Inhibitors of Protein Tyrosine Phosphatase 1B from Marine Natural Products
Yue Zhou, Weirui Zhang, Xiaoyu Liu, Haobing Yu, Xiaoling Lu, and Binghua Jiao

Marine Biopharmaceutical Institute, Second Military Medical University, Xiangyin Road 800, Shanghai 200433, P. R. China, e-mail: luxiaoling80@126.com, jiaobh@live.cn

Department of Biochemistry and Molecular Biology, College of Basic Medical Sciences, Second Military Medical University, Shanghai 200433, P. R. China, e-mail: luxiaoling80@126.com, jiaobh@live.cn

The ocean is a capacious area with the most abundant biological resources on the earth. The particularity of the marine ecological environment (high pressure, high salt, and hypoxia) makes the marine species survival competition fiercely, forcing many marine organisms in the process of life to produce a great deal of secondary metabolites with special structures and biological activities. In this article, 118 natural products which were isolated from four kinds of marine organisms, sponges, algae, soft corals and fungus, showing PTP1B inhibitory activity were summarized from 2010 to 2016, which may become the leading compounds towards treating Diabetes mellitus (DM). What’s more, we briefly summarized the structure–activity relationship of PTP1B inhibitors.

Keywords: Natural products, Secondary metabolites, PTP1B, Inhibitory activity.

Contents
1. Introduction
2. Sponges
3. Algae
4. Soft Corals
5. Fungi
6. Conclusions

1. Introduction

The ocean is a huge treasure trove of natural products, from where many drugs have been developed against various diseases.

Protein tyrosine phosphatase 1B (PTP1B) belongs to the protein tyrosine phosphatase family, which specifically hydrolyses the aromatic phosphate. On one hand, in insulin signaling, it plays a key role as a negative regulator through dephosphorylating activated insulin receptor (IR) and insulin receptor substrate (1IRS-1). Besides, under conditions of growth factor receptor bound protein (Grb2), the dephosphorylation of IRS-1 catalyzed by PTP1B was accelerated. The overexpression of PTP1B in the tissue cells will reduce protein tyrosine kinase (PTK) activity, the insulin receptor cannot be combined with insulin, thereby causing insulin resistance.[1 – 3] On the other hand, in the JAK-STAT signaling pathway, which is the main axis of leptin receptor signaling transduction, inactive leptin receptor can couple with janus kinase (JAK) to get tyrosine kinases activity. The leptin receptor related kinase JAK2 and activator of transcription-3 (STAT3) can be dephosphorylated by PTP1B and be inactive, leading leptin receptor does not respond to leptin and induce leptin resistance.[4 – 7]

These may all induce the occurrence and development of type-2 diabetes mellitus (T2DM) and obesity. Diabetes mellitus (DM) is a chronic endocrine disorder metabolic disease, which is characterized by hyperglycemia. Among all the types, the overwhelming majority is T2DM, which is based on insufficient insulin secretion and insulin resistance. In recent years, PTP1B has become a new target as a negative regulatory factor to treat T2DM and obesity.[8]

Based on these previous studies, PTP1B, as a new diabetes target, sparked the interest of the scientists to find new secondary metabolites as PTP1B inhibitor...
with corresponding PTP1B inhibitory activity. According to the specifically structures and activities of the marine natural compounds, we summarized the new compounds isolated from marine organisms in four aspects, sponges, algae, soft corals and fungi, possessing PTP1B inhibitory activity from 2010 to 2016 in this review.

2. Sponges

The extract from the Indonesian marine sponge Hyatella sp. led to the isolation of sesterterpene phyllofllactone F (1; Fig. 1) and a unique sesterterpene hyattellactone A (2). They were the first examples to show an ethyl group at C(4) and C(10) position, respectively, and showed PTP1B inhibitory activity with IC$_{50}$ values of 7.47 and 7.45 µM. They both possessed an $\alpha,\beta$-unsaturated-$\gamma$-lactone ring and C-ethyl group, which demonstrated that the configuration at the C(24) position was very important for the inhibitory activities of these scalarane sesterterpenes.[9]

