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The first synthesis of natural disulfide bruguiesulfurol and biological evaluation of its derivatives as a novel scaffold for PTP1B inhibitors

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ABSTRACT

Bruguiesulfurol (**1**), a cyclic 4-hydroxy-dithiosulfonate isolated from mangrove plant *Bruguiera gymnorrhiza*, was concisely synthesized for the first time in four steps, and a series of its synthetic derivatives were evaluated for in vitro inhibitory effects on PTP1B and related PTPs. Some derivatives were found to have improved pharmacological profile compared with hit **1**. Among them, **5a** showed the potent selectivity towards PTP1B over other PTPs, including TCPTP, and **7j** exhibited the strongest PTP1B inhibitory activity with an IC_{50} value of 4.54 μM.

According to the World Health Organization (WHO), about 346 million people worldwide suffer from diabetes and its prevalence is projected to roughly double by 2030.[1] Type 2 diabetes, resulting from the body's ineffective use of insulin, makes up 90% of diabetes cases.[2] Protein tyrosine phosphatase 1B (PTP1B), the first mammalian PTP to be purified and characterized, has been demonstrated to play a key role in the insulin-dependent signaling cascade.[3] Tremendous experimental data have validated PTP1B as one of the best therapeutical targets for the treatment of type 2 diabetes and obesity.[4] For example, PTP1B-deficient mice have remarkably low adiposity, and are protected from diet-induced obesity by increasing basal metabolic rate and total energy expenditure. This result is consistent with the inference that PTP1B is a major regulator of energy balance insulin sensitivity and body fat stores in vivo.[5] In addition, accumulating evidence also indicates that PTP1B is involved in cancer.[6] The positive physiological role of PTP1B attracts great interest of medicinal chemists, and in the past decades numerous drug-like PTP1B inhibitors, mostly involving phosphotyroine (pTyr) mimetics, have been developed.[7,8] However, discovery of anti-type 2 diabetes drugs targeting PTP1B is still a big challenging task because of the fundamental nature of highly conserved and positively charged active-site pocket.[9] The current pTyr mimetics usually have undesirable cell permeability and oral bioavailability due to the presence of highly negative charged polar residues in their structures, or show poor PTP1B selectivity versus TCPTP (T-cell protein tyrosine phosphatase) due to their highly homologous catalytic domain and identical active sites.[10] Therefore, there is an urgent need to develop novel potential drug scaffolds targeting PTP1B.

Marine natural products are a prolific source of lead molecules for discovering clinically drugs for human diseases.[11] As a special and important member, marine disulfide- and multisulfide-containing metabolites possess varying bioactivities and fantastic molecular skeletons, which have been paid more and more attentions by pharmacologists and chemists recently.[12–16] Our group has focused on this field for many years, and in our research project for finding promising anti-type 2 diabetes drug candidates a series of unique marine cyclic disulfides and multisulfides with PTP1B inhibitory activity had been isolated and synthesized.[17] Bruguiesulfurol (**1**, Fig. 1), a cyclic 4-hydroxy-dithiosulfonate isolated for the first time from the flowers of mangrove plant *Bruguiera gymnorrhiza*,[18] was found to exhibit PTP1B inhibitory activity (IC_{50} = 17.5 μM) by our group.[17b] The uncommon structure, significant bioactivity, and low natural yield of **1** stimulated our interest to synthesize and perform a more-in-depth pharmacological evaluation. Herein, the present letter describes the first concise synthesis of **1** and biological evaluation of its synthetic derivatives as selective PTP1B inhibitors.

