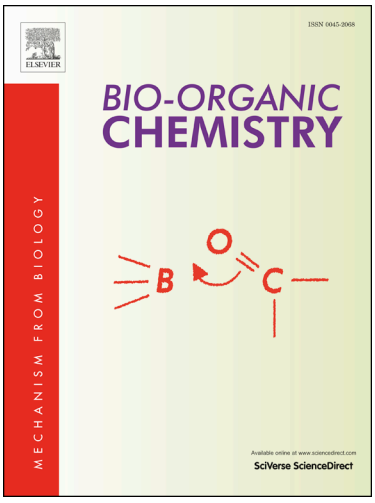

Synthesis and biological evaluation of (3'-amino -[1,1'-biphenyl]-4-yl) sulfamic acid derivatives as novel HPTPβ inhibitors

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Synthesis and biological evaluation of (3'-amino -[1,1'-biphenyl]-4-yl) sulfamic acid derivatives as novel HPTPβ inhibitors

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A series of novel (3'-amino-[1,1'-biphenyl]-4-yl) sulfamic acid derivatives were designed as nonphosphonate-based phosphotyrosy (pTyr) mimetics, synthesized and screened for use as HPTPβ inhibitors. Compounds C22 and C2 showed favorable HPTPβ inhibitory activity and better selectivity for HPTPβ than for PTP1B and SHP2. Docking results suggested that compounds C2 and C22 could not only efficiently fit into the catalytic site of the HPTPβ enzyme but also interact with the Lys1807, Arg1809 and Lys1811 residues of the secondary binding site, which was next to the catalytic center of the enzyme. The mode of interaction of the synthesized compound with the protein was different from the one found in a complex crystal of small molecules with HPTPβ (2I4H), in which the inhibitory molecule formed hydrogen bonds with the Gln1948 and Asn1735 residues of the secondary binding site.

Keywords: HPTPβ; Inhibitor; Drug design; Synthesis; Activity evaluation

1. Introduction

The phosphorylation of proteins on tyrosine is a post-translational modification and the proper level of phosphorylation plays a vital role in the control of cell signal transduction. The state of protein tyrosine phosphorylation is regulated by two kinds of enzymes with opposing action. Protein tyrosine kinases (PTKs) catalyze the phosphorylation of proteins on tyrosine residues, and protein tyrosine phosphatases (PTPases) show the function of dephosphorylation. [1] This dynamic balance affects a range of cellular processes such as survival, growth, migration, differentiation and energy metabolism, and a disruption in the balance between these processes leads to numerous human diseases. Agents targeting PTKs and PTPs have been heavily pursued for treating diseases such as cancer, atherosclerosis, and diabetes. [2]

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HPTPβ is a member of the classical protein tyrosine phosphatases family, specifically expressed in endothelial cells. The mouse ortholog of HPTPβ is named vascular endothelial protein tyrosine phosphatase (VE-PTP). [3] HPTPβ consists of an extracellular domain with multiple fibronectin type III repeats, a single transmembrane region and one cytoplasmic catalytic domain. [4] VE-PTP null mice suffered from vasculogenesis but died embryonically due to defects in angiogenesis, indicating that VE-PTP plays an important role in blood vessel development. [5, 6] HPTPβ is a negative regulator of Tie2, an endothelial cell specific receptor PTK, whose activation has been implicated in the development of lymphatic and blood vessel maturation, stabilization and integrity. [3, 7-9] Antibodies against the extracellular domain of HPTPβ imitated the effect of VE-PTP gene deletion, triggering enlargement of vascular structures and enhancing endothelial cell proliferation through the activation of Tie-2 and Erk1/2. [10] VE-PTP was inhibited by an inhibitor that contributed to the activation of Tie-2 and triggering of eNOS (endothelial nitric oxide synthase), which prevented extravasation of tumor cells, delayed micrometastatic progression and prolonged survival in mouse models of breast cancer. Consequently, these results suggested that HPTPβ was crucial for remodeling the blood vessel and maintaining the integrity of the blood vessel. HPTPβ may be a potential target for treating tumor growth, occlusive cardiovascular disease, vascular leaking syndrome and other vascular-related diseases. Therefore, HPTPβ has attracted close attention of researchers as a drug target for disease treatment. To date, while a series of phosphatase inhibitors had been reported, these usually showed the drawbacks of poor cell membrane permeability for their negatively charged polar residues, and poor selectivity for the conservation of the enzyme family catalytic center. In this work, we sought to discover the HPTPβ inhibitors with potent inhibitory activity and high selectivity for enzyme family by designing low molecular weight, non-phosphonate phosphotyrosyl mimetics inhibitors based on known literature compounds A and B (Fig. 1). The P&GP corporation identified sulfamic acid as a potential phosphotyrosine mimetic through high-throughput screening of its compound repository. [11] Subsequently, Peters et al used sulfamic acid as a core

group to design and synthesize a series of compounds as B, and identified one lead candidate for the treatment of patients with diabetic macular edema (DME) by inhibiting HPTPβ. [12] Zhang et al combined hydroxyindole carboxylic acid with a large and diverse number of carboxylic acids and synthesized a series of compounds as A which had selectivity and excellent cellular activity. [13] Therefore, we have full exploited the combination principle of drug design to generate compound C through coupling the sulfamic acid phosphotyrosine mimetic with amide. As shown in Figure 1, the structural hybridization of compounds A and B should show the following advantages: (i) the hydroxyindole carboxylic acid group in A was replaced with phenethylamino sulfamic acid from B to improve the affinity, and (ii) the amide side chain of compound A was retained to improve the selectivity. A series of diphenyl amino sulfonylic acid derivatives were designed and synthesized, and a few of them showed potent activity and favorable selectivity.

