Bioorg. Med. Chem. 28 (2020) 115777

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Study of triaryl-based sulfamic acid derivatives as HPTPβ inhibitors

Wenjuan Zhang [a], Zhao Wei [b], Guozhi Huang [c], Fei Xie [a], Zhibing Zheng [a,*], Song Li [a]

[a] National Engineering Research Center for the Emergency Strategic Drug, Beijing Institute of Pharmacology and Toxicology, Beijing 100850, China
[b] Department of Medicinal Chemistry, School of Pharmacy, Fourth Military Medical University, Xi'an 300071, China
[c] School of Chemical and Environmental Engineering, Shanghai Institute of Technology, Shanghai 201203, China

ARTICLE INFO

Keywords:
HPTPβ inhibitor
Drug design
Synthesis
Docking simulation
Triaryl-based derivatives

ABSTRACT

A series of novel triaryl-based sulfamic acid analogs was designed, synthesized and evaluated as inhibitors of human protein tyrosine phosphatase beta (HPTPβ). A novel, easy and efficient synthetic method was developed for target compounds, and the activity determination results showed that most of compounds were good HPTPβ inhibitors. Interestingly, the compounds **G4** and **G25** with simple structure not only showed potent inhibitory activity on HPTPβ but also had good inhibitory selectivity over other PTPs (PTP1B, SHP2, LAR and TC-PTP). The molecular docking simulation of compounds with the protein HPTPβ helped us understand the structure–activity relationship and clarify some confusing assay results. This research provides references for further drug design of HPTPβ and other PTPs inhibitors.

1. Introduction

Protein tyrosine phosphatases (PTPs) catalyze the removal of the phosphate from the tyrosine residues of proteins, thus antagonizing the functions of protein tyrosine kinases (PTKs).[1] The level of protein phosphorylation regulates by PTPs and PTKs plays an essential role in a number of physiological and pathogenic processes in human body. The alteration of PTP expression is related to numerous human diseases including cancer, diabetes, autoimmune disorders, etc.[2,3] Therefore, PTPs have attracted considerable attention as the targets for disease treatment, such as PTP1B (protein tyrosine phosphatase 1B), LAR (leukocyte antigen related protein) for diabetes and obesity, SHP2 (SH2 domain-containing protein phosphatase), TC-PTP (T cell protein tyrosine phosphatase) for cancer, and HPTPβ (human protein tyrosine phosphatase beta) for diabetic macular edema.

HPTPβ is an endothelial cell-specific receptor tyrosine phosphatase composed of an extracellular domain, a transmembrane region and a cytoplasmic catalytic domain.[4] Fachinger, et al. found that HPTPβ was a negative regulator of Tie2 and specifically modulates the angiopoietin (Ang)-tyrosine-protein kinase receptor 2 (Tie2) function.[5,6] The Ang-Tie signaling pathway has an important effect on regulating vascular angiogenesis, remodeling, vascular permeability and stability. Tie, including Tie1 and Tie2, is the receptor of Ang.Tie1 is regarded as an orphan receptor without a ligand and negatively regulates the Tie2 activation by forming heterodimers with Tie2.[7] Tie2 is predominantly located in vascular endothelial cells and plays a central role in vascular stability. Angiopoietin 1 (Ang1) and angiopoietin 2 (Ang2) are the ligands of Tie2. When Ang1 binds to Tie2, the signaling pathway and the corresponding cascade response are triggered to stabilize the blood vessels.[8,9] Ang2 acts as a context-dependent Tie2 agonist or antagonist that can inhibit the Ang1-Tie2 axis.[10] Therefore, the HPTPβ-Tie2 signaling pathway is used to treat the diseases related to vascular leakage, such as cancer and retinal and choroidal vascular diseases.[11,12]

The following difficulties are encountered in the process of development of PTPs inhibitors. First, the key cysteine of the catalytic center of PTPs results in obtaining compounds with undesirable physicochemical properties such as high oxidizing and alkylation abilities in the high throughput screening.[13] Second, the key cysteine has an extremely low pKa (-5) compared with that of a general Cys in protein (−8.5).[14] The study found that the active-site residues such as histidine and threonine could lower the p*K*a of Cys.[15] The cysteine with low p*K*a is deprotonated at physiological conditions, which acts as a nucleophilic reagent to attack on pTyr. Therefore, the identified molecules generally contain an electronegative group to match the electropositive environment of the catalytic center of PTPs, which results in the poor bioavailability of the compounds. Third, PTPs share a common active-site motif that is the sequence C(X)5R(S/T) (X can denote any amino acid). Therefore, the obtained compounds have poor selectivity to other PTPs by now. Despite these difficulties, many promising molecules and probes have been found in the PTP family.[3,16]

* Corresponding author.
E-mail address: zbzheng@bmi.ac.cn (Z. Zheng).

https://doi.org/10.1016/j.bmc.2020.115777
Received 11 July 2020; Received in revised form 14 September 2020; Accepted 15 September 2020
Available online 21 September 2020

The triaryl-based derivatives had been extensively studied by Affymax Inc. as potent inhibitors of protein tyrosine phosphatase 1B (PTP1B).[17,18] Most of them belong to a series of efficient non-hydrolyzable difluoromethylenephosphonic acid (DFMP) analogs. However, the electronegative phosphonate group in compounds, DFMP, leads to poor cell membrane permeability. Therefore, the DFMP structural moiety of compounds was replaced by potential bioisosteric or other groups to explore the change in the activity.[19,20] The HPTPβ inhibitors containing sulfamic acid group had been studied by Proctor and Gamble (P&G)[21] and Ontogen corporation[22], and a series of amino-sulfonic acid derivatives with good inhibitory effect on HPTPβ and good selectivity to other PTPs has been reported.[23] At the same time, our previous studies also showed that phenylsulfamic acid was a good pTyr mimetics.[24] Therefore, we designed new inhibitors of HPTPβ through hybridizing the drug inclusions and structural fragments of the two compounds, which have a simple scaffold structure and are easy to synthesize (Fig. 1).

2. Results and discussions

2.1. Chemistry

The synthetic route of triaryl-based sulfamic acid derivatives was outlined in Schemes 1–2. Compounds **G1-G5** was synthesized via four steps (Scheme 1). Commercially available 4-nitrobenzyl bromide reacted with aniline through a substitution reaction to yield intermediate **2**.[25] Various carboxylic acids reacted with phosphorus pentachloride in dry DCM, and then the intermediate **2** was added into the reaction mixture to produce compounds **3**.[26] In the presence of a reducing agent, the nitro group of compounds **3** was reduced to the amino group and then the sulfonation reaction was conducted with the resulting amine **4** to obtain the target compounds.

Scheme 2 described the synthetic route for compounds **G6-G25**. The route started with the condensation of an aryl amine and a carboxylic acid in the presence of (Benzotriazol1yloxy)tris(dimethylamino)phosphonium hexafluophosphate (BOP) to produce compound **7**.[27] Compound **8** were synthesized by electrophilic substitution of 4-nitrobenzyl-bromide with compound **7** using potassium carbonate as a base and then were converted to compounds **9** via reduction in the presence of $FeCl_3{\cdot}6H_2O$, charcoal and hydrazine hydrate. Sulfonation of compound **9** produced the target compounds. Sodium hydride as the strong base was needed to yield compounds **7** in the reaction of an aryl amine with sulfonyl chloride and then compounds **8** were synthesized in the presence of K_2CO_3 and 4-nitrobenzyl bromide.[28] However, the nitro group of **8** must be reduced in the presence of Fe and ammonia chloride. The synthetic method of compounds **10** was the same as that of compounds **5**. All synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR and mass spectrometry.

2.2. Biological evaluation

The inhibitory activity of the triaryl-based sulfamic acid derivatives against HPTPβ was evaluated *in vitro* using 6, 8-difluoro-4-methylumbelliferyl phosphate (DiFMUP) as a substrate. The compund **3** reported in the literature was a competitive and kind of sulfamic acid inhibitor of HPTPβ. Because its structure was similar to the novel sythesized compounds, it was chosen as a postivie control in the biological evaluation. The percentage of inhibition of each compound was assessed at a single concentration (10 μM). If the %inhibition of a compound was higher than 65%, the compound was selected for the subsequent IC_{50} assay. All results are shown in Table 1.