Aldisin (= 6,7-dihydropyrrolo[2,3-c]azepine-4,8-(1H,5H)-dione; 3), was a secondary metabolite originally isolated from the marine sponge Hymeniacidon aldis DE LAUBENFELS, which was collected at Guam Island. A series of pyrrolo[2,3-c]azepine derivaties was

Figure 1. Natural products (1 – 21) from sponges with PTP1B inhibitory activity.
synthesized, in which 4, 5, and 6 showed interesting inhibition against PTP1B with $IC_{50}$ values of 16.36, 14.93, 13.92 $\mu M$, respectively. Primary structure–activity relationships (SARs) analysis showed that the biphenyl moiety at 1-positon and aromatic groups at 4-positon contributed to the increase of inhibitory activity while the indolazaepine analogue 6 exhibiting comparable inhibitory potency implied another scaffold for design of PTP1B inhibitor.\cite{10}

Bioassay-guided separation of the ethanol extract of an Indonesian marine sponge *Lamellodysidea herba-cea* led to the isolation of 2-(3',5'-dibromo-2'-methoxyphenoxyl)-3,5-dibromophenol (7). Furthermore, its methyl ether derivative 8 and four ester derivatives (acetyl (9), butyryl (10), hexanoyl (11), and benzoyl (12)) were prepared. All of them showed potent inhibitory activity with $IC_{50}$ values of 0.85, 1.7, 0.62, 0.68, 0.69, and 0.97 $\mu M$, respectively. Among them, compound 8 may be the most interesting one as a new leading compound possessing potent PTP1B inhibitory activity and no apparent cytotoxicity.\cite{11}

Separation of the EtOH extracts of two Indonesian marine sponges led to the isolation of two furanoses-terterpenoids (7E,12E,18S,20Z)-variabilin (13) and (12E,18S,20Z)-8-hydroxyvariabilin (14) from *Ircinia* sp. and a C21 furanoterpenoid furopspongin-1 (15) from *Spongia* sp., which inhibited PTP1B activity with $IC_{50}$ values of 1.5, 7.1, and 9.9 $\mu M$, respectively. The comparison of compounds 13 and 14 indicating that the OH group at C(8) in 14 was unfavorable for the inhibition of PTP1B activity.\cite{12}

$N,N'$-Bis[(6R,7S)-7-amino-7,8-dihydro-2H-bisabolen-7-yl]urea (16), (1R,6S,7S,10S)-10-isothiocyanato-4- amorphone (17) were isolated from the EtOH extract of the Okinawan marine sponge *Axinyssa* sp. collected at Irinomote Island. Compound 16 inhibited PTP1B activity with $IC_{50}$ value of 1.9 $\mu M$, while 17 inhibited PTP1B activity in a dose-dependent manner with $IC_{50}$ values of 17 $\mu M$.\cite{13}

The sesquiterpene euryspongin A (18) was isolated from a marine sponge *Euryspongia* sp., collected at Irinomote Island, Okinawa, Japan. Though this compound showed novel unique sesquiterpenes structure, no potent inhibition activity towards PTP1B was found. Dehydroeuryspongin A (19), the dehydro derivative of 18, had PTP1B inhibitory activity with $IC_{50}$ value of 3.6 $\mu M$.\cite{14}

The acetone extract of the Hainan sponge *Stelletta* sp., belonging to the family Ancorinidae, which may have taxonomic relationships with genus *Jaspis* of an unidentified sponge, due to the isolation of the same compound, 22,23-dihydrostellettin D (20), yielded a strong PTP1B inhibitor named stellettin G (21) with $IC_{50}$ value of 4.1 ± 0.9 $\mu M$. Besides, stellettin G also showed moderate cytotoxic activity against A549 and HL-60 cells.\cite{15}

A new meroditerpene, 26-O-ethylstronglylophorine-14 (22; Fig. 2), with known 26-O-methylstronglylophorine-16 (23), stronglylophorines-3 (24), -15 (25) and -17 (26), were isolated from the Okinawan marine sponge *Stronglylophorastrongiline*. Compounds 22 – 26 inhibited the activity of PTP1B with $IC_{50}$ values of 8.7, 8.5, 9.0, 11.9, and 14.8 $\mu M$, respectively. The compounds which possessed an acetal moiety (22, 23, 25) showed stronger inhibitory activities than those of the lactone derivatives and diol derivative (26).\cite{16}