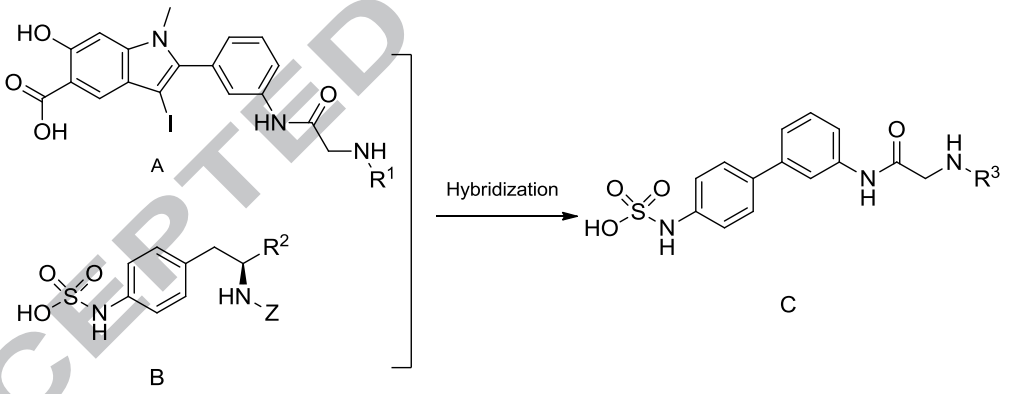


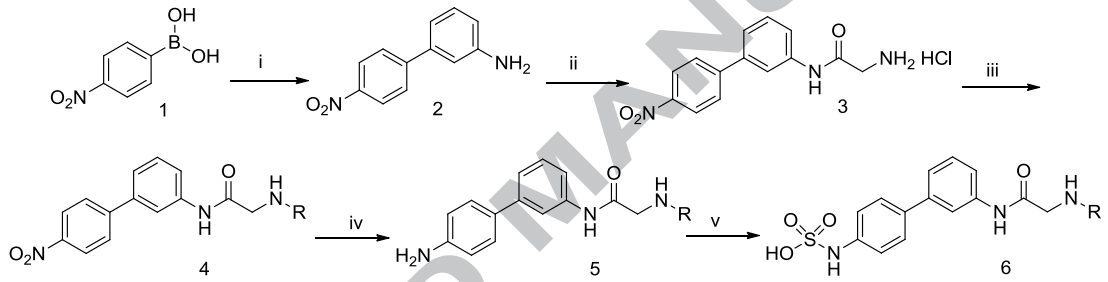
Figure 1. Structure of HPTPβ inhibitors. R^1, R^3 and Z: carboxylic acid group; R^2 and Z: aryl group

2. Results and discussion

2.1. Synthetic studies

The synthesis of the designed compounds (C1-22) was accomplished by using known synthetic approaches. The synthesis of (3'-amino-[1,1'-biphenyl]-4-yl) sulfamic acid derivatives is outlined in Scheme 1. The synthetic process started with 4-nitrophenylboronic (1) and 3-iodoaniline through the Suzuki reaction to afford 4'-nitro-[1,1'-biphenyl]-3-amine (2). [14] The condensation of compound (2) with

BOC-glycine in the presence of DCC afforded the intermediate, and then, the deprotection was carried out on the intermediate by concentrated hydrochloric acid to give compound (3). [15] The key intermediate 2-amino-N-(4'-nitro-[1,1'-biphenyl]-3-yl) acetamide hydrochloride (3) was acylated by various carboxylic acids, acyl chloride, or sulfonyl chloride to give intermediates (4). [16] Intermediates (4) underwent the reduction in the nitro group to afford intermediate (5). Then, the final target compounds were prepared by sulfonylation of intermediates (5). The structures of the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR and high-resolution mass spectrometry.



Scheme 1. (i) 3-iodoaniline, $Pd(dppf)Cl_2$, NaOH THF, refluxed, overnight; (ii) a: BOC-Glycine, DCC, EA, r.t, b: HCl, r.t, 8h; (iii) aromatic carboxylic acid, EDCI, HOBT, DIPEA, DMF, r.t, overnight; (iv) $FeCl_3.6H_2O$, C, $N_2H_4.H_2O$, EtOH, reflux

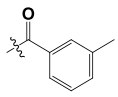
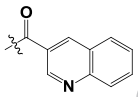
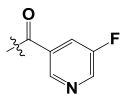
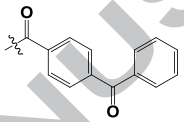
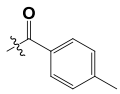
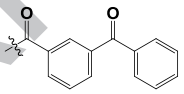
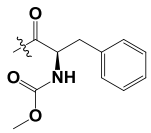
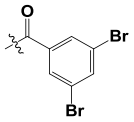
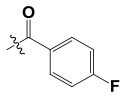
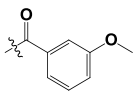
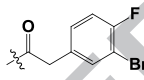
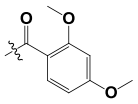
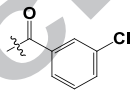
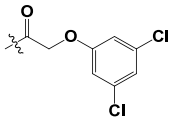
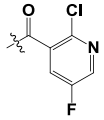
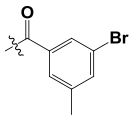
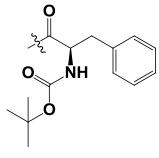
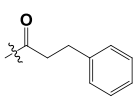
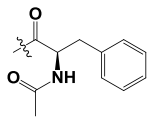
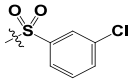
2.2. In vitro HPTPβ inhibition and selectivity

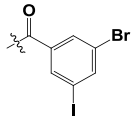
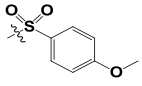
The newly synthesized diphenyl amino sulfonyl acid derivatives (C1–22) were first evaluated for the human recombinant PTPRB protein inhibitory activity at the concentration of 10 μM. [17] Then, the IC_{50} of the compounds for which the %inhibition was greater than 60 were further determined. The results are shown in Table 1. It was found that the IC_{50} values of nine compounds were below 4 μM and that the vales for two compounds were smaller than 1 μM against HPTPβ.

According to the literature [13, 18], we initially focused on the optimization of the aromatic carboxylic acid of the side chain of the compounds. The results showed that the %inhibition varied with the position of the substituent group on the aromatic ring. The compounds with meta-substitution on the phenyl had better inhibitory effect on HPTPβ than the compounds with the para- (C1 vs. C3) and ortho-substitutions (C2 vs.

C8). The activity of the compounds was improved when the meta-substituted groups were strong electron-donating groups (C16 vs. C1) or electron-withdrawing groups (C15 vs. C11). The same type of substituent group may be more suitable (C11 vs. C19).