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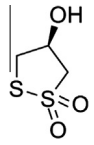
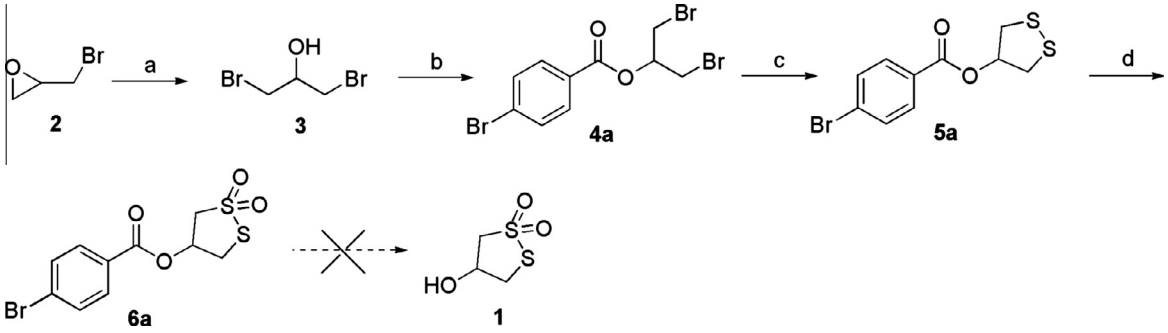


Figure 1. Structure of bruguiesulfurol (**1**).

The construction of sulfur–sulfur bond is the decisive step for the synthesis of **1**. Many methods for the formation of disulfides have been reported, such as oxidative coupling of thiols or Bunte salts,[19] reductive formation from sulfenyl, sulfinyl, sulfonyl or thiocyanate derivatives,[20] or the reaction of alkyl halide with sodium disulfide (Na_2S_2).[21] Based on our previous study and analysis of structural features of **1**, the last method was used to form disulfide bond. In addition, it is also vital to select a suitable and practical hydroxyl protecting group. 4-Bromobenzoyl as a common hydroxyl protecting group was used since it makes small-molecule compound easy to crystallize, which is helpful for purification and structural identification. The initial approach to synthesize **1** (shown in Scheme 1) started from commercially available epibromohydrin (**2**). Treatment of **2** with 40% aqueous HBr gave 1,3-dibromo-2-propano (**3**). The esterification between bromide **3** and 4-bromobenzene carboxylic acid yielded ester **4a**. Then, ester **4a** was reacted with Na_2S_2 (prepared from Na_2S and S)[22] to form the key intermediate **5a** with the assistance of tetrabutyl ammonium bromide (TBAB) as phase transfer catalyst, following oxidization by treatment with oxone to give oxidative product **6a**. The structures of **5a** and **6a** were confirmed through X-ray diffraction analysis (Fig. 2).[23] Disappointingly, no expected compound **1** was



Scheme 1. Reagents and conditions: (a) 40% aqueous HBr, CH_2Cl_2, 0 °C, 5 h, 85%; (b) 4-bromobenzene carboxylic acid, EDCI, DMAP, CH_2Cl_2, rt, 12 h, 88%; (c) Na_2S_2, cat. TBAB, $CHCl_3$, rt, 5 h, 60%; (d) Oxone, $NaHCO_3$, acetone, 2 h, 81%.