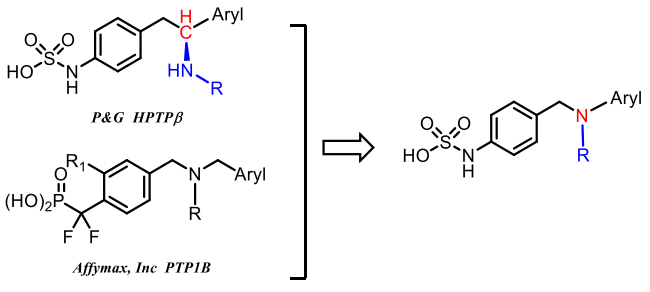


Figure 1. The design strategy of triaryl-based sulfamic acid derivatives, R stands for acyl or sulfonyl groups, Aryl denotes an aromatic group.

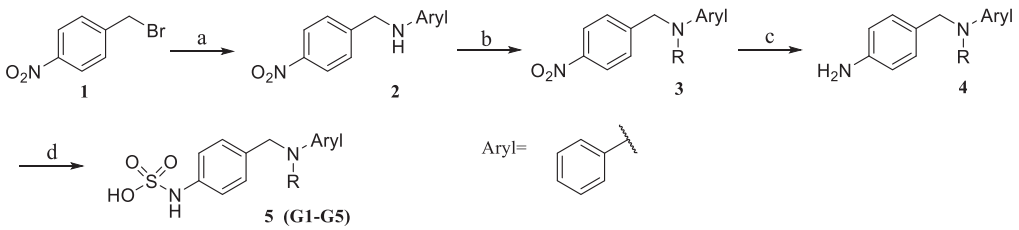
We investigated the effect of the R and Aryl groups on the activity of the compounds. Compounds with diverse carboxylic acids at R position showed slight differences in the inhibitory effect on HPTPβ when Aryl was a phenyl. According to the previous report[21], connection of (4-(thiophen-2-yl)thiazol)-2-yl or (4-(phenyl-2-yl)thiazol)-2-yl groups would improve activity. Therefore, new compounds were coupled with them. However, the activity of **G6-G9** and **G10-G13** was lower than that of **G1-G4**, respectively. It seems that (4-(thiophen-2-yl)thiazol)-2-yl or (4-(phenyl-2-yl)thiazol)-2-yl at Aryl position was not favorable for improving activity. However, compounds incorporated with sulfonyl group could increase the activity (**G16**, **G18**, **G19**, **G21** and **G23**)[30] and surprisingly by-product **G25** with a hydrogen atom at R showed the same activity to **G16**, which offered us the information that the sulfonyl and the hydrogen atom was possibly favorable for increasing activity.

Four compounds (**G4**, **G14**, **G16** and **G25**) with different structures were chosen to evaluate their inhibition selectivity against other PTPs targets (TC-PTP, PTP1B, SHP-2, and LAR). As shown in Table 2, the secondary amine **G25** demonstrated the highest selectivity (250-fold, 26-fold, 130-fold and 250-fold for HPTPβ versus PTP1B, SHP2, LAR, and TC-PTP, respectively) in contrast to the other tertiary amines **G4, G14** and **G16**, while compound **G4** with a phenyl and *N*-BOC-piperidine-4-carbonyl group showed higher selectivity than compounds **G16** and **G14**.

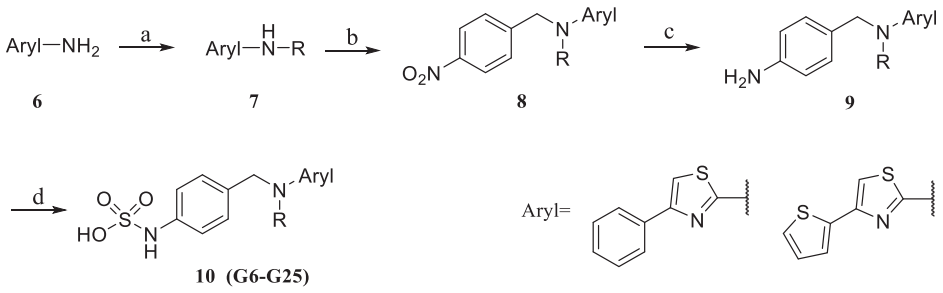
2.3. Docking simulations

To better understand why different types of compounds had variable affinities to the protein and to guide further optimization of the compounds, the molecular docking simulation was performed to study the interaction between HPTPβ with the compounds **G4**, **G14**, **G16** and **G25**. The catalytic pocket of HPTPβ includes a P-loop, a WPD-loop, a pTyr-loop, a Q-loop and an undefined loop (Fig. 2E).[31] The P-loop comprising Cys1904, Ser1905, Gly1907, Val1908, Gly1909 and Arg1910 that produce a positive electrostatic potential to accommodate the negatively charged group in inhibitors located in the bottom of the catalytic pocket. The WPD-loop included Pro1869, Asp1870 and His1871, and the Asp1870 showed acid/base-effect on binding and catalyzing the substrate. The Asn1735 and Tyr 1733 of the pTyr-loop showed the ability to recognize and bind compounds. Some residues of the Q-loop and undefined loop are nonconservative, such as Gln1948 and Lys1811, when forming H-bond with them was beneficial for increasing selectivity.

The docking results of chosen compounds were shown in Fig. 2. It was discovered that the sulfamic acid group of synthesized compounds could bind to the P-loop and WPD-loop like the reference ligand. The other substitutions on the N atom interacted with the other loops. From the docking results, the interaction mode of compounds **G4**, **G14** and **G16** with the protein were similar in Fig. 2A, 2B, 2D and 2F. The Aryl group was located in a gap between the Q-loop and pTyr-loop and various R groups extended to the undefined loop and the pTyr-loop. In Fig. 2B and Fig. 2D, the hydrogen bond interaction between (4-(phenyl-2-yl)thiazol)-2-yl and Asn1735 that was conservative among PTPs, but the H-bond interaction between the benzene ring of **G4** and Asn1735 was lack in Fig. 2A, which might be the reason why the inhibitory selectivity of **G4** was better than that of **G14** and **G16**. Additionally, other interactions between **G16** and protein such as Pi-Pi stacking interaction of phenyl with Tyr1733 and Pi-sigma interaction of (4-



Scheme 1. Reagents and conditions: (a) Aryl amine, K_2CO_3, CH_3CN, 85% yield; (b) carboxylic acid, PCl_5, CH_2Cl_2, 30–50% yield; (c) $FeCl_3{\cdot}6H_2O$, charcoal, $N_2H_4{\cdot}H_2O$, EtOH, 75–95% yield; (d) $Me_3N{\cdot}SO_3$, CH_3CN, 30–70% yield.



Scheme 2. Reagents and conditions: (a) carboxylic acid, BOP, CH_3CN or sulfonyl chloride, NaH, DCM; (b) 4-Nitrobenzyl-bromide, K_2CO_3, DMF; (c) $FeCl_3{\cdot}6H_2O$, charcoal, $N_2H_4{\cdot}H_2O$, EtOH or Fe, NH_4Cl, EtOH:H_2O; (d) $Me_3N{\cdot}SO_3$, CH_3CN.

(phenyl-2-yl)thiazol)-2-yl with Ile1736 results in **G16** having better activity than **G4** and **G14**. In Fig. 2C, although the H-bond interaction was also existed between N atom of **G25** with the conservative Asn1735, the two additional H-bond and Pi-Pi stacking interactions of (4-(phenyl-2-yl)thiazol)-2-yl with special Gln1948 and His1871 were detected, which may be the reson why **G25** has higher activity and selectivity.

3. Conclusion

In this paper, a sequence of new triaryl-based sulfamic acid derivatives was designed, synthesized and evaluated *in vitro* against the recombinant HPTPβ. The inhibitory potency against HPTPβ and inhibitory selectivity over other PTPs proteins of the compounds were improved based on the ligand-based drug design, and it was proved that sulfamic acid was a potential bioisoster of the DFMP moiety. Additionally, the structure–activity relationship analysis suggested that the hydrogen atom might be good for improving the activity and selectivity of compounds when incorporated (4-(thiophen-2-yl)thiazol)-2-yl at Aryl position. The phenyl and sulfonyl groups were favorable for improving the selectivity and activity of compounds, respectively. Meanwhile, the molecular docking study helped us understand the difference of inhibitory activity and selectivity among the compounds. These results obtained in this study can provide a new direction for the further design of HPTPβ inhibitors.