Table 1. In vitro HPTPβ enzyme inhibitory activity of the compound

compd	R^3	%inhibition [a]	IC_{50}(μM)	compd	R^3	%Inhibition [a]	IC_{50}(μM)
C1		80.28	1.88	C12		63.66	8.95
C2		88.49	0.81	C13		51.37	
C3		33.91		C14		49.34	
C4		54.84		C15		92.16	1.02
C5		67.62	3.54	C16		85.23	1.64
C6		33.70		C17		45.10	
C7		34.94		C18		61.99	7.06
C8		69.83	3.72	C19		38.10	
C9		84.04	2.63	C20		40.82	
C10		50.61		C21		78.82	2.68

C11		40.72	C22		91.70	0.59

[a] The percent inhibition of the tested compounds against HPTPβ was measured at the concentration of 10 μM.

It was also observed that the compound containing the sulfonamide group showed better affinity than the compounds containing amide groups (C22 vs. C16). A new round of design, synthesis and evaluation of the compounds containing sulfonyl groups will be carried out in our subsequent work. In this work, the compound C22 (IC_{50}: 0.59 μ M) with the best activity was similar to the lead compound L87B44 [13] (IC_{50}: 0.38 μ M) that was the best compound among the A derivatives.

For the diphenyl aminosulfonyl acid derivatives with IC_{50} values smaller than 1 uM on HPTPβ, the selectivity over PTPs (SHP2 and PTP1B) was evaluated in vitro by using the same test method, with the results for the potent compounds (C2, C22) listed in Table 2. [17, 19] As shown in Table 2, the two diphenyl aminosulfonyl acid derivatives showed favorable selective inhibitory activity for HPTPβ over PTP1B and SHP2. More than 170-fold and 230-fold selectivity for HPTPβ versus PTP1B and SHP2, respectively, was observed for compound C22. However, the selectivity of L87B44 was enhanced only by approximately a factor of 15. [13]

Table 2. Inhibitory effect of compounds C2 and C22 on HPTPβ, PTP1B and SHP2

Phosphatase	IC_{50} (μM)		
	C2	C22	BVT948 [b]
HPTPβ	0.81	0.59	-
PTP1B	ND [a]	150.3	0.21
SHP2	ND	138.0	0.25

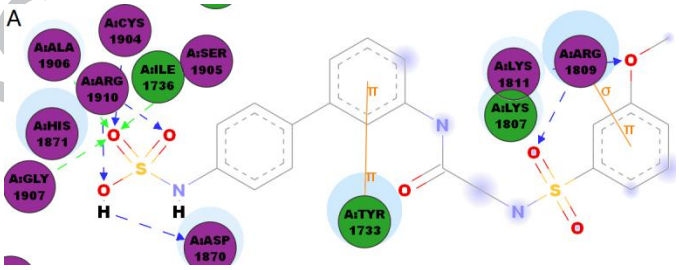
[a] ND: not determined (under the test concentration of compound from 0.49 μM to 250 μM.)

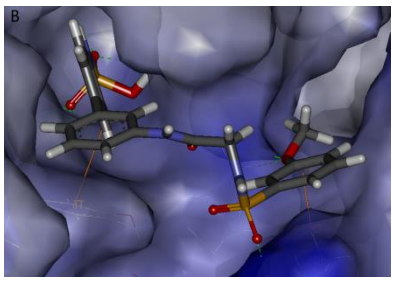
[b] BVT948: a potent inhibitor against PTP1B and SHP2

2.3.Molecular docking simulation

Molecular docking was used to imitate the interaction mode between the synthesized compounds and the HPTPβ protein. The docking of compounds C2 and C22 with HPTPβ was performed using GOLD in Discover Studio. Figure 3 shows that the

amino sulfonylic acid of compounds C2 and C22 could extend deeply into the active site of HPTPβ (PDB: 2I4H) and formed several hydrogen bonds with key residues including Ala215, Arg221 Cys1904, Ser1905, Ala1906, Gly1907, Val1908, Gly1909 and Arg1910. [20] The observed H-bond poses were similar to that of phenethylamino sulfamic acid in the crystal structure of 2I4H. A π-π stacking interaction was formed between the second phenyl ring of the compounds and the phenyl ring of Tyr1733 of HPTPβ. In addition, we found that the interaction between the compounds with the secondary binding pocket in the vicinity of the PTP active site was completely different from that of the interaction in the crystal structure of 2I4H. The aromatic ring of the amide side chain of compound C22 showed σ-π interaction with Arg1809, and the sulfonyl group formed H-bonds with Lys1811 and Arg1809 (Fig. 2A). Compound C2 showed the same docking pose as C22, but the interaction between C2 and HPTPβ was slightly different from that of C22 in several ways (Figs. 2B and 2D). The first phenyl ring of compound C2 showed a π-π interaction with the phenyl ring of Tyr1733, and the two extra H-bonds were formed (Fig. 2C). The two docking results were similar not only in the number of hydrogen bonds but also in the strength of the van der Waals' force, and the docking result was consistent with the activity of the compounds. This different mode of interaction may be the origin of the enhanced selectivity of the compounds against other PTPs, providing a new strategy for the future design of new inhibitors of HPTPβ.





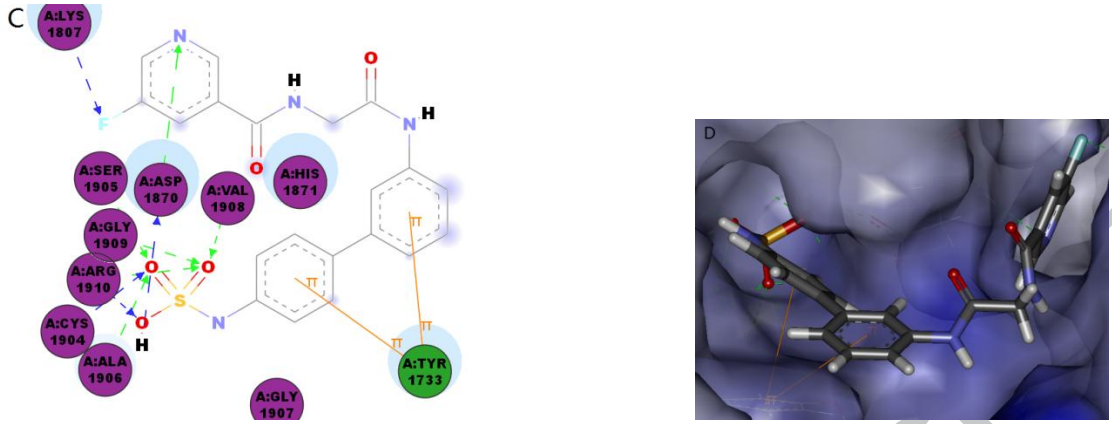


Figure 2. A and C: the interaction mode of compounds C22 and C2 with HPTPβ; B and D: binding conformations of compounds C-22 and C2 with HPTPβ. Hydrogen bonds are depicted with blue and green arrows.

