pericarps are used as soap, cough medicine and a piscicidal agent[171]. Of the isolates, **253** and **254** exhibited the strongest inhibitory activities with IC_{50} values of 7.8 and 9.3 μmol/L, respectively. Triterpenoid **252**, which converted a carbonyl group at C-28 to a hydroxymethyl group, showed weak inhibitory activity (IC_{50}=44.4 μmol/L) compared with **253**. Moreover, replacement of a carbonyl group at C-28 to a hydroxyl group (**255**, IC_{50}>50 μmol/L) and/or a methyl group (**256**, IC_{50}>50 μmol/L) resulted in the loss of *in vitro* inhibitory activity. These results also indicated that the C-28 carbonyl group in oleanane-type triterpenoids might be required for PTP1B inhibitory activity.

24-Norursane triterpenes, ilekudinols A **257** and B **258**, were isolated as active metabolites from the MeOH extract of the leaves and stems of the plant *Weigela subsessilis*[172]. Both ilekudinols inhibited PTP1B in a non-competitive manner with IC_{50} values of 29.1±2.8 and 5.3±0.5 μmol/L, respectively. Comparison of the activities of **257** and **258** indicated that the free carboxyl group at C-28 in this type of triterpenes might play a critical role in the inhibition of PTP1B.

Activity-guided fractionation of a MeOH extract of the roots of the plant *S lappa* led to the isolation of two active constituents, betulinic acid **259** and betulinic acid methyl ester **260**[138]. The bioassay revealed that **259** and **260** inhibited PTP1B activity with IC_{50} values of 0.70±0.03 and 0.93±0.07 μg/mL, respectively. Bioassay-guided fractionation of the MeOH extract of the stem barks of the plant *Sorbus commixta* resulted in the isolation of two lupine-type triterpenes, lupenone **261** and lupeol **262**[173]. Both **261** and **262** inhibited PTP1B in a non-competitive manner with IC_{50} values of 13.7±2.1 and 5.6±0.9 μmol/L, respectively. A bioassay for the inhibitory effects on other PPs revealed that **261** and **262** had no inhibitory effects toward VHR and PP1 at levels up to 100 μmol/L. Csuk *et al* developed a practical synthetic route for the synthesis of **259** in one step with a 92% yield. The synthesis used TEMPO, $NaCl_2O$ and NaClO to selectively oxidize the primary alcohol function of **251** without affecting the secondary hydroxyl group[174]. A successful multistep enantioselective synthesis of **262** was reported by Surendra *et al*[175].

Hopane-6α,22-diol **263**, a hopane-based triterpene isolated from an MeOH extract of the Antarctic lichen *L carpathica*, inhibited PTP1B in a competitive manner with an IC_{50} value of 3.7 μmol/L[80]. Additionally, compound **263** displayed selectivity toward PTP1B over other PTPs, such as TCPTP (IC_{50}=8.4 μmol/L), SHP-2 (IC_{50}>68 μmol/L), LAR (IC_{50}>68 μmol/L), and CD45 (IC_{50}>68 μmol/L) (Figure 15).

The plant *Gynostemma pentaphyllum* is traditionally used as in Vietnamese folk medicine for the treatment of diabetes. Isolation of the $CHCl_3$-soluble extract of *G pentaphyllum* produced dammarne derivatives **264–270**, which display inhibitory activity[176]. Compound **270** is a 20R epimer of **269**, compounds **264–266** possess an epoxy group, while **267** and **268** possess a side chain of 20S, 23-ene, respectively. Compared with those compounds above, dammarne derivative **269** showed the most potent inhibitory activity (IC_{50}=5.3±0.4 μmol/L). Additionally, all these isolates showed a very weak inhibitory effect toward VHR with IC_{50} values of more than 100 μmol/L, and kinetic analysis indicated that **269** inhibited PTP1B by a competitive manner (K_i=2.8 μmol/L).