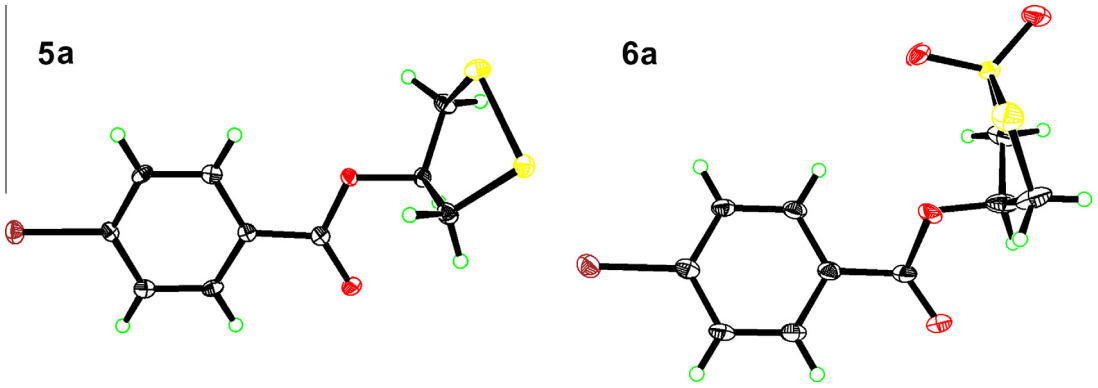
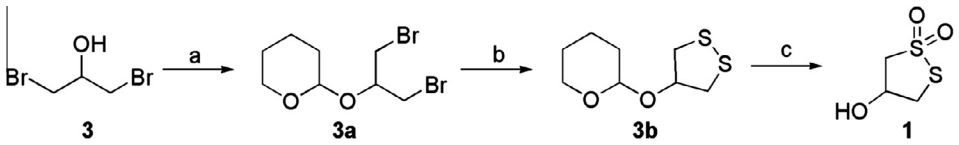
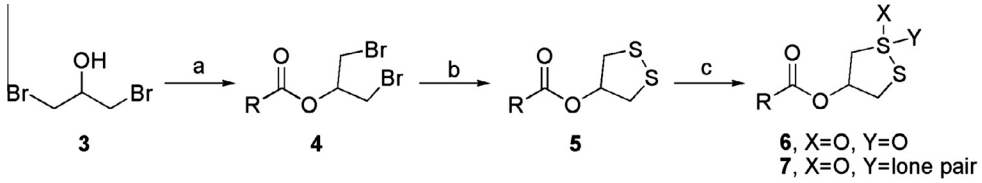


Figure 2. Single-crystal X-ray structures of **5a** and **6a**.

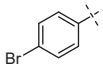
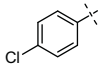
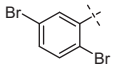
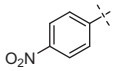
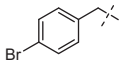
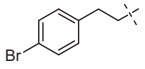
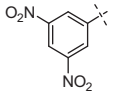
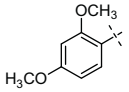
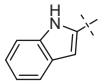


Scheme 2. Reagents and conditions: (a) pyridinium-*p*-toluene sulfonate, 2,3-dihydropyran, THF, rt, 2 h, 85%; (b) Na_2S_2, cat. TBAB, $CHCl_3$, rt, 5 h, 58%; (c) mCPBA, CH_2Cl_2, rt, 4 h, 30%.



Scheme 3. Reagents and conditions: (a) RCO_2H, EDCI, DMAP, CH_2Cl_2, rt, 12 h; (b) Na_2S_2, cat. TBAB, $CHCl_3$, rt, 5 h; (c) mCPBA, CH_2Cl_2, rt, 4 h.

Table 1
Inhibitory activity of **5a**–**t** against PTP1B and other PTPs presented as IC_{50} (μM)

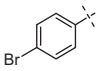
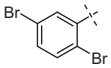
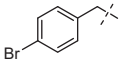
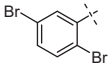
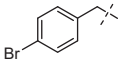
Compd	R	PTP1B	TCPTP	SHP-1	SHP-2	LAR
1	H	17.5	ND	ND	ND	ND
5a		11.01 ± 1.31	33.97 ± 3.47	NA	NA	34.57 ± 4.55
5b		NA[a]	ND[b]	ND	ND	ND
5c		NA	ND	ND	ND	ND
5d		NA	ND	ND	ND	ND
5e		NA	ND	ND	ND	ND
5f		33.42 ± 2.02	34.10 ± 3.63	NA	NA	NA
5g		48.18 ± 4.91	42.08 ± 7.86	NA	NA	20.36 ± 4.12
5h		25.62 ± 4.53	20.43 ± 3.15	10.91 ± 2.47	NA	NA
5i		24.88 ± 2.68	40.67 ± 0.46	14.05 ± 3.63	13.36 ± 2.98	NA
5j		22.56 ± 2.95	37.37 ± 5.86	NA	NA	NA
5k		NA	ND	ND	ND	ND
5l		NA	ND	ND	ND	ND
5m		14.83 ± 2.31	27.28 ± 7.43	24.37 ± 7.74	13.81 ± 2.72	NA
5n		NA	ND	ND	ND	ND
5o		NA	ND	ND	ND	ND
5p		NA	ND	ND	ND	ND
5q		78.19 ± 6.98	NA	17.94 ± 1.71	21.45 ± 2.13	NA
5r		35.23 ± 2.82	75.41 ± 4.21	15.77 ± 0.79	22.29 ± 3.01	NA
5s		NA	ND	ND	ND	ND
5t		24.08 ± 4.48	35.84 ± 4.29	NA	NA	NA
Oleanolic acid		3.02 ± 0.20	ND	ND	ND	ND