3. Conclusion

A series of diphenyl amino sulfonyl acid derivatives as HPTPβ inhibitors were designed and synthesized, and their inhibitory activity on HPTPβ was tested. Two compounds showed good inhibitory activity on HPTPβ with IC_{50} below 1 μM, and compound C22 also showed higher inhibition selectivity for HPTPβ compared to that of PTP1B and SHP2, with enhancement by factors of approximately 170 and 230 compared to that of PTP1B and SHP2, respectively. The preliminary structure-activity relationship demonstrated that meta-substitution on the aromatic ring of the side chain was favorable. Stronger electron-donating groups or electron withdrawing groups were favorable for enhancing the activity of the compounds. An increase in the length of the carboxylic chain showed a certain effect on the activity of the compounds. The activities of compounds containing sulfonamide were superior to those of the compounds with amide side chains. Docking results showed that the amino acid residues Lys1807, Arg1809 and Lys1811 located in the new secondary binding sites of HPTPβ were involved in the interaction with the synthesized compounds by forming hydrogen bonds.

4. Experimental section

4.1. Chemistry

The melting point of the compound was determined by the capillary tube method by using an RY-1G melting point instrument (uncorrected temperature) purchased from Tianjin tianguang optical instrument Co., Ltd.; 1H-NMR spectrum was measured

using a Japanese electron JNM-ECA-400 nuclear magnetic resonance spectrometer; ESI-MS mass spectrometry was performed by an API 3000 three heavy four stage tandem mass spectrometer. Silica gel used in column layer chromatography was purchased from Qingdao marine chemical plant and silica gel board was purchased from Yantai Chemical Industry Research Institute. The solvent used in the experiment was purchased from Beijing chemical plant and Beijing chemical reagent company, all sold as analytically pure.

4.1.1. Synthesis of intermediates

4'-nitro-[1, 1'-biphenyl]-3-amine ***(2)***

The mixture of 4-nitrophenylboronic acid (5.0 g, 30.0 mmol), 3-iodoaniline (6.2 g, 28.4 mmol) and Pd(dppf)Cl_2 (0.49 g, 0.60 mmol) were dissolved in tetrahydrofuran (150.0 mL) where 5 M NaOH (3.7 g, 92.8 mmol) was gradually added. The mixture was heated to reflux overnight. The reaction solution was filtered when the raw material was completely consumed as indicated by TLC. The filtrate was concentrated to dry, and the residue was taken up with AcOEt (80 mL). The AcOEt solution was washed with brine (3*20 mL). The organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The crude residue was purified by column chromatography to give the desired compound as a yellow solid (3.48 g, 54.3%).

M.P: 133-137°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 – 8.22 (m, 2H), 7.86 – 7.78 (m, 2H), 7.17 (t, J = 7.8 Hz, 1H), 6.94 (t, J = 1.9 Hz, 1H), 6.88 (ddd, J = 7.6, 1.8, 0.9 Hz, 1H), 6.68 (ddd, J = 8.0, 2.2, 0.9 Hz, 1H), 5.30 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.95, 149.94, 148.16, 146.93, 139.07, 130.29, 128.01 (2C), 124.55 (2C), 115.21, 115.17, 112.78; ESI-MS *m/z*: 215.08 $[M+H]^+$

2-amino-N-(4'-nitro-[1, 1'-biphenyl]-3-yl) acetamide hydrochloride ***(3)***

To a solution of 4'-nitro-[1, 1'-biphenyl]-3-amine 2 (2.5 g, 11.7 mmol) in AcOEt (25.0 mL), BOC-glycine (2.2 g, 12.3 mmol) and DCC (2.9 g, 14.0 mmol) were added at room temperature (r.t). The mixture was stirred overnight, filtered and washed by EA. Concentrated hydrochloric acid was added into filtrate with stirring overnight at r.t. Finally, the mixture was filtered to give the title compound as a yellow solid (2.9 g,

80.1%).

M.P: 225-230°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 8.34 (m, 4H), 8.04 (s, 1H), 7.89 (d, J = 8.6 Hz, 2H), 7.72 (m, 1H), 7.52 (d, J = 5.0 Hz, 2H), 3.83 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.63, 147.35, 146.90, 139.72, 139.08, 130.49, 128.32 (C2), 124.80 (2C), 123.25, 120.21, 118.25, 41.58; ESI-MS *m/z*: 272.10 $[M+H]^+$

4.1.2. General procedure for the target compounds ***(C1-22)***

To a solution of 2-amino-N-(4'-nitro-[1,1'-biphenyl]-3-yl)acetamide hydrochloride 3 (0.3 g, 0.97 mmol) in DMF (10 mL), a variety of aromatic acid (1.02 mmol), HOBT (0.13 g, 0.97 mmol), EDCI (0.19 g, 0.97 mmol) and DIPEA (0.38 g, 2.9 mmol) were added at room temperature and stirred overnight at r.t. Plenty of water was added into the reaction solution with stirring until precipitate formation was no longer observed and then intermediate 4 was obtained by filtration as a faint yellow solid (75%~95%). It was then directly used for the next step without further purification.

To a solution of intermediate 4 in ethanol (15 mL), $FeCl_3.6H_2O$ (0.05 g, 0.19 mmol), charcoal (0.14 g, 11.6 mmol) and hydrazine hydrate (0.58 g, 11.6 mmol) were added at room temperature and the mixture was heated to reflux. The charcoal and the inorganic salts were filtered off through a Celite pad until the compound was completely consumed as indicated by TLC (4 h). The filtrate was concentrated to give a crude product of compound 5 (75%~95%) as a white solid, which was directly used for next step without further purification.