New hippolides-related sesterterpenes, 27 – 29, were isolated from the crude fractions with PTP1B inhibitory activity of the South China Sea sponge *Hippospongia lachne*. Compounds 27 and 29 exhibited moderate PTP1B inhibitory activities with $IC_{50}$ values of 5.2 and 8.7 $\mu M$, while compound 28 with a weak $IC_{50}$ values of 14 $\mu M$, respectively.\cite{17}

A new steroidal ketone, (22E,24S)-24-methylcholesta-4,7,22,25-tetraene-3-one (30), with an ergosta-22,25-diene side chain, exhibited significant inhibitory activity against PTP1B with an $IC_{50}$ value of 4.27 ± 0.55 $\mu M$, was obtained from the South China Sea marine sponge *Xestospongia testudinaria*.\cite{18}

A new polyacetylene, named isopetrosynol (31), together with three known compounds, petrosynol (32), adociacetylene D (33), (5R)-3,15,27-triacontatriene-1,29-diyne-5-ol (34) were isolated from the EtOH extract of the marine sponge *Halichondria* cf. *panicea* collected at Irionomote Island. Compound 31 inhibited PTP1B activity with $IC_{50}$ values of 8.2 ± 0.3 $\mu M$, while its stereoisomer 32 showed only 28.9 ± 4.5% inhibition at 21.6 $\mu M$, indicating that the configurations of OH groups at C(14) and C(17) markedly affected this activity. Besides, compounds 33 and 34 inhibited PTP1B activity with $IC_{50}$ values of 7.8 ± 0.5 and 12.2 ± 0.5 $\mu M$, respectively.\cite{19}

Four new sesquiterpene quinines, dysidavarones A – D, possessing the novel ‘dysidavarane’ carbon skeleton, were isolated from the sponge *Dysidea avara*, South China Sea. Among them, dysidavarones A (35) and D (36) suppressed the activity of PTP1B with $IC_{50}$ values of 9.98 and 21.6 $\mu M$.\cite{20}

Melophin C (37) was isolated from the EtOH extract of the marine sponge *Petrosia* sp., collected in the coral reefs of North Sulawesi, Indonesia in 2013, showing PTP1B inhibitory activity with an $IC_{50}$ value of 14.6 $\mu M$.\cite{21}

Three novel polyketides, woodylides A – C, were obtained from the ethanol extract of the South China Sea sponge *Plakortis simplex*, which showed new
skeleton of linear polyketides. Although they all had some biological activities, such as antifungal and cytotoxic activities, only woodylde C (38) showed PTP1B inhibitory activity with IC₅₀ value of 4.7 μg/ml.²²

3. Algae

A series of bromophenol derivatives with PTP1B inhibitory activity were synthesized based on

Figure 2. Natural products (22 – 38) from sponges with PTP1B inhibitory activity.
bromophenol 39 (see Figs. 3 and 4), which was isolated from red alga *Rhodomela confervoides*. The assay of enzyme inhibition against human recombinant PTP1B showed that derivatives 40, 41, 42, 43 and bromophenol 39 have significant activities with IC$_{50}$ values of 3.26, 2.02, 2.45, 0.68, 2.42 μM, respectively. In
addition, it was shown that the flexibility of diarylmethane scaffold and increased number of bromine substitutions on phenyl ring increase PTP1B inhibitory activity. In addition, 43 demonstrated excellent selectivity against other protein tyrosine phosphatases (PTPs), such as T-cell protein tyrosine phosphatase (TCPTP), leukocyte antigen-related protein (LAR), Src homology 1 (SHP-1), Src homology 2 (SHP-2).[23]