Steroids

Thousands of distinct steroids are found in natural resources.

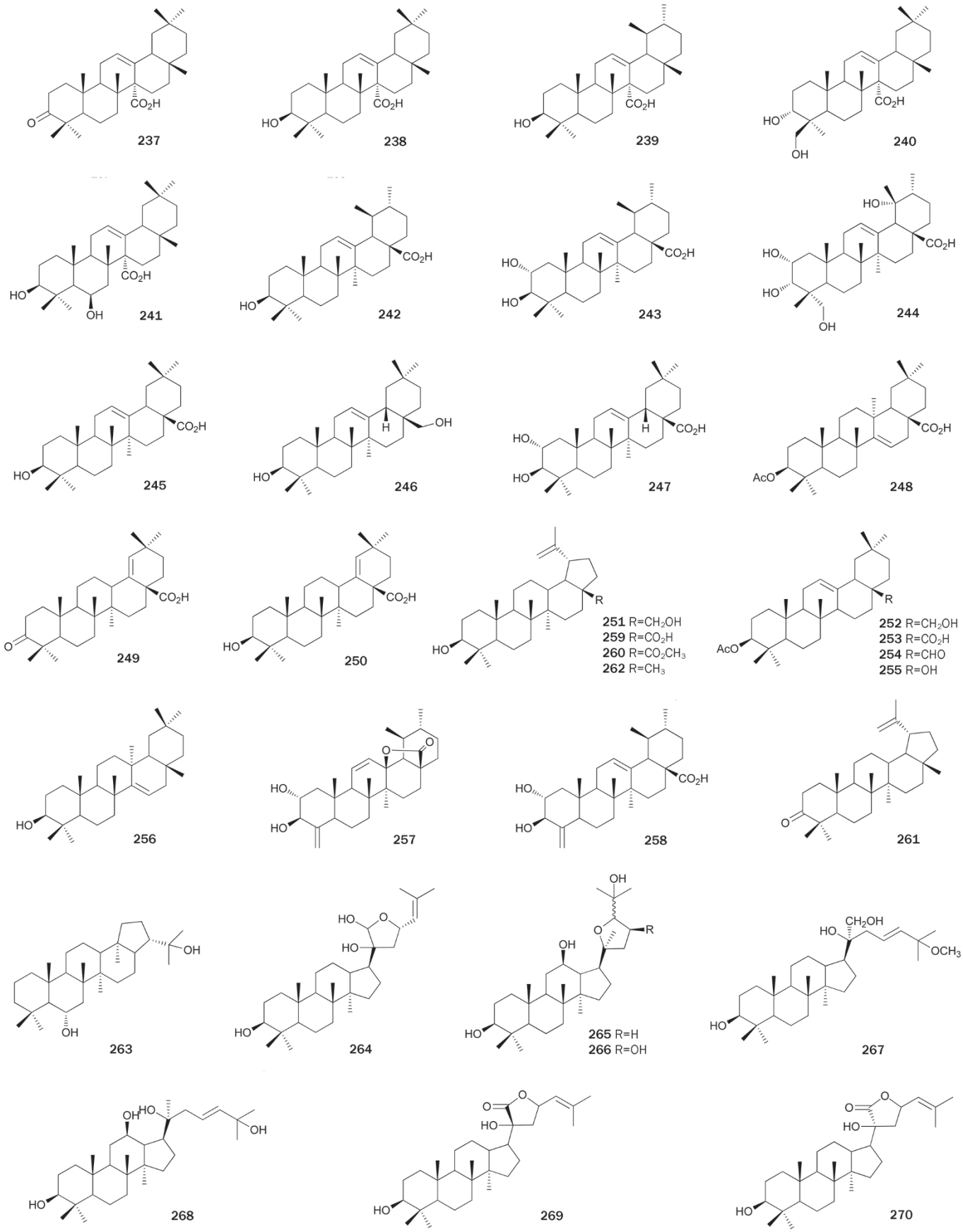

Figure 15. Structures of triterpenes **237**–**270**.