To create compound 6 Me_3NSO_3 (0.2 g, 1.4 mmol) and the TEA (0.10 g, 0.97 mmol) were added to a solution of compound 5 in THF at 50~60°C. TLC analysis monitored the reaction indicating that compound 5 was not completely consumed. The reaction was stopped at that point. The crude product of compound 6 was purified by column chromatography to give the target compound as a solid containing TEA (30%-70%).

(3'-(2-(3-methylbenzamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C1)***

M.P: 198-201°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.89 (s, 1H), 8.81 (t, J = 5.8 Hz, 1H), 7.73 (dd, J = 22.5, 8.1 Hz, 3H), 7.55 (d, J = 7.2 Hz, 1H), 7.40 – 7.15 (m, 6H), 7.11 (d, J = 8.6 Hz, 2H), 4.08 (d, J = 5.7 Hz, 2H), 3.49 – 3.24 (m, 1H),

2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.43, 167.22, 144.17, 141.70, 139.93, 138.10, 134.49, 132.47, 130.32, 129.69, 128.76 (2C), 128.47, 127.64, 126.82 (2C), 125.01, 121.34, 116.93 (2C), 43.77, 21.51; HRMS (ESI-) *m/z* $[M-H]^-$ calculated for $C_{22}H_{20}N_3O_5S$: 438.1124 found: 438.1130.

(3'-(2-(5-fluoronicotinamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C2)***

M.P: 225-227°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H), 9.21 (t, *J* = 5.8 Hz, 1H), 8.96 (t, *J* = 1.6 Hz, 1H), 8.78 (d, *J* = 2.8 Hz, 1H), 8.15 (ddd, *J* = 9.6, 2.8, 1.7 Hz, 1H), 8.04 (s, 1H), 7.76 (s, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.41 – 7.28 (m, 3H), 7.29 – 7.21 (m, 1H), 7.11 (d, *J* = 8.7 Hz, 2H), 4.13 (d, *J* = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.90, 164.49, 159.32 (d, J = 255.2 Hz), 145.33 (d, J = 3.8 Hz), 144.22, 141.74, 140.97 (d, J = 23.2 Hz), 139.79, 130.22, 129.70, 127.66, 126.81 (2C), 122.49 (d, J = 19.5 Hz), 121.47, 117.53, 117.03, 116.91 (2C), 43.80; HRMS (ESI-) *m/z* $[M-H]^-$ calculated for $C_{20}H_{16}FN_4O_5S$: 443.0825 found: 443.0831.

(3'-(2-(4-methylbenzamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C3)***

M.P: 210-211°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.77 (t, *J* = 5.5 Hz, 2H), 8.04 (s, 1H), 7.92 – 7.68 (m, 3H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.41 – 7.18 (m, 6H), 7.11 (d, *J* = 8.3 Hz, 2H), 4.07 (d, *J* = 5.6 Hz, 2H), 2.76 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.13, 167.64, 156.65, 143.74, 141.27, 139.27, 138.28, 129.77, 129.24 (2C), 129.19, 128.11 (2C), 126.31 (2C), 120.97, 116.96, 116.46 (2C), 56.35, 51.45, 42.84, 37.33; HRMS (ESI-) *m/z* $[M-H]^-$ calculated for $C_{22}H_{20}N_3O_5S$: 438.1124 found: 438.1129.

(S)-(3'-(2-(2-((methoxycarbonyl)amino)-3-phenylpropanamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C4)***

M.P: 188-191°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.47 (s, 1H), 8.04 (s, 1H), 7.76 (s, 1H), 7.54 (dd, *J* = 25.4, 8.1 Hz, 2H), 7.31 (dt, *J* = 18.7, 8.1 Hz, 9H), 7.20 (d, *J* = 6.7 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 2H), 4.26 (d, *J* = 7.7 Hz, 1H), 3.93 (s, 2H), 3.52 – 3.41 (s, 3H), 3.05 (d, *J* = 10.3 Hz, 1H), 2.82 – 2.69 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.13, 167.64, 156.65, 143.74, 141.27, 139.27, 138.28, 129.77, 129.24 (2C), 129.19, 128.11 (2C), 126.31 (2C), 120.97, 116.96, 116.46 (2C), 56.35, 51.45, 42.84, 37.33; HRMS (ESI-) *m/z* $[M-H]^-$ calculated for $C_{25}H_{25}N_4O_7S$: 525.1444

found: 525.1449.

(3'-(2-(4-fluorobenzamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C5)***

M.P: 177-180°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.92 (t, J = 5.9 Hz, 1H), 8.09 – 7.92 (m, 3H), 7.77 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.41 – 7.12 (m, 6H), 7.10 (d, J = 2.0 Hz, 2H), 4.08 (d, J = 5.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.88, 165.61, 164.02 (d, J = 248.6 Hz), 143.68, 141.22, 139.43, 130.49 (d, J = 2.8 Hz), 130.12, 130.03, 129.85, 129.21, 126.35 (2C), 120.89, 116.99, 116.47, 116.45 (2C), 115.44, 115.23; HRMS (ESI-) *m/z* [M-H]$^-$ calculated for $C_{21}H_{17}FN_3O_5S$: 442.0873 found: 442.0873.

(3'-(2-(2-(3-bromo-4-fluorophenyl)acetamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C6)***

M.P: 121-123°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 8.49 (t, J = 5.7 Hz, 1H), 8.07 (s, 1H), 7.75 (d, J = 1.4 Hz, 1H), 7.70 – 7.62 (m, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.43 – 7.22 (m, 6H), 7.12 (d, J = 8.6 Hz, 2H), 5.77 (s, 1H), 3.93 (d, J = 5.8 Hz, 2H), 3.55 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.66, 168.21, 157.62 (d, J = 243.5 Hz), 144.19, 141.76 (d, J = 7.5 Hz), 139.80, 135.06, 134.40 (2C), 130.99, 129.69, 127.64, 126.83 (2C), 117.02, 116.93 (2C), 116.80, 114.76, 108.01, 43.34, 41.04; HRMS (ESI-) *m/z* [M-H]$^-$ calculated for $C_{22}H_{18}BrFN_3O_5S$: 534.0135 found: 534.0136.