The isolated compounds with inhibitory activity toward PTP1B from green alga Caulerpa racemosa included 4',5'-dehydrodiodictyonema A (44), α-tocopherolquinone (45), α-tocospirone (46), (23E)-3β-hydroxystigmastera-5,23-dien-28-one (47), and (3β,24R)-stigmastera-5,28-diene-3,24-diol (48), which exhibited significant activity with IC_{50} values of 2.30, 3.85, 11.01, 3.80, 10.34 μM, respectively. Besides, compounds 44, 45, and 47 also showed high selectivity for PTP1B over the highly homologous TCPTP and other PTPs. The structural comparison suggested that the esterification of the C(1) hydroxy group impacted the PTP1B inhibitory activity while the hematinic acid ester group may dramatically increase it in linear diterpenoids. What’s more, the (R)-configuration at C(24) in 48 may be important for PTP1B inhibitory activity compared with its epimeride.[24]

Two bromophenols, 3-bromo-4,5-bis(2,3-dibromo-4,5-dihydroxybenzyl)-1,2-benzenediol (BDB; 49) and 3,4-dibromo-5-(2-bromo-3,4-dihydroxy-6-(ethoxymethyl)-benzyl)benzene-1,2-diol (BPN; 50), were isolated from the marine red alga Rhodomela confervoides, and inhibited PTP1B activity potently with IC_{50} values of 1.7 and 0.84 μM. Then, a series of derivatives were designed from BDB and synthesized, some of which showed potent PTP1B inhibitory activity especially 1-(2-(2,3-dibromo-4,5-dimethoxybenzyl)-4,5-dimethoxybenzyl)-2,3-dibromo-4,5-dimethoxybenzene (51) with an IC_{50} value of 0.89 μM, nearly two-fold more potent than the initial compound BDB. The results of structures and activities indicated that the tricyclic scaffold were important for activity of PTP1B inhibition.
and the multi-bromine atoms (4 – 5) attached to the aryl rings for PTP1B inhibition. In addition, 3,4-dibromo-5-(2-bromo-3,4-dihydroxy-6-(isopropoxy)methyl)benzyl)benzene-1,2-diol (HPN; [52]) was a synthetic analogue of BPN with enhanced inhibitory activity against PTP1B with IC_{50} value at 0.63 μM and highly selectivity against other PTPs (TCPTP, LAR, SHP-1, SHP-2).\[25\][26]

Six phlorotannins, phloroglucinol ([53]), dioxinodehydroeckol ([54]), eckol ([55]), phlorofurofuceckol-A ([56]), dieckol ([57]), and 7-phloroeckol ([58]), were isolated from two perennial brown algae, Ecklonia stolonifera and Eisenia bicyclus, belonging to the family Laminareaceae in the mid-Pacific coast. Compounds [55 – 58] showed stronger inhibitory activity against PTP1B than the positive control with IC_{50} values of 2.64 ± 0.04, 0.56 ± 0.10, 1.18 ± 0.02, and 2.09 ± 0.09 μM, respectively, while the other two compounds showed moderate activity (Table 1).\[27\]

Five new highly brominated metabolites, 2-bromo-4,6-dimethylphenyl 2,3,5-tribromophenyl ether ([59]), 1,2,5-tribromo-3-bromoamino-7-bromomethylnaphthalene ([60]), 2,5,8-tribromo-3-bromoamino-7-bromomethylnaphthalene ([61]), 2,5,6-Tribromo-3-bromoamino-7-bromomethylnaphthalene ([62])