A variety of steroids play important roles in the life of animals and plants and are extensively used in medicinal chemistry[177]. There are also several steroids that act as PTP1B inhibitors.

The MeOH extract of the sclerotia of the fungus *Polyporus umbellatus* showed PTP1B inhibitory activity at a level of 30 μg/mL and produced three steroids **271–273**[178]. These steroids showed inhibitory activity with IC_{50} values of 8.9±0.3, 6.5±0.6, and 7.5±0.2 μg/mL, respectively.

Arenicolsterol A **274**, a novel cytotoxic enolic sulphated sterol, was isolated from the marine annelid *Arenicola cristata*[179]. The study of its selectivity on other PTPs indicated that **274** exhibited inhibition on intracellular PTP1B, with a similar potency to Cdc25a, Cdc25b, JSP1, and SHP1, weaker inhibition on mPTPσ, TCPTP, and PTP-PEST, and almost no inhibition on receptor-like PTP-LAR and PTPα. The reduction in apoptosis of HeLa cells caused by **274** was found to be correlative with the inhibition of the PTPs.

Phytochemical investigation on the stem bark of the plant *Toona ciliata* var *pubescens* produced (*Z*)-aglawone **275**[180]. (*Z*)-aglawone **275** inhibited PTP1B in a competitive manner with an IC_{50} value of 1.12 μg/mL. It is interesting to note that the (*E*)-isomer of **275** showed no inhibition of PTP1B.

Calicoferol E **276**, a secosterol isolated from the gorgonian *Muricella sinensis* collected from the South China Sea, exhibited inhibitory activity with an IC_{50} value of 27.28 μmol/L[181]. Compound **276** has been synthesized via a concise linear synthesis[182]. Key steps of the synthetic process included the preparation of 9α-hydroxycholest-1,4-diene-3-one from commercially available 5α-cholestan-3β-ol followed by acid-catalyzed rearrangement (Figure 16).

N- or S-containing compounds

Acylic manoalide derivatives, hippolides A **277** and B **278**, were isolated from the sponge *Hippospongia lachne* of the South China Sea. Their absolute configurations were established by the modified Mosher's method and CD data[183]. Both hippolides exhibited inhibitory activity with IC_{50} values of 23.81 and 39.67 μmol/L, respectively, and showed moderate cytotoxicity against HCT-116 cell lines. Additionally, hippolides A **277** showed weak anti-inflammatory activity.

Caulerpin **279**, an indole derivative isolated from the Chinese green alga *Caulerpa taxifolia*, showed inhibitory activity with an IC_{50} value of 3.77 μmol/L[184]. Three 3-bromoamino-7-bromomethylnaphthalene analogs **280–282**, isolated from the red alga *L similis*, showed weak inhibitory activity with IC_{50} values ranging from 65.3 to 102 μmol/L[73].

Berberine **283** is an isoquinoline alkaloid of wide distribution in nature[185] that is widely used in traditional eastern homeotherapy, particularly in treating gastrointestinal infections and as an anti-hyperglycemic agent by many Chinese physicians[186]. In docking experiments, compound **283** was found to fit readily within the binding pocket of PTP1B in a low energy orientation and to potently and competitively inhibit recombinant PTP1B *in vitro* (K_i=91.3 nmol/L). This finding suggests at least one of the reasons for the reported anti-hyperglycemic activities of berberine[186]. Additionally, compound **283** demonstrated insulin-mimicry effects on both adipocytes and myocytes, which may occur through the inhibition of PTP1B activity (inhibitory activity up to 40% and 60% at 50 and 100 μmol/L, respectively)[187].