(3'-(2-(3-chlorobenzamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C7)***

M.P: 234-237°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 9.02 (t, J = 5.8 Hz, 1H), 7.99 – 7.90 (m, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.76 (s, 1H), 7.63 (ddd, J = 28.3, 14.2, 13.1 Hz, 1H), 7.53 (d, J = 7.8 Hz, 2H), 7.39 – 6.87 (m, 4H), 7.03 – 6.87 (m, 2H), 4.09 (d, J = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.18, 165.76, 144.15, 141.70, 139.87, 136.47, 133.74, 131.80, 130.95, 130.32, 129.70, 127.75, 126.83 (2C), 126.65, 121.41, 117.51, 116.99, 116.95 (2C), 43.8; HRMS (ESI-) *m/z* [M-H]$^-$ calculated for $C_{21}H_{17}ClN_3O_5S$: 458.0577 found: 458.0584.

(3'-(2-(2-chloro-5-fluoronicotinamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C8)***

M.P: 170-173°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 9.07 (t, J = 5.5 Hz,

1H), 8.58 (d, *J* = 3.0 Hz, 1H), 8.01 (dd, *J* = 7.9, 3.0 Hz, 1H), 7.76 (s, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.46 – 7.21 (m, 4H), 7.12 (d, *J* = 8.4 Hz, 2H), 4.13 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.42, 164.66, 158.54 (d, J = 255.4 Hz), 144.26, 142.28 (d, J = 2.5 Hz), 141.80, 139.74, 138.92 (d, J = 25.7 Hz), 134.08 (d, J = 3.8 Hz), 130.26, 129.72, 126.82(2C), 126.36 (d, J = 21.5 Hz), 121.53, 117.54, 117.04, 116.97(2C), 43.59; HRMS (ESI-) *m/z* [M-H]$^-$ calculated for $C_{21}H_{19}ClFN_4O_5S$: 477.0436 found: 477.0449.

(S)-(3'-(2-(2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C9)***

M.P: 93-95°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 9.24 (s, 1H), 8.37 (t, *J* = 5.3 Hz, 1H), 8.05 (s, 1H), 7.75 (s, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.44 – 7.22 (m, 8H), 7.22 – 7.15 (m, 1H), 7.10 (dd, *J* = 15.1, 8.5 Hz, 3H), 4.49 – 4.20 (m, 1H), 4.23 – 3.83 (m, 2H), 2.85 – 2.71 (m, 1H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.72, 168.15, 156.01, 149.05, 144.22, 141.80, 138.78, 129.75(2C), 128.56(3C), 127.63 (2C), 126.81 (2C), 126.70, 116.95 (2C), 114.72 (2C), 78.70, 56.40, 43.36, 37.81, 28.66 (3C); HRMS (ESI-) *m/z* [M-H]$^-$ calculated for $C_{28}H_{31}N_4O_7S$: 567.1913 found: 567.1919.

(S)-(3'-(2-(2-acetamido-3-phenylpropanamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C10)***

M.P: 95-97°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (s, 1H), 8.49 (t, J = 5.9 Hz, 1H), 8.28 (d, J = 7.7 Hz, 1H), 8.07 (s, 1H), 7.79 (s, 1H), 7.60 (d, J = 8.6 Hz, 1H), 7.43 – 7.23 (m, 8H), 7.20 (dd, J = 8.6, 4.4 Hz, 1H), 7.14 – 7.05 (m, 2H), 4.49 (ddd, J = 9.9, 7.8, 4.6 Hz, 1H), 3.90 (ddd, J = 40.4, 16.7, 5.9 Hz, 2H), 3.05 (dd, J = 13.8, 4.6 Hz, 1H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.43, 170.27, 168.15, 148.96, 144.21, 141.75, 139.72, 138.57, 130.28, 129.64 (2C), 128.61 (2C), 127.81, 127.61, 126.80, 121.22, 117.23, 116.96, 116.88, 114.77, 55.03, 43.33, 37.78, 23.04; HRMS (ESI-) *m/z* [M-H]$^-$ calculated for $C_{25}H_{25}N_4O_6S$: 627.9039 found: 627.9044.

(3'-(2-(3-bromo-5-iodobenzamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C11)***

M.P: 149-155°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 9.10 (s, 1H), 8.93 – 8.74 (m, 1H), 8.31 – 8.00 (m, 3H), 7.75 (s, 1H), 7.54 (d, *J* = 7.0 Hz, 1H), 7.42 – 7.16

(m, 4H), 7.11 (d, *J* = 8.5 Hz, 2H), 4.08 (d, *J* = 5.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.96, 164.36, 144.21, 141.98, 141.73, 139.80, 137.91, 135.65 (2C), 130.27, 129.67, 126.80 (2C), 123.07, 121.46, 117.59, 117.08, 116.97 (2C), 96.39, 43.89; HRMS (ESI-) *m/z* [M-H]$^-$ calculated for $C_{21}H_{16}BrIN_3O_5S$: 509.1495 found: 509.1498.

(3'-(5-fluoronicotinamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C12)***

M.P: 160-162°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 9.02 (t, *J* = 1.5 Hz, 1H), 8.81 (d, *J* = 2.8 Hz, 1H), 8.26 (ddd, *J* = 9.5, 2.8, 1.8 Hz, 1H), 8.09 (s, 1H), 7.93 (s, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.50 – 7.32 (m, 4H), 7.16 – 7.10 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.18, 159.24 (d, J = 255.3 Hz), 145.57 (d, J = 3.9 Hz), 140.97 (d, J = 22.9 Hz), 144.26, 141.68, 141.09, 140.86, 139.56, 132.72 (d, J = 3.0 Hz), 130.11, 129.69, 126.84 (2C), 122.89 (d, J = 19.7 Hz).122.25, 118.61, 118.22, 116.93 (2C); HRMS (ESI-) *m/z* [M-H]$^-$ calculated for $C_{24}H_{19}N_4O_5S$: 475.1076; found: 475.1085.