4. Materials and methods

4.1. Chemistry

The melting points of the compounds were determined by the capillary tube method by using an RY-1G melting point instrument (uncorrected temperature) purchased from Tianjin tianguang optical instrument Co. Ltd. (China); 1H NMR spectrum was measured by an electron JNM-ECA-400 nuclear magnetic resonance spectrometer (Japan); 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 a silica gel board was purchased from Yantai Chemical Industry Research Institute. The routine solvents used in the experiments were purchased from Sinopharm Chemical Reagent Co. Ltd. and were of the analytical grade.

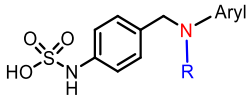
4.1.1. The synthesis of key intermediates

*4.1.1.1. N-(4-nitrobenzyl)aniline **(2)**.* The mixture of 4-nitrobenzyl bromide (5.00 g, 23.1 mmol), aniline (2.15 g, 23.1 mmol), and K_2CO_3 (3.19 g, 23.1 mmol) was dissolved in acetonitrile (70.0 mL) and stirred at room temperature (r.t). The reaction was stopped after the raw materials were completely consumed as indicated by TLC. The mixture was filtered and evaporated under reduced pressure to dryness and then the saturated ammonium chloride solution was added. The mixture was filtered to obtain a yellow target product (4.50 g, 85.1%). M.P.: 67.4–69.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.16 (m, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.17 (dd, J = 8.6, 7.4 Hz, 2H), 6.78 – 6.71 (m, 1H), 6.58 (dd, J = 8.6, 1.0 Hz, 2H), 4.48 (s, 2H). ESI-MS m/z: 229.11 $[M + H]^+$

*4.1.1.2. 2-phenylthiazol-4-amine hydrobromide **(6–1)**.* The mixture of 2-bromoacetophenone (3.0 g, 15.1 mmol) and thiourea (1.4 g, 18.1 mmol) was dissolved in ethanol (30.0 mL) and was heated to reflux. The reaction was stopped after 2-bromoacetophenone was completely consumed. The mixture was concentrated to nearly dry under reduced pressure and then EA was added. The solution was filtered to yield a white target product (3.58 g, 93.0%). These procedures were repeated until no solid precipitation was detected. M.P.: 178.9–181.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (t, J = 1.7 Hz, 1H), 7.69 (t, J = 1.4 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.43 – 7.38 (m, 1H), 7.23 (s, 1H). ESI-MS m/z: 177.04 $[M + H]^+$

*4.1.1.3. 2-(thiophen-2-yl)thiazol-4-amine hydrobromide **(6–2)**.* To a solution of 2-acetylthiophene (3.0 g, 24.8 mmol) in ether (70 mL), the catalytic amounts of $AlCl_3$ (0.13 g, 1.06 mmol) and bromine (1.9 mL, 37.2 mmol) were added in an ice-bath and the mixture was stirred overnight at r.t. The mixture was filtered and the filtrate was washed with saturated $NaHCO_3$ solution; water and brine (3*20 mL) were added stepwise. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Finally, thiourea (1.4 g, 18.1 mmol) reacted with the solution that was evaporated to dryness in a rotary evaporator. The purification method of compound **6–2** was

Table 1
The inhibitory activity of newly synthesized compounds against HPTPβ.



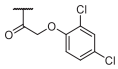
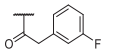
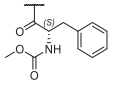
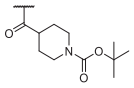
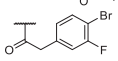
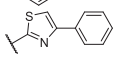
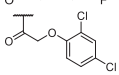
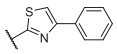
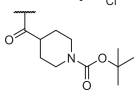
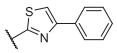
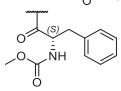
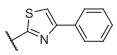
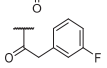
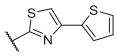
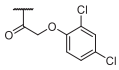
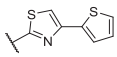
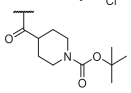
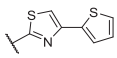
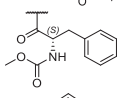
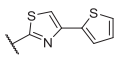
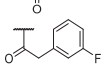
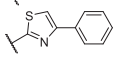
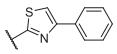
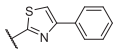
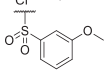
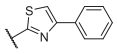
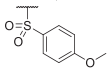
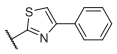
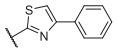
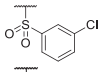
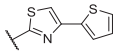
	Aryl	R	IC_{50} (μM)
G1			1.684
G2			1.715
G3			3.419
G4			1.453
G5			1.775
G6			ND
G7			6.397
G8			3.459
G9			4.099
G10			ND
G11			ND
G12			6.607
G13			ND
G14			2.976
G15			4.672
G16			0.9676
G17			2.066
G18			1.244
G19			1.317
G20			5.936
G21			1.414
G22			1.806
G23			1.071
G24			1.745

Table 1 (*continued*)

	Aryl	R	IC_{50} (μM)
G25		H	0.9950
3*	–	–	0.3200

ND: The IC_{50} of compounds was not determined when the % inhibiton of was less than 65% at concentration of 10 μM, the corresponding %inhibition of **G6**, **G10**, **G11**, **G13** were 38.3%, 61.2%, 34.5%, 61.0%. *: A positive control was tested and selected from the literature.[29]

Table 2
The inhibitory activities of selected compounds against a panel of PTPs.

PTPs	G4	G14	G16	G25	3 *
HPTPβ (μM)	1.453	2.976	0.9676	0.9950	0.3200
PTP1B (μM)	122.7	22.19	20.47	>250.0	15.70
SHP2 (μM)	24.68	19.59	6.413	25.61	55.33
LAR (μM)	111.6	42.29	34.79	129.8	76.41
TC-PTP(μM)	101.9	32.83	31.26	>250.0	20.11

* The positive control was tested and selected from the literature.[29]

consistent with that of compound **6**–**1** and a yellow solid was obtained (4.84 g, 73.9%). M.P.: 123.1–125.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (dd, J = 5.1, 1.1 Hz, 1H), 7.46 (dd, J = 3.6, 1.2 Hz, 1H), 7.10 (dd, J = 5.1, 3.7 Hz, 1H), 6.98 (s, 1H). ESI-MS m/z: 183.00 $[M + H]^+$

*4.1.2. General synthetic process of the target compounds **(G1-G5)***

To a solution of various aromatic acids (1.32 mmol) in DCM (15 mL), PCl_5 (0.33 g, 1.58 mmol) was added in an ice bath and stirred for an uncertain time. N-(4-Nitrobenzyl)aniline (0.3 g, 1.32 mmol) was added to the mixture in batches and stirred overnight at r.t. The reaction was filtered and then quenched by the addition of TEA. The filtrate was purified by column chromatography to give compounds **3** (30–50%).

To create compounds **4**, $FeCl_3{\cdot}6H_2O$ (0.05 g, 0.2 mmol), charcoal (0.14 g, 12.0 mmol) and hydrazine hydrate (12.0 mmol) were added to a solution of compounds **3** (1.00 mmol) in ethanol (10 mL) at room temperature and then the mixture was heated to reflux. After 4 h, the reaction mixture was filtered through a Celite pad. The filtrate was concentrated to give a crude product of compounds **4** (75–95%) as a white solid, which was directly used in the next step without further purification.

A solution of compounds **4** (1.00 mmol) in CH_3CN was supplemented with $Me_3N{\cdot}SO_3$ (0.28 g, 2.0 mmol). The reaction solution was heated and stirred overnight at 50–60 °C. Even though compounds **4** were not completely consumed according to TLC, the reaction was stopped at that point. A crude product was purified by column chromatography to give the target compounds **5** (30–70%).