Table 1. Natural products from marine organisms with weak activity

<table>
<thead>
<tr>
<th>Location</th>
<th>Sources/Species</th>
<th>Metabolite</th>
<th>IC_{50} (μM)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>The South China Sea</td>
<td>Sponge <em>Hippopongia lachne</em></td>
<td>Hippolide A ([96])</td>
<td>96: 23.81</td>
<td>[41]</td>
</tr>
<tr>
<td>Arctic regions</td>
<td>Sponge <em>Stryphus foris</em></td>
<td>Hippolide B ([97])</td>
<td>97: 39.67</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sponge <em>Aplysia</em> spp.</td>
<td>Lanthelline ([98])</td>
<td>Weak, dose-dependent manner</td>
<td>[42]</td>
</tr>
<tr>
<td>Okinawan</td>
<td>Sponge <em>Strongylophora strongilat</em></td>
<td>Strongylophorine-2 ([103])</td>
<td>103: &gt; 24.4</td>
<td>[16]</td>
</tr>
<tr>
<td></td>
<td>Sponge <em>Hippopongia lachne</em></td>
<td>Strongylophorine-8 ([104])</td>
<td>104: 21.2</td>
<td></td>
</tr>
<tr>
<td>The South China Sea</td>
<td>Sponge <em>SpHippopongia lachne</em></td>
<td>Compound 105</td>
<td>33</td>
<td>[17]</td>
</tr>
<tr>
<td>Hainan coastlines of China</td>
<td>Red alga <em>Laurencia okamurai</em></td>
<td>Axinisothiocyanate J ([106])</td>
<td>50% inhibition at 36 μM</td>
<td>[13]</td>
</tr>
<tr>
<td></td>
<td>Red alga <em>Laurencia similis</em></td>
<td>Compound 69</td>
<td>45.2</td>
<td>[29]</td>
</tr>
<tr>
<td></td>
<td>1,2,5-Tribromo-3-bromoamino-7-bromomethylnaphthalene ([60])</td>
<td>60: 102</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2,5,8-Tribromo-3-bromoamino-7-bromomethylnaphthalene ([61])</td>
<td>61: 65.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2,5,6-Tribromo-3-bromoamino-7-bromomethylnaphthalene ([62])</td>
<td>62: 69.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-Pacific coast</td>
<td><em>Ecklonia stolonifera</em> and <em>Eisenia bicyclus</em></td>
<td>Phloroglucinol ([53])</td>
<td>53: 55.48 ± 1.85</td>
<td>[27]</td>
</tr>
<tr>
<td></td>
<td><em>Caulerpa racemosa</em></td>
<td>Dioxinodehydroeckol ([54])</td>
<td>54: 29.97 ± 4.52</td>
<td>[24]</td>
</tr>
<tr>
<td></td>
<td><em>Marenzeller</em></td>
<td>Phloroglucinol ([53])</td>
<td>53: 55.48 ± 1.85</td>
<td>[27]</td>
</tr>
<tr>
<td></td>
<td><em>S. flexilis</em></td>
<td>Dioxinodehydroeckol ([54])</td>
<td>54: 29.97 ± 4.52</td>
<td>[24]</td>
</tr>
<tr>
<td></td>
<td><em>Cembrenea</em></td>
<td>Compound 111</td>
<td>111: 26.6</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td><em>Ketoemblide</em></td>
<td>Compound 112</td>
<td>112: 27.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Echinostrachys</em></td>
<td>7α-Hydroxycrassarosterol A ([113])</td>
<td>33.05</td>
<td>[44]</td>
</tr>
<tr>
<td></td>
<td><em>Tixier-Durivaule</em></td>
<td>Compound 114</td>
<td>22.7</td>
<td>[36]</td>
</tr>
<tr>
<td></td>
<td><em>Penicillium</em> sp. SF-5203</td>
<td>Cyclopentol ([115])</td>
<td>115: 30</td>
<td>[40]</td>
</tr>
<tr>
<td></td>
<td><em>Penicillium</em> sp. SF-5295</td>
<td>Echinulin ([116])</td>
<td>116: 29.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Viridicatol</em></td>
<td>Viridicatol ([117])</td>
<td>117: 64</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Guignardia</em></td>
<td>Guignardin C ([118])</td>
<td>118: 25.7</td>
<td>[45]</td>
</tr>
<tr>
<td></td>
<td><em>Kandelia candel</em></td>
<td>25.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
were isolated from the red alga *Laurencia similis*, collecting from Hainan coastlines of P. R. China. Compounds 59 and 63 showed strong PTP1B inhibitory activities with \( IC_{50} \) values of 2.97 and 2.66 \( \mu \)M, and the other three new compounds showed moderate inhibitory activity against PTP1B (Table 1).

From the East China Sea red alga *Laurencia okamurai* YAMADA, three novel heterodimeric laurane-type sesquiterpenoids, laurokamurols A – C (64 – 66), were isolated along with eight known related monomeric ones. The results for testing their activities showed that all of the dimers, compounds 64 – 66, and two synthetic compounds 67 and 68 exhibited significant inhibitory effect of PTP1B with \( IC_{50} \) values of 8.1, 12.5, 6.1, 10.0, and 5.6 \( \mu \)M, respectively, comparable with that of the positive control oleanolic acid (\( IC_{50} = 3.3 \) \( \mu \)M). All of the isolated monomers were not active, except for 69, which showed weak inhibitory activity.