(3'-(2-(4-benzoylbenzamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C13)***

M.P: 98-102°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 9.09 (t, *J* = 5.7 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 3H), 7.81 – 7.75 (m,4H), 7.72 (t, *J* = 7.4 Hz, 1H), 7.59 (dd, *J* = 16.2, 8.5 Hz, 3H), 7.45 – 7.19 (m, 4H), 7.12 (d, *J* = 8.6 Hz, 2H), 4.13 (d, *J* = 5.7 Hz, 2H);^{13}C NMR (100 MHz, DMSO-d_6) δ 195.99, 168.19, 166.42, 144.19, 141.73, 139.90, 139.85, 137.83, 137.22, 133.57 (2C), 130.25 (3C), 130.07 (3C), 129.23 (3C), 128.10 (2C), 127.63, 126.82 (2C), 116.98 (2C), 43.89; HRMS (ESI-) *m/z* [M-H]$^-$ calculated for $C_{28}H_{22}N_3O_6S$: 528.1229; found: 528.1236.

(3'-(2-(3-benzoylbenzamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C14)***

M.P: 101-105°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 9.10 (t, *J* = 5.5 Hz, 1H), 8.25 (dd, *J* = 30.1, 10.5 Hz, 2H), 8.05 (s, 1H), 7.97 – 7.85 (m, 1H), 7.83 – 7.66 (m, 5H), 7.65 – 7.50 (m, 3H), 7.44 – 7.19 (m, 4H), 7.11 (d, *J* = 8.7 Hz, 2H), 4.10 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.00, 168.22, 166.31, 144.21, 141.80, 141.72, 139.88, 137.78, 137.28, 134.74, 133.51 (2C), 131.85, 130.30, 130.24(3C), 129.36, 129.25 (3C), 128.90, 127.62, 126.81, 116.96 (2C), 114.75, 43.87; HRMS (ESI-) *m/z* [M-H]$^-$ calculated for $C_{28}H_{22}N_3O_6S$: 528.1229; found: 528.1237.

(3'-(2-(3,5-dibromobenzamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C15)***

M.P: 192-194°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 9.14 (t, J = 5.8 Hz, 1H), 8.12 – 8.00 (m, 4H), 7.79 – 7.70 (m, 1H), 7.52 (t, J = 11.8 Hz, 1H), 7.39 – 7.27 (m, 3H), 7.25 (d, J = 7.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H), 4.08 (d, J = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.94, 164.34, 144.19, 141.71, 139.80, 137.98, 136.65, 130.26, 129.97 (2C), 129.69, 126.82 (2C), 123.19 (2C), 121.45, 117.55, 117.02, 116.92 (2C), 43.89; HRMS (ESI-) *m/z* [M-H]$^-$ calculated for $C_{21}H_{16}Br_2N_3O_5S$: 579.9177; found: 579.9183.

(3'-(2-(3-methoxybenzamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C16)***

M.P: 169-172°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.84 (t, J = 5.7 Hz, 2H), 7.77 (s, 1H), 7.68 – 7.19 (m, 8H), 7.12 (dd, J = 8.6, 2.0 Hz, 3H), 4.08 (d, J = 5.8 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.39, 166.86, 159.69, 144.17, 141.70, 139.93, 135.91, 130.32, 130.01 (2C), 129.69, 126.83 (2C), 120.11, 117.85, 116.93 (3C), 112.93 (2C), 55.80, 43.81; HRMS (ESI-) *m/z* [M-H]$^-$ calculated for $C_{22}H_{20}N_3O_6S$: 454.1073; found: 454.1076.

(3'-(2-(2,4-dimethoxybenzamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C17)***

M.P: 177-180°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 9.84 (d, J = 13.4 Hz, 1H), 8.29 (t, J = 5.2 Hz, 1H), 7.70 (d, J = 8.7 Hz, 1H), 7.55 (s, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.17 – 7.07 (m, 3H), 7.04 (d, J = 7.9 Hz, 1H), 6.90 (d, J = 8.7 Hz, 2H), 6.51 – 6.39 (m, 2H), 3.94 (d, J = 5.2 Hz, 2H), 3.75 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.35, 164.78, 163.64, 159.52, 141.65, 139.88, 133.28 (2C), 129.69, 127.73 (3C), 121.06, 116.73, 114.37, 106.30 (3C), 99.03 (2C), 56.69, 56.06, 44.02; HRMS (ESI-) *m/z* [M-H]$^-$ calculated for $C_{23}H_{22}N_3O_7S$: 484.1178; found: 484.1187.

(3'-(2-(2-(3,5-dichlorophenoxy)acetamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C18)***

M.P: 169-173°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 1H), 8.31 (s, 1H), 8.05 (s, 1H), 7.72 (s, 1H), 7.62 (s, 1H), 7.58 – 7.48 (m, 1H), 7.32 (dt, J = 22.5, 8.2 Hz, 5H), 7.12 (t, J = 9.3 Hz, 3H), 4.74 (s, 2H), 4.01 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.96, 167.82, 152.94, 144.14, 141.71, 139.73, 130.34, 129.86 (2C), 129.72, 128.60,

127.64, 126.85, 125.64, 122.98, 117.01, 116.96 (2C), 116.00, 114.76, 68.15, 42.99; HRMS (ESI-) *m/z* [M-H]$^-$ calculated for $C_{22}H_{18}Cl_2N_3O_6S$: 522.0293; found: 522.0299.

(3'-(2-(3-bromo-5-methylbenzamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C19)***

M.P: 220-223°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.96 (t, *J* = 5.8 Hz, 1H), 7.90 (d, *J* = 1.2 Hz, 1H), 7.75 (dt, *J* = 2.2, 1.6 Hz, 2H), 7.62 (dd, *J* = 2.4, 1.6 Hz, 1H), 7.54 (t, *J* = 8.3 Hz, 1H), 7.43 – 7.21 (m, 4H), 7.18 – 7.03 (m, 2H), 4.08 (d, *J* = 5.7 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.17, 165.81, 141.77, 141.13 (2C), 139.85, 136.44, 134.96, 130.26, 129.65, 127.71, 127.76, 127.74, 127.64 (2C), 126.81, 121.98 (2C), 116.92, 114.85, 43.82, 21.11; HRMS (ESI-) *m/z* [M-H]$^-$ calculated for $C_{22}H_{19}BrN_3O_5S$: 516.0229; found: 516.0234.