*4.1.2.1. (S)-(4-((2-((methoxycarbonyl)amino)-N,3-diphenylpropanamido)methyl)phenyl)sulfamic acid**(G1)**.* White solid (0.31 g, 42.7%), m.p.: 166.0–168.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 1H, NH), 7.55 (d, J = 2.6 Hz, 1H, Ar-H), 7.39 (dd, J = 15.2, 7.7 Hz, 2H, Ar-H), 7.34 (dd, J = 8.9, 2.5 Hz, 2H, Ar-H), 7.28 (d, J = 7.3 Hz, 2H, Ar-H), 6.93 (t, J = 6.8 Hz, 3H, Ar-H), 6.88 (d, J = 8.3 Hz, 2H, Ar-H), 4.74 (s, 2H, CH_2), 4.60 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.33 (1C), 153.10 (1C), 143.50 (1C), 140.44 (1C), 130.12 (1C), 129.77 (2C), 128.79 (2C), 128.38 (2C), 126.71 (1C), 125.08 (2C), 122.68 (2C), 116.36 (2C), 115.46 (1C), 66.71 (1C), 52.42 (1C); ESI-MS m/z: 479.02 $[M-H]^-$

*4.1.2.2. (4-((2-(3-fluorophenyl)-N-phenylacetamido)methyl)phenyl)sulfamic acid **(G2)**.* White solid (80 mg, 14.8%), m.p.: 164.7–166.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (s, 1H, NH), 7.40 – 7.27 (m, 4H, Ar-H),

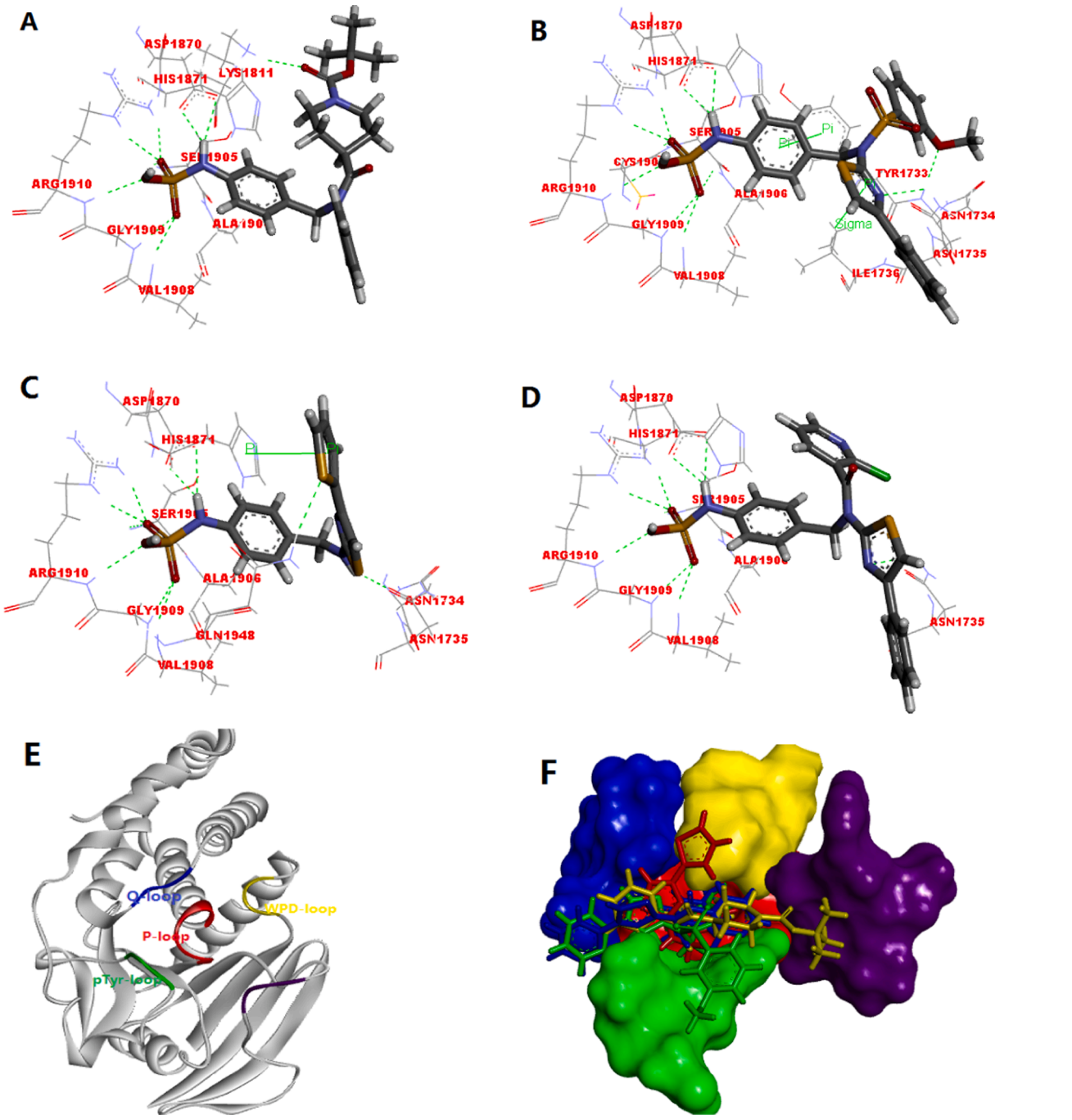


Figure 2. The compounds **G4** (A), **G14** (D), **G16** (B) and **G25** (C) interacted with HPTPβ. The 2E panel shows the composition of catalytic pocket. The 2F was the superimposition map of docking poses of **G4**, **G14**, **G16** and **G25** (in yellow, blue, green, red, respectively).

7.11 (d, $J = 7.3$ Hz, 2H, Ar-H), 7.03 (dd, $J = 9.4$, 7.6 Hz, 1H, Ar-H), 6.92 (d, $J = 8.5$ Hz, 2H, Ar-H), 6.87 (t, $J = 8.3$ Hz, 4H, Ar-H), 4.73 (s, 2H, CH_2), 3.44 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.74 (1C), 163.64 (1C), 143.33 (1C), 142.43 (1C), 139.21 (1C), 130.45 (1C), 129.95 (2C), 129.08 (2C), 128.69 (2C), 128.35 (1C), 127.32 (1C), 125.85 (1C), 116.67 (1C), 116.37 (2C), 113.78 (1C), 52.33 (1C), 45.04 (1C); ESI-MS *m/z*: 413.05 $[M-H]^-$

*4.1.2.3. (S)-(4-((2-((methoxycarbonyl)amino)-N,3-diphenylpropanamido)methyl)phenyl)sulfamic acid(**G3**).* Light yellow solid (90 mg, 14.1%), m.p.: 118.9–120.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H, NH), 7.61 (d, $J = 8.1$ Hz, 1H, Ar-H), 7.38 (d, $J = 7.4$ Hz, 3H, Ar-H), 7.16 – 7.11 (m, 3H, Ar-H, NH), 7.09 (d, $J = 7.9$ Hz, 2H, Ar-H), 6.92 (d, $J = 8.5$ Hz, 2H, Ar-H), 6.85 (d, $J = 8.5$ Hz, 2H, Ar-H), 6.80 – 6.72 (m, 2H, Ar-H), 4.83 (d, $J = 14.5$ Hz, 1H, CH), 4.60 (d, $J = 14.5$ Hz, 1H, CH), 4.16 (dd, $J = 10.0$, 3.9 Hz, 1H, CH), 3.47 (s, 3H, OCH_3), 2.82 (dd, $J = 13.4$, 3.8 Hz, 1H, CH), 2.67 (dd, $J = 13.4$, 10.3 Hz, 1H, CH). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.92 (1C), 157.01 (1C), 143.32 (1C), 141.70 (1C), 138.36 (1C), 129.83 (2C), 129.31 (2C), 128.59 (2C), 128.55 (2C), 126.96 (1C), 126.89 (2C), 116.34 (2C), 54.45 (1C), 52.61 (1C), 49.14 (1C), 37.14 (1C); ESI-MS *m/z*: 482.15 $[M-H]^-$

*4.1.2.4. (4-((1-(tert-butoxycarbonyl)-N-phenylpiperidine-4-carboxamido)methyl)phenyl)sulfamic acid **(G4)**.* White solid (70 mg, 10.6%), m.p.: 174.1–176.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43 – 7.30 (m, 4H, Ar-H), 7.19 – 7.02 (m, 4H, Ar-H), 6.91 (t, $J = 7.4$ Hz, 2H, Ar-H), 6.82 (d, $J =$

8.2 Hz, 1H, Ar-H), 6.68 (d, $J = 8.0$ Hz, 1H, Ar-H), 4.69 (s, 2H, CH_2), 2.31 (d, $J = 12.6$ Hz, 4H, piperidin-H), 1.57 – 1.42 (m, 5H, piperidin-H), 1.37 (s, 9H, $OC(CH_3)_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.96 (1C), 154.21 (1C), 143.34 (1C), 142.35 (1C), 139.83 (1C), 133.11 (1C), 130.07 (2C), 129.59 (1C), 128.74 (1C), 128.62 (1C) 127.41 (1C), 116.39 (2C), 60.30 (1C), 52.22 (4C), 39.39 (1C), 28.69 (4C), 28.58 (3C); ESI-MS *m/z*: 488.18 $[M-H]^-$