The red alga *Laurencia okamurai*, collected off the coast of Nanji Island, Zhejiang Province, China, in December 2013 led to the isolation of new sesquiterpenoid, debromo-3\( \beta \)-hydroperoxyaplysin (70), along with known compounds 3\( \beta \)-hydroperoxyaplysin (71), isolaurinterol (72), and laurokamurene A (73) with PTP1B inhibitory activity with \( IC_{50} \) values of 13.0, 14.9, 7.0, and 4.9 \( \mu \)g/ml, respectively. In a preliminary SAR study, both 70 and 71 with \( \text{R} \)-configuration at C(3) position exhibited strong PTP1B inhibitory activities, while their epimers were inactive, suggesting that the may be significant for the activity.

The investigation of the Chinese marine green alga *Caulerpa racemosa* resulted in the discovery of a new minor bisindole alkaloid, racemosin C (74), and one known related metabolite, caulersin (75), which were characterized by a naturally unprecedented 8-hydroxy-2,4,6-cyclooctatrienone ring fused with two indole systems. They both exhibited significant PTP1B inhibitory activity with \( IC_{50} \) values of 5.86 ± 0.57 and 7.14 ± 1.00 \( \mu \)M, respectively.

4. Soft Corals

There are some cembrane diterpenoids with anti-PTP1B activity were isolated from the South China Sea soft coral *Sarcophyton trocheliophorum* MARENZELLER. The isolated compounds were sarcophytolide N (79; see Fig. 5), sarcassin E (80), and (4\( \text{Z},12\text{Z},14\text{E})\)-sarcophytolide (81), which showed significant inhibitory activity against human PTP1B enzyme with \( IC_{50} \) values at 5.95,

![Figure 5](https://www.cb.wiley.com)

**Figure 5.** The natural products (79 – 85) from soft corals with PTP1B inhibitory activity.
6.33, and 15.4 μM, respectively. Later, a new capnosane diterpene sarsolilides B (82) and its known analogue sarsolilide A (83) were isolated from this soft coral, and exhibited PTP1B inhibitory activity with IC\textsubscript{50} values of 27.1 ± 2.6 and 6.8 ± 0.9 μM. Based on the preliminary comparison between the structures of those compounds, it’s provided that methyl ester group at C(18) significantly increases the enzyme inhibitory activity.[34][35]

(3β,4α,5α)-4-Methylergost-24(28)-ene-3-ol (84) and ergosta-4,24(28)-dien-3-one (85) were isolated from the soft coral Sinularia depressa TIXIER-DURIVAULT off Lingshui Bay, Hainan Province, exhibiting inhibitory activity with IC\textsubscript{50} values of 19.4, 15.3 μM. It was indicated that substitution of 8-OH should be responsible for the decrease of PTP1B inhibitory activity while acetylation on 3-OH may increase it.[36]

5. Fungi

A new styrylpyrone-type metabolite penstyrylpyrone (86; see Fig. 6) was isolated from the methylethylketone extract of marine-derived fungus Penicillium sp. JF-55 cultures, along with two known metabolites, anhydrofulvic acid (87) and citromycetin (88). Compounds 86 and 87 were suggested to bind to the active site within PTP1B, exhibiting PTP1B inhibitory activity in a competitive manner with IC\textsubscript{50} values of 5.28 and 1.90 μM, while compound 88, which shared close structural features to 87, did not show any inhibitory activity up to 25.8 μM, which manifested that the linear tricyclic system and the position of the carbonyl groups in compound 87 might be important for the binding with active site of PTP1B.[37]