[a] NA, not active.
[b] ND, not determined.

obtained upon subjection of **6a** to a variety of deprotection conditions.[24] Furthermore, **6a** is very stable in acidic conditions resulting in no reaction occurring. However, it rapidly decomposed in basic conditions, which suggested the disulfide bond might be unstable in basic condition, but stably exist in acidic condition.

Based on the experimental results above, using hydroxyl protection group that can be deprotected in acidic conditions seems available for access to **1**. Therefore, the 2-tetrahydropyranyl group was used as protecting group. The synthetic route to **1** was carried out as shown in Scheme 2. The hydroxyl group of **3** was protected

Table 2
Inhibitory activity of series of **6** and **7** against PTP1B and other PTPs presented as IC_{50} (μM)

Compd	R	X	Y	PTP1B	TCPTP	SHP-1	SHP-2	LAR
6a		O	O	NA[a]	ND[b]	ND	ND	ND
6b		O	O	NA	ND	ND	ND	ND
6c		O	O	29.00 ± 3.38	NA	NA	NA	NA
6d		O	O	NA	ND	ND	ND	ND
6f		O	O	NA	ND	ND	ND	ND
6g		O	O	NA	ND	ND	ND	ND
6j		O	O	NA	ND	ND	ND	ND
6n		O	O	NA	ND	ND	ND	ND
6t		O	O	NA	ND	ND	ND	ND
7a		O	Lone pair	NA	ND	ND	ND	ND
7b		O	Lone pair	NA	ND	ND	ND	ND
7c		O	Lone pair	27.96 ± 3.83	NA	NA	NA	NA
7d		O	Lone pair	NA	ND	ND	ND	ND
7f		O	Lone pair	22.38 ± 1.85	32.97 ± 2.33	NA	NA	NA
7g		O	Lone pair	29.68 ± 2.66	36.80 ± 0.89	NA	NA	NA
7j		O	Lone pair	4.54 ± 0.47	11.12 ± 1.14	NA	NA	NA
7n		O	Lone pair	31.42 ± 2.42	52.64 ± 2.87	NA	NA	NA
7t		O	Lone pair	44.98 ± 5.10	NA	NA	NA	NA

[a] NA, not active.
[b] ND, not determined.

by 2,3-dihydropyran to yield **3a**, which was reacted smoothly with Na_2S_2 to give the desired disulfide **3b** in 49% overall yield over two steps. In order to oxidize the disulfide bond in **3b**, several oxidants were tried.[25] Finally, 3-chloroperoxybenzoic acid (mCPBA) was found to be an efficient oxidant, and target compound **1** was produced by oxidation and deprotection in one pot with an overall yield of 30%. The physical and spectral data of **1** were in agreement with the literature data.[17b,18]

During the process for synthesizing **1**, the key intermediate **5a** was found to exhibit stronger PTP1B inhibitory activity than the original natural product **1**, with an IC_{50} value of 11.01 μM, and also showed significant selectivity toward PTP1B versus other PTPs, especially the most homologous PTPCP by threefold. These positive results encouraged us to prepare a series of derivatives of **1**, and to conduct a preliminary structure–activity relationship (SAR) study on these compounds.

The syntheses of three series of **5**, **6** and **7** were carried out as shown in Scheme 3. Esterification of bromide **3** with various carboxylic acids, and following nucleophilic substitution reaction between ester **4** and Na_2S_2 provided disulfide **5**. Compounds **6** and **7**

were finished by oxidative reaction of **5** with mCPBA. The synthetic derivatives were evaluated in the enzyme inhibition assay against PTP1B and other four PTPs (TCPTP, SHP-1, SHP-2 and LAR).

