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Benzo[*c*][1,2,5]thiadiazole derivatives: A new class of potent Src homology-2 domain containing protein tyrosine phosphatase-2 (SHP2) inhibitors

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ABSTRACT

The Src homology-2 domain containing protein tyrosine phosphatase-2 (SHP2) is an oncogenic phosphatase linked to various kinds of cancers. Consequently, SHP2 has emerged as a promising target for novel anti-cancer agents. Using scaffold-hopping strategy, a series of benzo[*c*][1,2,5]thiadiazole derivatives was designed from PTP1B inhibitors with *1H*-2,3-Dihydroperimidine motif, synthesized and evaluated their biological activities against PTP1B and SHP2. Among them, the representative compound **11g** displayed SHP2 inhibitory activity with IC_{50} of 2.11 ± 0.99 μM, exhibited 2.02-fold and 25-fold selectivity for SHP2 over SHP1 and PTP1B respectively and had no visible activity against TCPTP. These preliminary results could provide a possible opportunity for the development of novel SHP2 inhibitors with optimal potency and improved pharmacological properties.

Reversible protein tyrosine phosphorylation, catalyzed by the opposing actions of protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs), is considered the key pathway for controlling protein functions in living cells.[1] Dysregulation of protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs) is linked to numerous human diseases, including cancer, diabetes, obesity, infection, autoimmune, and neuropsychiatric disorders.[2,3] Hence, PTKs and PTPs are emerging as high value targets for therapeutic intervention.[3–6] Many drug discovery programs conducted to date have focused on the PTKs and more than a dozen small molecule inhibitors targeting the kinases have reached the market.[7] However, the therapeutic benefits of modulating PTPs are still underexplored despite the fact that several PTPs have been identified as high value targets.[8]

Among the members of PTPs superfamily, protein tyrosine phosphatase 1B (PTP1B) is a key negative regulator of insulin receptor and leptin receptor-mediated signaling pathway.[9] The inhibition of PTP1B is considered to be a potential therapeutic for the treatment of type 2 diabetes and obesity.[10] A variety of PTP1B inhibitors have been disclosed among academic and industrial laboratories.[11] Meanwhile, Src homology 2 (SH2) domain containing protein tyrosine phosphatase-2 (SHP2) is ubiquitously expressed and exerts as positive functions in multiple cell signaling processes.[12] Dysfunction of SHP2 has been correlated with cancers like lymphoma and leukemia.[12] Unfortunately, the detailed molecular mechanisms of SHP2 in cells are complicated and many questions remain unanswered regarding the SHP2-dependent signaling cascades.[13] Consequently, small molecule SHP2 inhibitors not only serve as powerful tools to define the physiological roles of SHP2 *in vivo*, but also as excellent lead compounds for the development of new therapeutic agents for hematologic malignancies.[14] However, known SHP2 inhibitors are limited and obtaining inhibitors with optimal potency and pharmacological properties has been difficult primarily because of the highly conserved and positively charged nature of the active site pocket shared by all PTPs family members.[14–22]

Previously, we identified 1*H*-2, 3-dihydroperimidine derivatives as potent PTP1B inhibitors.[23] To explore the structural diversity of 1*H*-2, 3-dihydroperimidine derivatives, we used scaffold-hopping strategy to replace the 1*H*-2, 3-dihydroperimidine motif with

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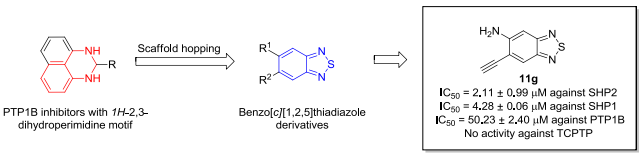
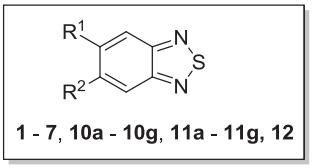


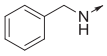
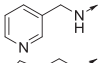
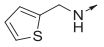
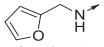
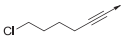
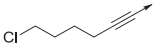
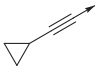
Fig. 1. Structure of 1H-2, 3-dihydroperimidine derivatives and benzo[*c*][1,2,5] thiadiazole derivatives.

benzo[*c*][1,2,5]thiadiazole motif, designed and synthesized a series of benzo[*c*][1,2,5]thiadiazole derivatives (Fig 1), evaluated their inhibitory activities toward PTP1B and SHP2. Among them, several benzo[*c*][1,2,5]thiadiazole derivatives were identified as SHP2 inhibitors and the representative compound **11g** was also subjected to selectivity analyses to determine whether its biological properties made it suitable for further development.

21 new benzo[*c*][1,2,5]thiadiazole derivatives (compounds **2**–**7**, **10a–10g, 11a–11g** and **12**) (Table 1) were designed and synthe-

Table 1
Inhibitory activities of compounds **1**–**7**, **10a**–**10g**, and **11a**–**11g** against PTP1B and SHP2.



Compd	R^1	R^2	IC_{50} (μM)[a]	
			PTP1B	SHP2
1	NH_2	H	NA[b]	39.13 ± 5.03
2		H	42.15 ± 12.36	26.51 ± 1.58
3		H	NA	30.62 ± 6.40
4		H	48.26 ± 27.94	23.92 ± 2.14
5		H	NA	NA
6		H	NA	NA
7		H	NA	NA
10a	NO_2		NA	NA
10b	NO_2		NA	NA
10c	NO_2		NA	NA
10d	NO_2		NA	NA
10e	NO_2		NA	NA
10f	NO_2		NA	NA
10g	NO_2		NA	29.95 ± 9.12
11a	NH_2		NA	NA
11b	NH_2		38.22 ± 1.29	5.81 ± 0.87
11c	NH_2		33.56 ± 1.04	13.98 ± 2.15
11d	NH_2		NA	15.53 ± 2.14
11e	NH_2		NA	25.80 ± 3.16
11f	NH_2		NA	NA
11g	NH_2		50.23 ± 2.40	2.11 ± 0.99
12	NH_2	Br	NA	42.39 ± 12.34
OA[c]			2.60 ± 0.48	
Na_3VO_4	–	–	–	7.43 ± 1.91

[a] IC_{50} values were determined by regression analyses and expressed as means ± SD of three replications; The *p*NPP substrate and 3-o-methylfluorescein phosphate (OMFP) substrate were utilized in PTP1B and SHP-2 respectively;
[b] NA: No activity (compound inhibitory ratio lower than 50% at the dose of 20 μg/mL);
[c] OA means oleanolic acid as positive control.