Papaverine **284**, found in the opium poppy, is an opium alkaloid used primarily in the treatment of visceral spasm, vasospasm (especially those involving the heart and the brain), and occasionally in the treatment of erectile dysfunction[188]. Inspired by the structural similarity with **283**, papaverine **284** was inferred to exhibit inhibitory activity. It was shown that **284** readily docked within the binding pocket of PTP1B in a low-energy orientation via an optimal set of attractive interactions[189]. Compound **284** exhibited a potent *in vitro* inhibitory effect (IC_{50}=1.20 μmol/L), and significantly decreased fasting blood glucose levels of Balb/c mice *in vivo*.

Ceramide **285**, determined to be a C_{23}-phytosphingosineing unit containing three hydroxyl groups and C_{19}-fatty acid, was isolated from a MeOH extract of the sclerotia of the fungus *P umbellatus*[178]. This compound showed inhibitory activity with an IC_{50} value of 25.1±0.1 μmol/L. Albidopyrone **286**, a α-pyrone-containing secondary metabolite isolated from the fungus *Streptomyces albidoflavus*, exhibited weak inhibitory activity[190]. A macrolactam polyketide antibiotic, piceamycin **287** was isolated from the extract of the fungus *Streptomyces* (unknown species) found in the mycorrhizosphere of the Norway spruce. Compound **287** showed inhibitory activity with an IC_{50} value of 10.1 μmol/L as well as antitumor and antifungal activities[191]. Stereocalpin A **288**, a unique cyclic peptide incorporating a 5-hydroxy-2,4-dimethyl-3-oxo-octanoic acid in the structure, was isolated from the MeOH extract of the Antarctic lichen *S alpinum*[192]. Compound **288** inhibited PTP1B with an IC_{50} value of 40 μmol/L and showed moderate cytotoxicity against three human solid tumor cell lines, including HT-29, B16/F10 and HepG2. However, the spectral data

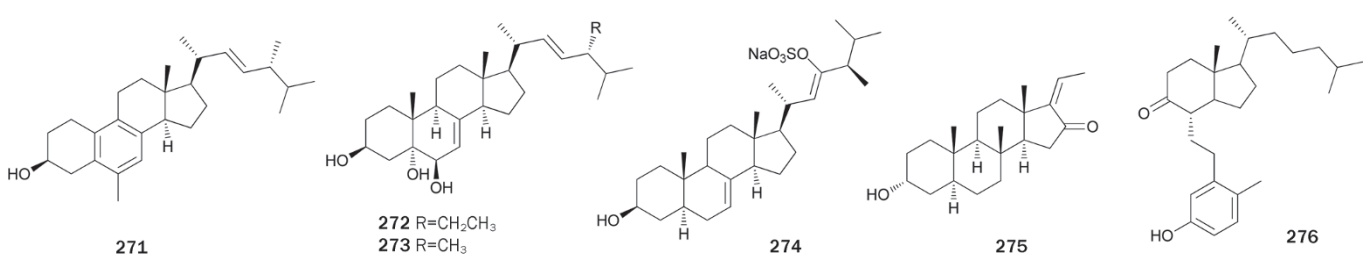

Figure 16. Structures of steroids **271–276**.

of synthetic **288** did not match with the data reported for the naturally derived **288**, suggesting that the structure of natural **288** had been assigned incorrectly[193].

Two 17-membered carbocyclic tetraenes, chejuenolides A **289** and B **290**, were isolated from the EtOAc extract of the marine bacteria *Hahella chejuensis* and their absolute configurations were assigned by application of modified Mosher method[194]. Both chejuenolides showed weak inhibitory activity (65% and 75% at a concentration of 150 μg/mL, respectively) (Figure 17).

Gymnorrhizol **291**, a novel, unusual 15-membered macyrocylic polydisulfide with an unprecedented carbon skeleton composed of three repeated 1,3-dimercaptopropan-2-ol units, was isolated from the Chinese mangrove *Brugiera gymnorrhiza*[195]. Its structure was determined by extensive spectroscopic studies and further confirmed by X-ray crystallographic analysis[196]. Compound **291** exhibited inhibitory activity with an IC_{50} value of 14.9 μmol/L. Its total synthesis was achieved in only three steps with a 25% overall yield[197].