4.1.2.5. (4-((2-(4-bromo-3-fluorophenyl)-N-phenylacetamido)methyl) phenyl)sulfamic acid ***(G5)***. White solid (0.13 g, 15.1%), m.p.: 140.2–163.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 1H, OH), 7.92 (s, 1H, NH), 7.50 – 7.37 (m, 4H, Ar-H), 7.32 (t, $J = 8.8$ Hz, 1H, Ar-H), 7.19 (d, $J = 7.4$ Hz, 3H, Ar-H), 6.97 (d, $J = 8.4$ Hz, 2H, Ar-H), 6.91 (d, $J = 8.3$ Hz, 2H, Ar-H), 4.78 (s, 2H, CH_2), 3.47 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.72 (1C), 157.51 (1C, $J = 244.4$ Hz), 143.41 (1C), 142.31 (1C), 134.72 (1C), 134.66 (1C, $J = 4.04$ Hz), 131.14 (1C, $J = 7.07$ Hz), 129.95 (2C), 129.11 (2C), 128.70 (2C), 128.36 (1C), 127.17 (1C), 116.70 (1C, $J = 22.2$ Hz), 116.33 (2C), 107.80 (1C, $J = 21.2$ Hz), 52.39 (1C), 46.03 (1C); ESI-MS *m/z*: 493.02 $[M-H]^-$

4.1.3. General synthetic process of target compounds ***(G6-G25)***

To a solution of compounds **6**–**1** (0.3 g, 1.17 mmol) or **6**–**2** (0.3 g, 1.14 mmol) in 15 mL of acetonitrile, BOP (1.04 g, 2.34 mmol; 1.01 g, 2.28 mmol, respectively), DIPEA (0.38 g mg, 2.92 mmol; 0.37 g, 2.85 mmol, respectively) and various aromatic acids (1.17 mmol; 1.14 mmol, respectively) were added. The mixture was stirred at 70 °C until amine was completely consumed according to TLC (8 h). The solution was evaporated to dryness and 4% sodium hydroxide was added; the mixture was extracted with EA and the extract was dried (Na_2SO_4). Concentrated solution was directly used to obtain compounds **7** in the next reaction step.

To a solution of compounds **7** in 15 mL of DMF, K_2CO_3 (0.16 g, 1.17 mmol; 0.14 g, 1.14 mmol, respectively) and 4-nitrobenzyl bromide (0.25 g mg, 1.17 mmol; 0.25 g, 1.14 mmol, respectively) were added in an ice bath. The mixture was stirred overnight at r.t. A large volume of water was added; the mixture was stirred and filtered to produce compounds **8**. The subsequent reduction of the nitro derivatives and sulfonation of the amino derivatives were consistent with that of compound **4** and compound **5**.

To a solution of compounds **6**–**1** (0.3 g, 1.17 mmol) or **6**–**2** (0.3 g, 1.14 mmol) in 15 mL of dry DCM, NaH (0.14 g, 5.85 mmol; 0.14 g, 5.70 mmol, respectively) and various sulfonyl chlorides (1.17 mmol; 1.14 mmol, respectively) were added in an ice bath and the mixture was stirred overnight. Even though compounds 6 did not disappear completely according to TLC, the reaction was stopped. The mixture was filtered and purified by column chromatography to give compounds **7**. Compounds **7** were reacted with 4-nitrobenzyl bromide in the presence of K_2CO_3 in DMF. The reaction solution was processed in a similar manner to give compounds **8**. The nitro group of compounds **8** was reduced in the presence of Fe and NH_4Cl in ethanol: water (5:1) system to obtain compounds **9**.

To prepare compounds **10**, $Me_3N{\cdot}SO_3$ (0.28 g, 2.0 mmol) was added to a solution of compounds **9** (1.00 mmol) in CH_3CN at r.t. The mixture was stirred overnight at 50–60 °C. Compounds **9** were still detected in the mixture according to TLC. However, the reaction was stopped and purification by column chromatography produced the target compounds **10**.

4.1.3.1. (4-((2-(2,4-dichlorophenoxy)-N-(4-phenylthiazol-2-yl)acetamido)methyl)phenyl)sulfamic acid ***(G6)***. Light yellow solid (50 mg, 7.6%), m.p.: 114.9–116.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (s, 1H, OH), 8.02 – 7.89 (m, 3H, Ar-H), 7.77 (s, 1H, NH), 7.60 (d, $J = 1.9$ Hz, 1H, thiazole-H), 7.43 (t, $J = 7.3$ Hz, 2H, Ar-H), 7.31 (d, $J = 6.0$ Hz, 2H, Ar-H), 7.14 (d, $J = 8.2$ Hz, 2H, Ar-H), 7.04 (d, $J = 8.1$ Hz, 2H, Ar-H), 6.86 (d, $J = 8.8$ Hz, 1H, Ar-H), 5.47 (s, 2H, CH_2), 5.32 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.84 (1C), 152.86 (2C), 143.99 (1C), 134.60 (2C), 129.95 (1C), 129.29 (2C), 128.49 (2C), 128.44 (1C), 127.50 (2C), 126.25 (2C), 125.51 (1C), 122.73 (1C), 116.84 (2C), 115.40 (1C), 110.55 (1C), 67.10 (1C), 49.20 (1C); ESI-MS *m/z*: 562.01 $[M-H]^-$

4.1.3.2. (4-((1-(tert-butoxycarbonyl)-N-(4-phenylthiazol-2-yl)piperidine-4-carboxamido)methyl)phenyl) sulfamic acid ***(G7)***. White solid (0.11 g, 16.4%), m.p.: 105.6–108.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (s, 1H, OH), 7.91 (dd, $J = 6.3$, 5.0 Hz, 3H, Ar-H), 7.71 (s, 1H, NH), 7.41 (t, $J = 7.6$ Hz, 2H, thiazole-H, Ar-H), 7.30 (t, $J = 7.3$ Hz, 1H, Ar-H), 7.07 (d, $J = 8.6$ Hz, 2H, Ar-H), 7.00 (d, $J = 8.6$ Hz, 2H, Ar-H), 5.56 (s, 2H, CH_2), 3.93 (s, 2H, piperidin-H), 3.17 (d, $J = 4.5$ Hz, 2H, piperidin-H), 2.76 (s, 1H, piperidin-H), 1.62 (s, 2H, piperidin-H), 1.53 – 1.44 (m, 2H, piperidin-H), 1.40 (s, 9H, $OC(CH_3)_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.43 (1C), 154.35 (1C), 143.70 (1C), 134.74 (2C), 129.25 (2C), 128.32 (2C), 127.30 (1C), 127.11 (2C), 126.17 (2C), 116.70 (2C), 110.51 (1C), 79.25 (1C), 50.29 (1C), 49.14 (2C), 30.95 (1C), 28.79 (2C), 28.60 (3C); ESI-MS *m/z*: 571.17 $[M-H]^-$

4.1.3.3. (S)-(4-((2-((methoxycarbonyl)amino)-3-phenyl-N-(4-phenylthiazol-2-yl)propanamido)methyl)phenyl) sulfamic acid ***(G8)***. Yellow solid (30 mg, 4.5%), m.p.: 147.8–151.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, $J = 8.0$ Hz, 1H, NH), 7.96 – 7.85 (m, 3H, Ar-H), 7.74 (s, 1H, thiazole-H), 7.42 (t, $J = 7.6$ Hz, 2H, Ar-H), 7.31 (t, $J = 7.2$ Hz, 1H, Ar-H), 7.27 – 7.13 (m, 3H, Ar-H), 7.09 (d, $J = 8.2$ Hz, 2H, Ar-H), 7.02 (d, $J = 6.6$ Hz, 4H, Ar-H), 5.69 (d, $J = 16.1$ Hz, 1H, CH), 5.40 (d, $J = 16.3$ Hz, 1H, CH), 4.86 (d, $J = 7.6$ Hz, 1H, CH), 3.50 (s, 3H, OCH_3), 2.86 (d, $J = 6.2$ Hz, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.37 (1C), 157.25 (1C), 148.61 (1C), 143.74 (1C), 137.52 (1C), 134.67 (2C), 129.77 (2C), 129.27 (2C), 128.77 (2C), 128.38 (1C), 127.26 (2C), 127.03 (1C), 126.81 (1C), 126.21 (2C), 116.70 (2C), 110.73 (1C), 53.41 (1C), 52.29 (1C), 50.42 (1C), 37.34 (1C); ESI-MS *m/z*: 565.12 $[M-H]^-$