The results of the first series of analogs (**5a**–**t**) are shown in Table 1. Among **5a**–**h** with halo-substituted group in benzene ring, *para*-bromo substituted compound **5a** was the most active towards PTP1B, and showed highest selectivity over other PTPs (about threefold selectivity over TCPTP and LAR; inactive toward to SHP-1 and SHP-2). Compounds **5f**–**h** were active towards PTP1B with IC_{50} values ranging from 25.62 ± 4.53 to 48.18 ± 4.91 μM, but they did not showed selectivity towards TCPTP with IC_{50} values ranging from 20.43 ± 3.15 to 42.08 ± 2.77 μM. Compounds **5i** and **5j**, also bearing *para*-substitutions (sulfonamide and nitro groups, respectively), showed significant improved PTP1B inhibitory activity compared with **5b**–**g**, however, these two compounds still did not show noticeable selectivity towards TCPTP as **5a**. The results above indicated that the *para*-bromo substitution might play a key role in the PTP1B inhibitory activity and selectivity for **5a**. Further, another two analogs (**5k** and **5l**) with *para*-bromo substitution in benzene ring were prepared, but it is disappointing that their PTP1B inhibitory activity were lost with increase in the amount of carbon atoms between benzene ring and carbonyl group. It is worth noting that compound **5m** (IC_{50} = 14.83 ± 2.31 μM), bearing two electron-withdrawing nitro groups at *ortho*- and *meta*-position, almost shows similar level of PTP1B inhibitory activity to that of **5a**, however, **5m** did not show good PTP1B selectivity as **5a**. Among compounds **5q**–**t** with heteroaromatic substitutions, **5q**, **5r** and **5t** showed weak or moderate PTP1B inhibitory activity, but they also did not have PTP1B selectivity as good as **5a**.

The results of series of oxidative products **6** and **7** are shown in Table 2. Surprisingly, most of sulfoxides **7** showed higher PTP1B inhibitory than their precursor **5**. Among all the tested sulfoxides, compound **7j** showed the highest PTP1B inhibitory activity with an IC_{50} value of 4.54 μM (about 2.4-fold selectivity over TCPTP), and no effect against other PTPs. Interestingly, the PTP1B inhibitory activity of **7a** was lost compared with **5a**, so that there seems to be ambiguous effect about the formation of sulfoxide. Compared with sulfoxides **7**, sulfones **6** nearly did not have PTP1B inhibitory activity except compound **6c**. It was speculated that the introduction of another oxygen atom change the configuration of 1,2-dithiolane and/or increase steric hindrance, which might make these sulfones can not bind to the active site of PTP1B resulting in the loss of PTP1B inhibitory activity.

In summary, the first concise synthesis of bruguiesulfurol (**1**) has been achieved in only four steps in 12.6% overall yield, and a series of its derivatives were developed and evaluated for in vitro inhibitory activity against a panel of PTPs. Some derivatives were found to have improved PTP1B inhibitory activity compared with hit **1**, such as **5a** and **7j** showing high PTP1B inhibitory activity and relatively good selectivity. The preliminary SAR study provides a novel potential scaffolds for designing novel class of PTP1B inhibitors. Further studies to improve pharmacological profile and clarify action mechanism for this class of disulfide PTP1B inhibitors are in progress and will be reported in due time.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.07.039.

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23. Crystallographic data for the structures of **5a** and **6a** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 934510 and 934511 respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44 (0) 1223 336033 or E-mail: deposit@ccdc.cam.ac.uk].
24. Among these attempts were reactions with concd hydrochloric acid, acetic acid, concd sulfuric acid, sodium bicarbonate, sodium carbonate, and potassium carbonate in MeOH, respectively.
25. The oxidants are mCPBA, oxone, and *tert*-butyl hydroperoxide, respectively.