From the Indonesian ascidian-derived Penicillium verruculosum strain TPU1311, a new merosesquiterpene, verruculide A (89), and two known congeners, chrodrimanins A (90) and H (91), were isolated and demonstrated to have PTP1B inhibitory activity. The study showed that 89, 90, and 91 inhibited the activity of PTP1B with IC\textsubscript{50} values of 8.4, 8.5, and 14.9 μM, respectively. According to the comparison of their activities and structures with others revealed that the acetylation of the 4'-OH group rather than the two OH groups at the C(7) and C(7') positions should be responsible for the significantly reducing of the PTP1B activity. It was the first time demonstrating compounds in the chrodrimanin family can exhibit inhibitory activity against PTP1B.[38]

Tanzawaic acids A (92) and B (93) were discovered from a marine-derived fungus Penicillium sp. SF-6013 and showed equivalent inhibitory effects against
PTP1B activity with the $IC_{50}$ value of 8.2 $\mu$m. They were isolated from the sea urchin *Brisaster latifrons*, collected from the Sea of Okhotsk (N 53°22.626' E 144°24.200'). The assay based on structural–activity relationships between tanzawaic acids and its derivatives suggested that the presence of the hydroxy

![Figure 7](image-url). The natural products with weak activity (96 – 118).
group at C(10) might be the important structure in diminishing PTP1B inhibitory.\[39\]

Fructigenine A (94) was isolated from the strain Penicillium sp. SF-5203, an intertidal sediment sample, collected from Wan Island, Korea, in January 2008. Flavoglaucin (95) was extracted from the strain SF-5295, isolated from an unidentified sponge manually collected using scuba diving equipment off the shores of Jeju Island in February 2009. Compound 94 exhibited the PTP1B inhibitory activity in a noncompetitive manner with an IC$_{50}$ value of 10.7 \(\mu\)M, while the IC$_{50}$ value of Compound 95 was determined as 13.4 \(\mu\)M in a competitive manner.\[40\]

There are also some compounds (Fig. 7) from marine organisms with weak activity up to 20 \(\mu\)M summarizing in the Table 1.

### 6. Conclusion

In this review, 118 marine natural products from 2010 to 2016 with PTP1B inhibitory activity were reported. To base on the sources, compounds with PTP1B inhibitory activity can be mostly classified as following: sponges, algae, soft corals and fungi. Fig. 8 shows the proportion of the four general categories. The figure shows that the activated products were mainly found in sponges and algae, which produced abundant secondary metabolites due to their unique chemical defense system formed in the deep sea environment and surrounding with large amounts of symbiotic bacteria. However, more than 1000 new compounds of marine natural products with particular types of bioactivity were discovered every year and the main focus of attention was the anticancer activity. So more awareness of the detection of PTP1B inhibitory activity should be raised in novel natural compounds.

In view of the remarkable value of drug targeting in PTP1B, there has been a few methods screening for the inhibitor, such as colorimetric method using \(p\)-nitrophenyl phosphate (PNPP) as substrate, fluorescence method, scintillation proximity assay (SPA) and so on. Besides, a high-throughput method was established based on those to screen high activity PTP1B inhibitors more efficiently. However, at present stage those technologies may lead to the emergence of the false positive results which will bring more difficulties to drug follow-up studies. Moreover, the mechanism actions of those compounds have not yet fully clear and prevent the further related research development.

In a word, the immaturity of the detection method and the unclear mechanism of action of those compounds were responsible for the unlisted effective PTP1B inhibitor drugs in the clinic. What’s more, as a new target for treating DM or obesity, a lot of work still need to be carried out such as studying the drug metabolism and the side effects in the body. Till now, there are only two PTP1B inhibitors in clinical trials: the MSI-1436 in the USA,\[46\] JTT-551 in Japan.\[47\]

In order to further development, searching for new active natural compounds and derivatives as useful targeted drugs, finding appropriate methods to test PTP1B inhibitory activity, strengthening the related mechanism research and establishing medicine model still need our efforts for a period time in the future. In these aspects, searching for effective leading compounds was the most fundamental and most urgent affair we need to do in recent times.

### Acknowledgements

The work was funded by National Natural Science Foundation of China (NSFC) (41306197, 41606173), Guangdong Innovative Development of Marine Economy Regional Demonstration Project (GD2012-D01-001).

### Conflict of Interest

The authors declare no conflict of interest.

### References