Further research on the chemical constituents of *B gymnorrhiza* collected from Guangdong Province, China, led to the isolation of bruguiesulfurol **292**, an analog of **291**. Compound **292** inhibited PTP1B with an IC_{50} value of 17.5 μmol/L[198].

Miscellaneous

RK-682 **293** (3-hexadecanoyl-5-hydroxymethyl tetronic acid), isolated from the fungus *Streptomyces* (unknown species), was originally found to be a potent inhibitor of tyrosine phosphatease[199] and was therefore used as a positive control in PTP1B inhibitory activity assays (IC_{50}=4.5±0.5 μmol/L)[66]. Early stereoselective syntheses by Sodeoka *et al*[200] and others[201,202] served to ascertain the absolute configuration of **293**. Recently, **293** was prepared in solution and on a solid support from (2R)-glycerates in five steps with a yield of approximately 40%[203]. A chemical constituent study of *S griseoruber* produced an α-pyrone-containing secondary metabolite, BE 51068 **294**, with weak inhibitory activity[204]. Dihydrocarolic acid **295** and penitricin D **296**, isolated from a fermentation

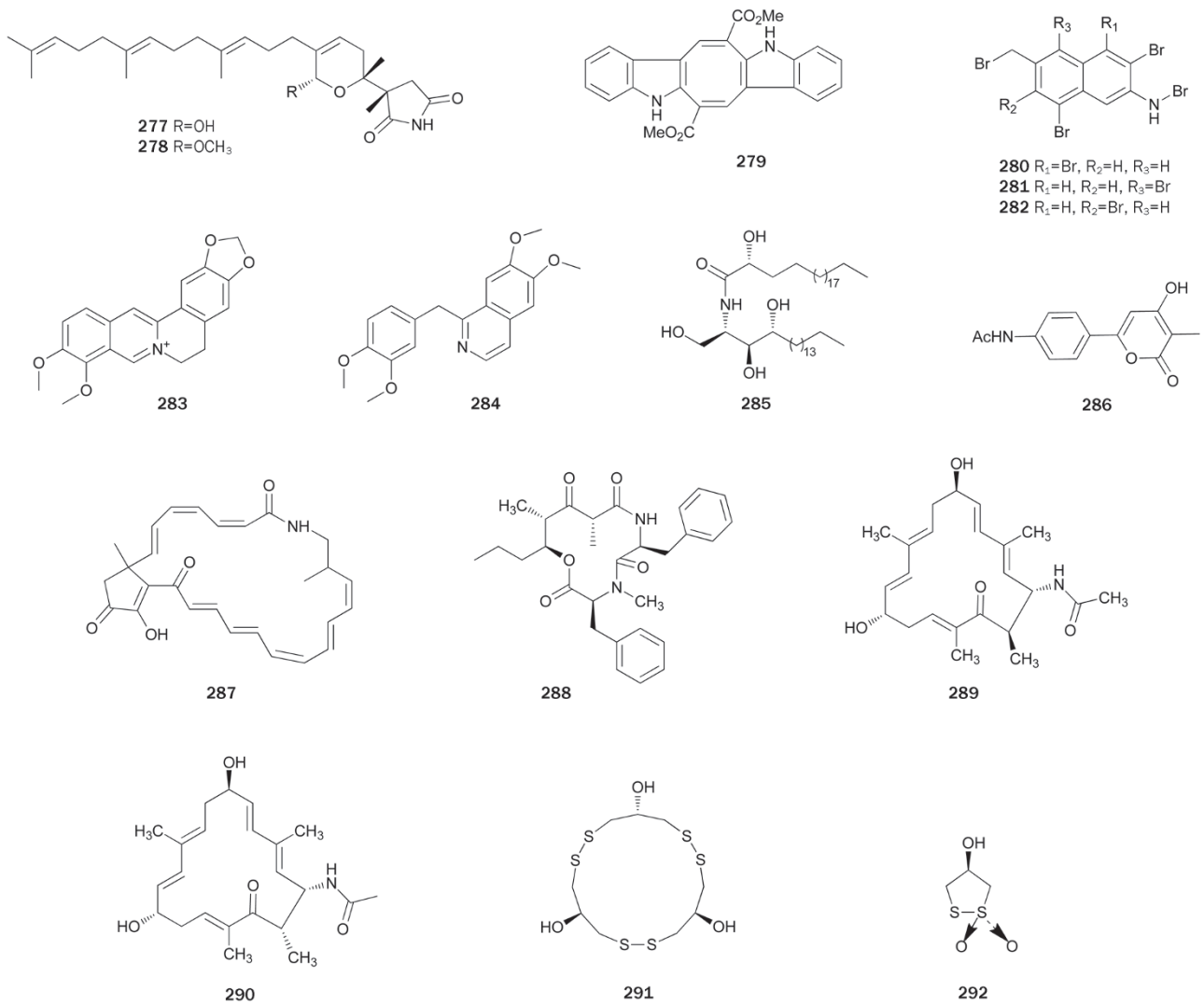

Figure 17. Structures of N- or S-containing compounds **277–292**.

broth of the fungus *Aspergillus niger*, inhibited PTP1B with IC_{50} values of 38.0 and 15.8 μmol/L, respectively[205]. Both compounds **295** and **296** also exhibited a dose-dependent inhibition of CD45. Ascochitine **297**, a polyketide isolated from the marine-derived fungus *Ascochyta salicorniae*, was found to inhibit PTP1B with an IC_{50} value of 38.5±6.5 μmol/L[206]. Compound **297** was also active against other PPs, such as Cdc25a and MPtpB, but inactive against VHR, MPtpA, and VE-PTP. The first total synthesis of **297** was reported by Galbraith *et al* in 1966[207].