4.1.3.4. (4-((2-(3-fluorophenyl)-N-(4-phenylthiazol-2-yl)acetamido) methyl)phenyl)sulfamic acid ***(G9)***. Light yellow solid (0.12 g, 20.0%), m.p.: 153.2–154.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.32 (s, 1H, OH), 7.94 – 7.86 (m, 2H, Ar-H), 7.72 (s, 1H, NH), 7.37 (ddd, $J = 17.6$, 12.0, 7.4 Hz, 4H, thiazole-H, Ar-H), 7.11 (t, $J = 8.3$ Hz, 3H, Ar-H), 7.04 (t, $J = 9.8$ Hz, 3H, Ar-H), 6.57 (d, $J = 8.4$ Hz, 1H, Ar-H), 5.54 (d, $J = 10.8$ Hz, 2H, CH_2), 4.11 (d, $J = 4.7$ Hz, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.40 (1C), 162.54 (1C, $J = 244.42$ Hz), 148.48 (1C), 143.82 (1C), 137.67 (1C, $J = 8.1$ Hz), 134.73 (2C), 130.63 (1C, $J = 8.6$ Hz), 129.26 (2C), 128.34 (1C), 127.30 (2C), 126.53 (1C) (d, $J = 3.03$ Hz), 126.20 (2C), 117.30 (1C, $J = 21.2$ Hz), 116.78 (2C), 114.84 (1C), 114.19 (1C, $J = 21.2$ Hz), 110.55 (1C), 50.51 (1C), 44.68 (1C); ESI-MS *m/z*: 496.08 $[M-H]^-$

4.1.3.5. (4-((2-(2,4-dichlorophenoxy)-N-(4-(thiophen-2-yl)thiazol-2-yl) acetamido)methyl)phenyl)sulfamic acid ***(G10)***. White solid (30 mg, 4.6%), m.p.: 130.2–133.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 1H, NH), 7.66 – 7.45 (m, 4H, Ar-H, thiazole-H, thiophen-H), 7.32 (d, $J = 8.8$ Hz, 1H, Ar-H), 7.16 (d, $J = 7.4$ Hz, 2H, Ar-H), 7.10 (s, 1H, Ar-H), 7.02 (d, $J = 8.1$ Hz, 2H, Ar-H), 6.87 (d, $J = 8.6$ Hz, 1H, thiophen-H), 5.38 (s, 2H, CH_2), 5.34 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.82 (1C), 152.84 (1C), 144.09 (1C), 138.81 (2C), 129.96 (2C), 128.58 (1C), 128.50 (1C), 127.90 (2C), 126.28 (1C), 125.96 (1C), 125.52 (1C), 124.50 (1C), 122.73 (1C), 116.70 (1C), 115.43 (2C), 108.97 (1C), 67.13 (1C), 49.35 (1C); ESI-MS *m/z*: 567.96 $[M-H]^-$

4.1.3.6. (4-((1-(tert-butoxycarbonyl)-N-(4-(thiophen-2-yl)thiazol-2-yl) piperidine-4-carboxamido)methyl)pheny)sulfamic acid ***(G11)***. White solid (60 mg, 13.0%), m.p.: 117.8–119.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H, NH), 7.59 – 7.43 (m, 3H, thiazole-H, thiophen-H), 7.08 (dd, $J = 7.7$, 2.4 Hz, 3H, Ar-H), 6.99 (d, $J = 8.4$ Hz, 2H, Ar-H, thiophen-H),

5.48 (s, 2H, CH_2), 3.92 (s, 2H, piperidin-H), 3.19 (s, 1H, piperidin-H), 2.76 (s, 2H, piperidin-H), 1.61 (s, 2H, piperidin-H), 1.46 (d, J = 11.3 Hz, 2H, piperidin-H), 1.40 (s, 9H, $OC(CH_3)_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.43 (1C), 159.48 (1C), 154.35 (1C), 143.75 (1C), 138.92 (2C), 128.54 (1C), 127.47 (2C), 127.47 (1C), 126.14 (1C), 124.31 (1C), 116.59 (2C), 108.98 (1C), 79.26 (1C), 50.14 (1C), 43.42 (2C), 29.54 (1C), 28.75 (2C), 28.60 (3C); ESI-MS *m/z*: 577.12 $[M-H]^-$

4.1.3.7. (S)-(4-((2-((methoxycarbonyl)amino)-3-phenyl-N-(4-(thiophen-2-yl)thiazol-2-yl)propanamido)methyl) phenyl)sulfamic acid ***(G12)***. White solid (30 mg, 4.6%), m.p.: 158.9–161.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, J = 7.4 Hz, 1H, NH), 7.91 (s, 1H, NH), 7.56 (s, 1H, thiazole-H), 7.49 (dd, J = 10.5, 3.6 Hz, 2H, Ar-H thiophen-H), 7.23 (d, J = 7.3 Hz, 2H, Ar-H), 7.18 (d, J = 6.3 Hz, 1H, Ar-H), 7.14 – 7.03 (m, 5H), 6.99 (d, J = 8.1 Hz, 2H, Ar-H, thiophen-H), 5.54 (t, J = 12.8 Hz, 1H, CH), 5.33 (d, J = 15.6 Hz, 1H, CH), 4.94 – 4.83 (m, 1H, CH), 3.50 (s, 3H, OCH_3), 2.87 (d, J = 6.0 Hz, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.75 (1C), 157.25 (2C), 143.83 (1C), 138.92 (1C), 137.51 (2C), 129.77 (2C), 128.84 (2C), 128.54 (1C), 127.69 (4C), 127.06 (1C), 126.22 (1C), 124.39 (1C), 116.53 (2C), 109.14 (1C), 54.59 (1C), 50.39 (1C), 37.30 (1C); ESI-MS *m/z*: 571.08 $[M-H]^-$

4.1.3.8. (4-((2-(3-fluorophenyl)-N-(4-(thiophen-2-yl)thiazol-2-yl)acetamido)methyl)phenyl)sulfamic acid ***(G13)***. White solid (30 mg, 5.3%), m.p.: 165.5–167.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 1H, NH), 7.53 (s, 1H, thiazole-H), 7.50 (dd, J = 3.5, 1.2 Hz, 1H, thiophen-H), 7.47 (dd, J = 5.0, 1.1 Hz, 1H, Ar-H), 7.36 (ddd, J = 8.9, 4.4, 2.9 Hz, 1H, thiophen-H), 7.16 – 7.07 (m, 5H, Ar-H), 7.02 (dd, J = 12.3, 5.5 Hz, 3H, Ar-H), 5.47 (s, 2H, CH_2), 4.15 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.39 (1C), 162.54 (1C, J = 243.0 Hz), 159.58 (1C), 143.90 (1C), 138.99 (2C), 137.64 (1C, J = 8.2 Hz), 130.63 (1C, J = 8.5 Hz), 128.54 (2C), 127.72 (2C), 126.55 (1C, J = 4.6 Hz), 126.16 (1C), 124.34 (1C), 117.32 (1C, J = 21.5 Hz), 116.65 (2C), 114.20 (1C, J = 20.8 Hz), 108.96 (1C) 50.53 (1C), 39.70 (1C); ESI-MS *m/z*: 502.03 $[M-H]^-$

4.1.3.9. (4-((2-chloro-N-(4-phenylthiazol-2-yl)nicotinamido)methyl) phenyl)sulfamic acid ***(G14)***. Yellow solid (50 mg, 8.5%), ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (d, J = 3.4 Hz, 1H, NH), 8.10 (d, J = 6.2 Hz, 1H, pyridin-H), 8.00 – 7.90 (m, 3H, Ar-H, pyridin-H), 7.87 (s, 1H, thiazole-H), 7.59 (dd, J = 7.1, 5.1 Hz, 1H, Ar-H), 7.44 (t, J = 7.5 Hz, 2H, Ar-H), 7.33 (t, J = 7.3 Hz, 1H, Ar-H), 6.89 (d, J = 8.2 Hz, 2H, Ar-H), 6.83 (d, J = 8.5 Hz, 2H, Ar-H), 5.41 (d, J = 17.8 Hz, 1H, CH), 5.04 (d, J = 12.6 Hz, 1H, CH); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.42 (1C), 158.60 (1C), 151.85 (1C), 148.90 (1C), 146.51 (1C), 143.81 (1C), 138.64 (1C), 134.52 (1C), 130.99 (1C), 129.33 (2C), 128.55 (1C), 127.61 (2C), 126.26 (2C), 123.82 (1C), 116.40 (2C), 111.10 (1C), 49.14 (1C). ESI-MS *m/z*: 499.04 $[M-H]^-$ *(4-((2-chloro-N-(4-phenylthiazol-2-yl)benzamido) methyl)phenyl)sulfamic acid* ***(G15)***