(3'-(2-(3-phenylpropanamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C20)***

M.P: 180-183°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 9.34 (t, *J* = 25.2 Hz, 1H), 8.25 (d, *J* = 5.5 Hz, 1H), 8.06 (s, 1H), 7.74 (s, 1H), 7.52 (d, *J* = 7.3 Hz, 1H), 7.38 – 7.13 (m, 9H), 7.11 (d, *J* = 8.4 Hz, 2H), 3.90 (d, *J* = 5.9 Hz, 2H), 3.59(m, 1H), 3.08(m, 1H),2.90 – 2.78 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.42, 168.43, 144.19, 141.90, 141.71, 139.84, 130.29, 129.68, 128.83 (2C), 128.76 (2C), 126.83 (2C), 126.41, 121.38, 117.46, 116.96, 116.92 (2C), 43.22, 37.29, 31.51; HRMS (ESI-) *m/z* [M-H]$^-$ calculated for $C_{23}H_{22}N_3O_5S$: 452.1280; found: 452.1288.

(3'-(2-(3-chlorophenylsulfonamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C21)***

M.P: 112-1143°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (s, 1H), 8.36 (d, *J* = 26.4 Hz, 1H), 8.07 (s, 1H), 7.86 (d, *J* = 1.7 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.72 – 7.53 (m, 3H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.28 (ddd, *J* = 21.8, 13.4, 7.8 Hz, 4H), 7.11 (d, *J* = 8.6 Hz, 2H), 3.75 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.65, 144.15, 142.92, 141.63, 139.44, 134.21, 132.93, 131.69, 130.25, 129.65, 126.85, 126.81 (2C), 125.85, 121.59, 117.54, 117.05, 116.93 (2C), 46.32; HRMS (ESI-) *m/z* [M-H]$^-$ calculated for $C_{20}H_{17}ClN_3O_6S_2$: 494.0247; found: 490.0254.

(3'-(2-(4-methoxyphenylsulfonamido)acetamido)-[1,1'-biphenyl]-4-yl)sulfamic acid ***(C22)***

M.P: 79-81°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.92 (s, 1H), 8.07 (s, 1H), 7.94 (dd, J = 22.7, 16.5 Hz, 1H), 7.76 (d, J = 8.9 Hz, 2H), 7.60 (d, J = 10.1 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.28 (dt, J = 24.1, 8.2 Hz, 4H), 7.09 (dd, J = 12.7, 8.8 Hz, 4H), 3.77 (s, 3H), 3.64 (d, J = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.85, 162.73, 144.19, 141.65, 139.49, 132.50, 130.28, 129.60, 129.38 (2C), 127.60, 126.79, 121.55, 117.16, 116.97 (2C), 114.75 (2C), 114.73, 56.12, 46.45; HRMS (ESI-) m/z [M-H]$^-$ calculated for $C_{21}H_{20}N_3O_7S_2$: 490.0743; found: 490.0746.

4.2 Bioactivity

4.2.1. Biological activity assay for HPTPβ

The HPTPβ enzyme reaction was carried out under the conditions described in a previous report [17]. The initial screening was carried out using a single concentration of compound (10 uM) and was repeated three times for the calculation of the percentage inhibition (%inhibition) of the tested compounds against HPTPβ. IC_{50} values were determined for the compounds for which %inhibition was greater than 60. Compounds were 3-fold diluted from 10 mM for 10 doses in DMSO and then diluted in assay buffer (50 mM Tris-HCl, 150 mM NaCl, 5 mM DTT, 1 mM EDTA, 0.01% BSA) in a 96 well plate. The plate was shaken for 15 minutes in the shaker, and the compounds were transferred into a 384-well assay plate. The recombinant human PTPRB protein (Abcam) was diluted in an assay buffer prior to use and then delivered to the 384-well assay plate. The enzyme and compound were preincubated for 10 minutes at room temperature. Then, DiFMUP (Invitrogen), a fluorogenic phosphatase substrate, was delivered to the plate. The assay plate was incubated at room temperature for 2 h and then scanned using an Enspire X (PerkinElmer) instrument.

4.4.2. Selectivity over other PTPs

The inhibition assay for these PTPs (PTP1B, SHP2) was performed under the same conditions as for HPTPβ except using a different DiFMUP and enzyme concentration identical to that used in Ref. [19]. Briefly, BVT 948 was used for quality control to prove the suitability of the evaluation method. Different reaction mixtures were prepared for different PTPs. For the PTP1B assay, the assay contains 50 mM Tris-HCl (pH 7.0), 150 mM NaCl, 5 mM DTT, 1mM EDTA, 0.005% BSA, 0.01 ng/μL PTP1B,

20 μM DiFMUP and different concentrations of the compounds. Whereas for the SHP2 assay, the assay contains 50 mM Tris-HCl (pH 7.0), 150 mM NaCl, 5 mM DTT, 1 mM EDTA, 0.003% BSA, 0.008 ng/μL SHP2, 20 μM DiFMUP and different concentrations of compounds. The reaction mixture was incubated at r.t for 2 h. Following the incubation, the plate was scanned using an Enspire X (PerkinElmer) instrument.

4.3. Molecular docking

Molecular docking was performed to predict the efficiency of binding between the HPTPβ and compounds C2, C22 by using GOLD. The structure of HPTPβ was retrieved from the Protein Data Bank (PDB ID: 2I4H, www.rcsb.org). The docking pocket was generated based on the observed binding site of the original ligand based on the PDB structure. The small molecule ligand was then re-docked into the corresponding protein structure. The docking reliability was evaluated through a comparison of the root mean square deviation between the positions of the heavy atoms of the ligand in the calculated crystal structure. This protocol successfully re-docked the original ligand with a low RMSD value of 0.8498 Å and was subsequently used in the molecular docking simulations. The interactions between the residues of the HPTPβ protein and sulfamic acid analogues were examined. The derivatives were energy minimized by ChemBio3D and SYBYL-X. After obtaining the docking results, the best pose out of 20 poses provided for each chemical structure was retained to understand the molecular interactions. The best pose score values in the series were used for the analysis of docking and the interactions.

Conflict of Interest

The authors are certain that this content of this article involves no conflict of interest.

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Highlights

- Designed and synthesized a series of novel compounds for inhibition HPTPβ.
- The minimum IC50 was less than 1 μM.
- Compounds C2 and C22 showed potent affinity and good selectivity for HPTPβ over PTP1B and SHP2.
- Analyzing the structure-activity relationship.
- Molecular docking simulation suggested the interaction between enzyme and inhibitor was different from the previous one.

Graphical abstract