Research on the chemical constituents of the Chinese mangrove *Aegiceras corniculatum* led to the isolation of falcarindiol **298**, which showed inhibitory activity with an IC_{50} value of 9.15±2.48 μmol/L[208]. Zheng *et al* reported the first stereoselective synthesis of **298** from *L*-tartaric acid and *D*-xylose via the Cadiot-Chodkiczwicz reaction as a key step[209]. Further synthetic studies have reported several strategies for the stereoselective synthesis of **298**[210–212].

Further research on the chemical constituents of the EtOH extract of the plant *Ardisia japonica* by Li *et al* led to the isolation of [1,4]benzoquinones **299–302**[213]. Benzoquinones **299–302** showed significant *in vitro* inhibitory activities with IC_{50} values ranging from 3.01±0.9 to 19.15±1.0 μmol/L. Because **299–302** have the same substituted [1,4]benzoquinone skeleton and length of the aliphatic side chain at C-3, it seems that nonpolar 5-*O*-substituents increase inhibitory activity. In 1992, Yadav *et al* reported a practical route for preparing **299** from 3-bromo-4-hydroxy-5-methoxybenzaldehyde[214]. Later, two synthetic routes for the preparation of **299** were reported by Poigny *et al* and Pfeifer *et al*, respectively[215, 216].

A naphthoquinone derivative, cyclonoside A **303**, was isolated from the leaves of the plant *C paliurus*. The absolute configuration of **303** was determined by X-ray analysis. This compound showed inhibition of PTP1B with an IC_{50} value of 2.11±0.66 μmol/L[35]. Research on an extract of the Okinawan sponge *Plakortis* (unknown species) led to the isolation of manzamenones B **304** and E **305**, which are fatty acid derivatives possessing a bicycle[4,3,0]nonane skeketon[217]. Both manzamenones exhibited inhibitory activity with IC_{50} values of 10.8 and 13.5 μmol/L, respectively[218] (Figure 18).