Yellow solid (30 mg, 5.1%), m.p.: 180.1–181.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (dd, J = 37.1, 12.1 Hz, 4H, NH, thiazole-H, Ar-H), 7.61 (dd, J = 24.0, 7.1 Hz, 3H, Ar-H), 7.52 – 7.36 (m, 3H, Ar-H), 7.32 (t, J = 7.1 Hz, 1H, Ar-H), 6.87 (d, J = 7.6 Hz, 4H, Ar-H), 5.43 (d, J = 11.4 Hz, 1H, CH), 4.92 (d, J = 11.2 Hz, 1H, CH); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.83 (1C), 158.50 (1C), 148.83 (1C), 143.69 (1C), 134.57 (1C), 134.43 (1C), 132.37 (1C), 130.26 (1C), 130.09 (1C), 129.33 (2C), 128.50 (1C), 128.20 (1C), 127.70 (2C), 126.23 (2C), 126.12 (2C), 116.27 (2C), 110.89 (1C), 52.05 (1C). ESI-MS *m/z*: 498.04 $[M-H]^-$

4.1.3.10. (4-(((3-methoxy-N-(4-phenylthiazol-2-yl)phenyl)sulfonamido) methyl)phenyl)sulfamic acid ***(G16)***. Yellow solid (20 mg, 3.2%), m.p.: 175.1–176.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 1H, NH), 7.68 – 7.42 (m, 8H, Ar-H, thiazole-H), 7.36 (d, J = 7.3 Hz, 1H, Ar-H), 7.26 (s, 1H, Ar-H), 7.15 (d, J = 8.2 Hz, 1H, Ar-H), 6.99 (d, J = 8.3 Hz, 2H, Ar-H), 6.91 (d, J = 7.9 Hz, 2H, Ar-H), 3.84 (s, 2H, CH_2), 3.77 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.12 (1C), 159.69 (1C), 144.19 (1C), 143.18 (1C), 130.78 (3C), 129.65 (1C), 129.34 (2C), 129.05 (2C), 128.59 (2C), 121.22 (1C), 118.48 (2C), 116.88 (2C), 111.11 (2C), 56.04 (1C), 49.13 (1C); ESI-MS *m/z*: 530.05 $[M-H]^-$

4.1.3.11. (4-(((4-methoxy-N-(4-phenylthiazol-2-yl)phenyl)sulfonamido) methyl)phenyl)sulfamic acid ***(G17)***. Pink solid (20 mg, 3.2%), m.p.: 133.5–135.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (s, 1H, NH), 7.72 (d, J = 8.9 Hz, 2H, Ar-H, thiazole-H), 7.50 (s, 2H, Ar-H), 7.49 (s, 2H, Ar-H), 7.47 – 7.44 (m, 1H, Ar-H), 7.06 (d, J = 8.9 Hz, 2H, Ar-H), 6.99 (d, J = 8.5 Hz, 2H, Ar-H), 6.90 (d, J = 8.6 Hz, 2H, Ar-H), 3.82 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.91 (1C), 162.43 (1C), 143.23 (1C), 134.74 (2C), 129.67 (1C), 129.36 (2C), 129.03 (2C), 128.58 (2C), 128.51 (1C), 128.44 (2C), 116.91 (2C), 115.96 (1C), 114.63 (3C), 56.12 (1C), 53.38 (1C); ESI-MS *m/z*: 530.03 $[M-H]^-$

4.1.3.12. (4-(((3-fluoro-N-(4-phenylthiazol-2-yl)phenyl)sulfonamido) methyl)phenyl)sulfamic acid ***(G18)***. White solid (30 mg, 4.9%), m.p.: 184.9–186.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 1H, NH), 7.63 (dt, J = 13.1, 7.9 Hz, 2H, Ar-H, thiazole-H), 7.57 – 7.42 (m, 8H, Ar-H), 7.00 (d, J = 8.4 Hz, 2H, Ar-H), 6.91 (d, J = 8.5 Hz, 2H, Ar-H), 3.85 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.24 (1C), 162.14 (1C, J = 249.47 Hz), 145.04 (1C, J = 6.3 Hz), 143.18 (2C), 132.02 (1C, J = 8.0 Hz), 129.76 (1C), 129.37 (2C), 129.09 (2C), 128.61 (2C), 128.51 (1C), 122.57 (1C, J = 2.9 Hz), 121.47 (1C), 119.75 (1C, J = 21.2 Hz), 116.93 (2C), 114.66 (1C), 113.26 (1C, J = 24.3 Hz), 44.65 (1C); ESI-MS *m/z*: 518.03 $[M-H]^-$

4.1.3.13. (4-(((3-chloro-N-(4-phenylthiazol-2-yl)phenyl)sulfonamido) methyl)phenyl)sulfamic acid ***(G19)***. Yellow solid (30 mg, 4.8%), m.p.: 189.9–191.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H, NH), 7.76 (ddt, J = 5.4, 3.4, 1.7 Hz, 2H, Ar-H, thiazole-H), 7.68 (ddd, J = 8.0, 2.0, 1.2 Hz, 1H, Ar-H), 7.59 (t, J = 8.1 Hz, 2H, Ar-H), 7.54 – 7.44 (m, 5H, Ar-H), 7.00 (d, J = 8.6 Hz, 2H, Ar-H), 6.92 (d, J = 8.6 Hz, 2H, Ar-H), 3.85 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.22 (1C), 144.79 (1C), 143.19 (1C), 134.09 (2C), 132.56 (1C), 131.77 (2C), 129.79 (1C), 129.38 (2C), 129.11 (2C), 128.62 (2C), 128.50 (1C), 125.84 (1C), 125.01 (1C), 116.94 (2C), 114.74 (1C), 49.14 (1C); ESI-MS *m/z*: 534.00 $[M-H]^-$

4.1.3.14. (4-((2-chloro-N-(4-(thiophen-2-yl)thiazol-2-yl)benzamido) methyl)phenyl)sulfamic acid ***(G20)***. White solid (50 mg, 8.6%), m.p.: 145.8–148.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 1H, NH), 7.69 – 7.48 (m, 7H, Ar-H, thiazole-H, thiophen-H), 7.13 – 7.08 (m, 1H, Ar-H, thiophen-H), 6.88 (s, 4H, Ar-H), 5.32 (d, J = 14.3 Hz, 1H, CH), 4.96 – 4.81 (m, 1H, CH); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.74 (1C), 158.40 (1C), 143.81 (1C), 138.78 (1C), 134.29 (2C), 132.44 (1C), 130.30 (1C), 130.16 (1C), 129.46 (1C), 128.61 (1C), 128.25 (2C), 126.40 (2C), 125.81 (1C), 124.54 (1C), 116.13 (2C), 109.27 (1C), 52.08 (1C); ESI-MS *m/z*: 503.99 $[M-H]^-$

4.1.3.15. (4-(((3-methoxy-N-(4-(thiophen-2-yl)thiazol-2-yl)phenyl)sulfonamido)methyl)phenyl)sulfamic acid ***(G21)***. Pink solid (20 mg, 3.3%), m.p.: 180.9–182.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H, NH), 7.70 (d, J = 4.9 Hz, 1H, thiazole-H), 7.46 (dd, J = 9.0, 6.5 Hz, 2H, thiophen-H), 7.36 (d, J = 7.7 Hz, 1H, Ar-H), 7.28 – 7.23 (m, 1H, Ar-H), 7.20 – 7.12 (m, 2H, Ar-H), 7.01 (d, J = 8.5 Hz, 2H, Ar-H), 6.96 (d, J = 8.5 Hz, 2H, Ar-H, thiophen-H), 3.97 (s, 2H, CH_2), 3.77 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.43 (1C), 159.72 (1C), 144.03 (1C), 143.29 (1C), 131.49 (2C), 130.82 (1C), 128.71 (2C), 128.31 (1C), 128.21 (1C), 128.06 (1C), 121.68 (1C), 118.60 (1C), 118.48 (1C), 116.88 (2C), 114.66 (1C), 111.12 (1C), 56.05 (1C), 49.13 (1C); ESI-MS *m/z*: 535.99 $[M-H]^-$