Conclusions

Much research has established PTP1B inhibitors as potential therapeutic options for the treatment of type 2 diabetes and obesity. Research has led to the development of approximately 300 PTP1B inhibitors isolated from a variety of natural resources, which have been reviewed here in detail. Many of these inhibitors have promising *in vivo* activities and selectivity profiles. These inhibitors should be considered for development as promising clinical drug candidates or drugs.

For example, in the group of phenolics, compounds **24** and **25** showed potent anti-hyperglycemic activity in the STZ-induced diabetic rats and db/db mouse models. Compound **75** exhibited inhibition on PTP1B without cytotoxicity against CHO cells at concentrations greater than 20 μmol/L for 48 h. Compounds **94**, **96**, **99**, and **101** showed PTP1B inhibitory activity and strong *in vitro* anticancer activity against an array of cancer cells. Compounds **116–118** showed good selectivity over other PPs. The preliminary SAR of some flavonoids suggests that less polar substituents (*eg*, isoprenyl group, methylation or aceylation of hydroxyl group) on their skeletons are usually beneficial to activity, while addition of one

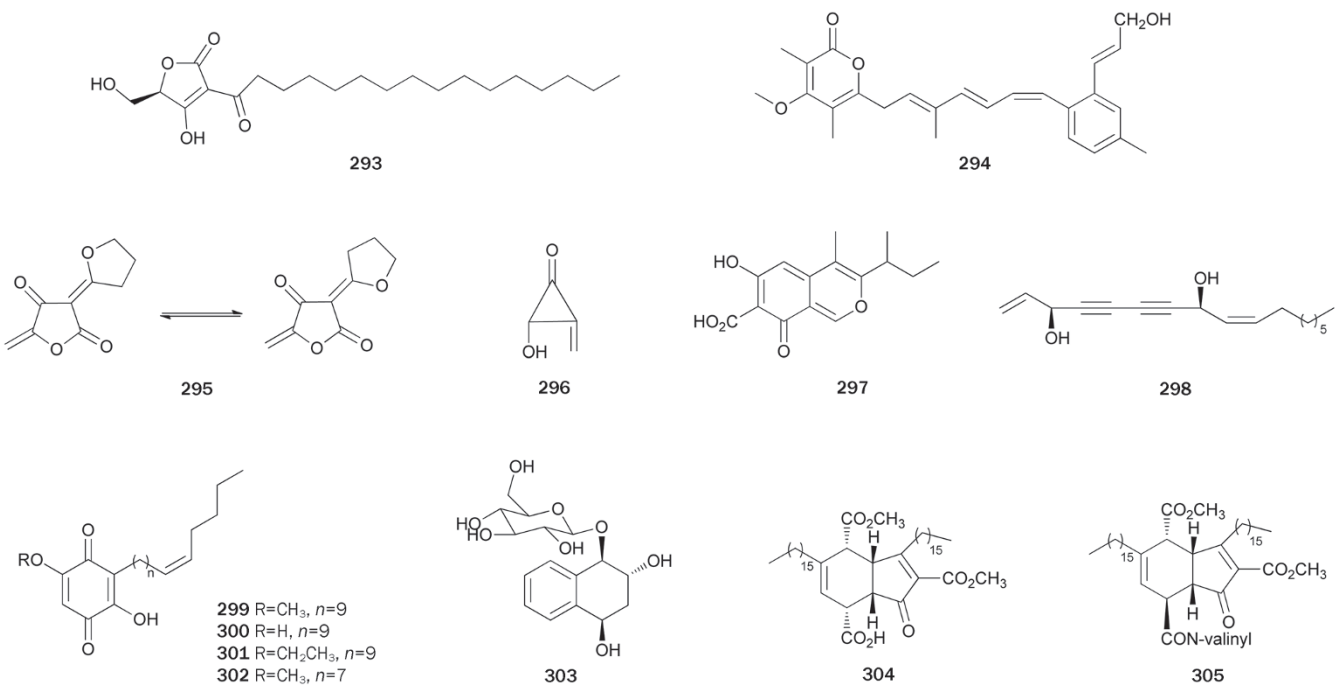

Figure 18. Structures of miscellaneous **293–305**.

hydroxyl group may lead to decreased activity. According to these results, various series of flavonoid PTP1B inhibitors with different substituents on the aromatic rings should be synthesized and evaluated to find PTP1B inhibitors with better activities and selectivity profiles. Moreover, the flavonoid skeleton is easily synthesized, providing many opportunities for medicinal chemists to carry out detailed SAR studies. Additionally, flavonoids are abundant in many foods (*eg*, fruits or vegetable) and usually have antiviral, antitumor, antiplatelet, anti-inflammatory or antioxidant activities, which makes them a preferred scaffold with favorable properties for drug design. Other phenolics also exhibited good activity profiles. For example, bromophenols **120–123** might be responsible for the *in vivo* anti-hyperglycemic activity of the extract from red alga. Phenolic acids **149**, **150**, **152**, **184** also showed good selectivity over other PPs.

In the terpene group, diterpene **214** and its isobutyryloxy derivate **215** exhibited inhibition on PTP1B without inhibitory effects toward VHR and PP1. Compounds **231** and **232** are inactive against PTPs, such as LAR, SHP-1, and MKPX. The preliminary SAR for kaurane-type diterpene PTP1B inhibitors suggests that an ester moiety at C-17 position, such as isobutyryloxy group, is essential for activity. Additionally, the hydroxyl group substituent at the C-17 or C-16 position usually decreases activity. Some important triterpene PTP1B inhibitors, such as **245**, **247**, and **269**, are widely distributed in food and medicinal plants. Additionally, compound **245** is relatively non-toxic, hepatoprotective, and exhibits antitumor and antiviral properties. Currently, many studies on the structural modification of this class of PTP1B inhibitors have been performed by several research groups. The SAR information obtained is very helpful for the design of triterpene-type antidiabetic drug candidates.

Most of the pharmaceuticals currently on the market are N-containing compounds, so the finding that alkaloid drugs (*eg*, berberine **283** and papaverine **284**) have inhibitory activity on PTP1B is very important and positive to design new N-containing PTP1B inhibitors. Moreover, the rare natural polydisulfides **291** and **292** represent a group of PTP1B inhibitors with an unusual carbon skeleton. These compounds provide a new chemical molecular template for designing novel anti-diabetic drug candidates. More synthetic and pharmacologic studies on this type of compounds are needed to obtain detailed SAR information.

As presented above, although many natural PTP1B inhibitors exhibit promising clinical potential, to the best of our knowledge there are no clinically used PTP1B inhibitors approved by the FDA for use in the USA, which is most likely due to relatively low activities (micromole level for IC_{50}) or lack of selectivity. Designing more drug-like PTP1B inhibitors as oral agents is a challenging task for two reasons. The first reason is the highly charged nature of the catalytic domain of PTP1B. The other reason is the structural homogeneity of the active and secondary binding sites in PTPs, which leads to a lack of targeting selectivity. However, it is very important to note that many of the natural PTP1B inhibitors, summarized herein, possess fascinating molecular architectures, potent activity, and better PTP1B selectivity. These compounds could be developed as anti-diabetic drugs or at least promising drug candidates in the near future. Additionally, the information provided herein is helpful for designing and synthesizing new PTP1B inhibitors. With the ongoing efforts and interest from chemists and pharmacologists, it is highly probable that more potent and selective PTP1B inhibitors will emerge, either directly from natural resources or derived from the structural optimization of natural products.

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Supplementary information

Supplementary data (names, PTP1B inhibitory activity data, source species, and references of compounds **1–305**) associated with this article are available at website of Acta Pharmacologica Sinica on NPG.

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