4.1.3.16. (4-(((4-methoxy-N-(4-(thiophen-2-yl)thiazol-2-yl)phenyl)sulfonamido)methyl)phenyl)sulfamic acid ***(G22)***. Pain pink solid (30 mg, 4.9%), m.p.: 183.5–184.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 1H, NH), 7.70 (d, J = 8.6 Hz, 2H, thiazole-H, thiophen-H), 7.56 (d, J = 4.4 Hz, 1H, thiophen-H), 7.30 (s, 1H, Ar-H), 7.15 – 7.07 (m, 1H, Ar-H), 7.04 – 6.96 (m, 5H, Ar-H), 6.93 (d, J = 8.4 Hz, 2H, thiophen-H, Ar-H), 3.95 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.32 (1C), 161.86 (1C), 142.96 (1C), 138.60 (1C), 136.05 (1C), 128.93 (1C), 128.53 (2C), 128.46 (1C), 128.09 (1C), 126.87 (2C), 126.29 (1C), 120.79 (1C), 116.86 (2C), 114.25 (2C), 107.19 (1C), 56.03 (1C), 32.19 (1C); ESI-MS m/z: 535.99 $[M-H]^-$

4.1.3.17. (4-(((3-fluoro-N-(4-(thiophen-2-yl)thiazol-2-yl)phenyl)sulfonamido)methyl)phenyl)sulfamic acid ***(G23)***. Pink solid (30 mg, 5.0%), m.p.: 178.9–181.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H, NH), 7.69 – 7.58 (m, 3H, thiazole-H, thiophen-H), 7.55 (d, J = 7.4 Hz, 1H, Ar-H), 7.49 – 7.39 (m, 2H, Ar-H), 7.17 (d, J = 3.6 Hz, 1H, Ar-H), 7.01 (d, J = 8.5 Hz, 2H, Ar-H), 6.96 (d, J = 7.7 Hz, 2H, Ar-H, thiophen-H), 3.98 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.64 (1C), 162.12 (1C, J = 248.0 Hz), 148.00 (1C), 145.32 (1C), 143.20 (2C), 131.93 (1C, J = 7.8 Hz), 129.53 (1C), 128.70 (2C), 128.20 (2C), 122.58 (1C, J = 3.0 Hz), 121.69 (1C), 119.56 (1C, J = 21.3 Hz), 116.91 (2C), 114.70 (1C), 113.29 (1C, J = 23.9 Hz), 49.14 (1C); ESI-MS m/z: 523.99 $[M-H]^-$

4.1.3.18. (4-(((3-chloro-N-(4-(thiophen-2-yl)thiazol-2-yl)phenyl)sulfonamido)methyl)phenyl)sulfamic acid ***(G24)***. Pink solid (30 mg, 4.8%), m.p.: 136.7–140.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 1H, NH), 7.79 – 7.73 (m, 2H, thiazole-H, thiophen-H), 7.71 – 7.64 (m, 2H, thiophen-H, Ar-H), 7.58 (t, J = 8.2 Hz, 1H, Ar-H), 7.42 (d, J = 3.5 Hz, 1H, Ar-H), 7.16 (dd, J = 5.1, 3.7 Hz, 1H, Ar-H), 7.01 (t, J = 6.6 Hz, 2H, Ar-H), 6.96 (d, J = 8.7 Hz, 2H, Ar-H, thiophen-H), 3.98 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.62 (1C), 147.94 (1C), 144.96 (1C), 143.21 (1C), 134.04 (1C), 132.46 (1C), 131.70 (1C), 129.54 (1C), 128.72 (2C), 128.21 (2C), 128.16 (1C), 125.89 (1C), 125.03 (1C), 121.78 (1C), 116.93 (2C), 114.75 (1C), 49.14 (1C); ESI-MS m/z: 539.95 $[M-H]^-$

4.1.3.19. (4-(((4-(thiophen-2-yl)thiazol-2-yl)amino)methyl)phenyl)sulfamic acid ***(G25)***. Yellow solid (30 mg, 7.1%), m.p.: 211.4–214.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H, NH), 7.89 (s, 1H, thiazole-H), 7.40 (d, J = 5.1 Hz, 2H, thiophen-H), 7.07 (dd, J = 42.5, 8.1 Hz, 5H, Ar-H, thiophen-H), 6.87 (s, 1H), 4.29 (d, J = 5.0 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.94 (1C), 145.16 (1C), 143.35 (1C), 139.77 (1C), 128.83 (1C), 128.35 (2C), 128.27 (1C), 125.32 (1C), 123.43 (1C), 116.60 (2C), 99.86 (1C), 48.42 (1C); ESI-MS m/z: 366.01 $[M-H]^-$

4.2. Biological evaluation

4.2.1. Measurements of %inhibition and IC_{50} of HPTPβ

The recombinant human PTPRB protein was purchased from Abcam. DiFMUP (Invitrogen) was used as the substrate. Buffer solution included 50 mM Tris-HCl, 150 mM NaCl, 5 mM DTT, 1 mM EDTA and 0.01% BSA. The *in vitro* method of assay of the synthesized compounds has been described in the literature.32 Initially, the compounds were tested at a single concentration (10 μM); the assay was repeated three times to determine the percentage inhibition of HPTPβ (%inhibition) by the tested compounds. If %inhibition of the compounds was higher than 65, the IC_{50} values of the compounds were determined. Compounds were diluted 3-fold from the 10 mM stock to obtain 10 concentrations in a 96 well plate. The diluted compounds (5 μL) were transferred into an assay plate and 10 μL of the dilution of HPTPβ was added into the assay plate wells. The compounds were premixed with the enzyme for 10 min at room temperature. Then, the reaction was started by the addition of 10 μL DiFMUP (20 μM) to the wells. The assay plate was scanned using an Enspire X (PerkinElmer) instrument two hours later.

4.2.2. Selectivity evaluation

The selectivity assays were performed using 2 μL of recombinant PTPs: PTP1B (0.01 ng/μL), TC-PTP (0.002 ng/μL), SHP2 (0.008 ng/μL) and LAR (0.002 ng/μL) and DiFMUP (20 μM, 20 μM, 10 μM, 20 μM and 10 μM, respectively). Assays were performed as described above.

4.2.3. Molecular docking

Molecular docking was carried out to predict the binding mode of HPTPβ and compounds **G4**, **G14**, **G16** and **G25** by using the SYBYL software. The docking results were analyzed by the DS software. The structure of protein was retrieved from the Protein Data Bank (PDB ID: 2H02, www.rcsb.org). The energy-lowest conformation of a molecule was explored before docking. Therefore, the molecules underwent initial minimization and simulated annealing calculation; then, the obtained conformations were docked to the protein. To prove reliability of optimization and the docking methods, the ligand of the complex was redocked into HPTPβ. The docking results showed that the redocked ligand overlaps with the original ligand (similarity: 8.1). This protocol was subsequently used for the selected compounds. The pose with the highest value of C-score was selected from a series of docking poses and was used for analysis and explanation of the activity differences between the compounds.

5. Notes

Authors guarantee that there is no conflict of interest in the described content of the article.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

Acknowledgements

This work was supported by the Major New Drugs Innovation and Development (grant numbers 2018ZX09J18102-002).

References

1 Zhang ZY. Chemical and mechanistic approaches to the study of protein tyrosine phosphatases. *Acc Chem Res*. 2003;36:385–392.
2 Tony H. The genesis of tyrosine phosphorylation. *Csh Perspect Biol*. 2014;6, a020644.
3 Zhang ZY. Drugging the undruggable: therapeutic potential of targeting protein tyrosine phosphatases. *Acc Chem Res*. 2016;50:122.
4 Krueger NX, Streuli M, Saito H. Structural diversity and evolution of human receptor-like protein tyrosine phosphatases. *EMBO J*. 1990;9:3241–3252.
5 Yacyshyn OK, Lai PFH, Forse K, Teichert-Kuliszewska K, Jurasz P, Stewart DJ. Tyrosine phosphatase beta regulates angiopoietin-Tie2 signaling in human endothelial cells. *Angiogenesis*. 2009;12:25–33.
6 Mark W, Linda K, Giuseppe C, et al. VE-PTP controls blood vessel development by balancing Tie-2 activity. *J Cell Biol*. 2009;185:657–671.
7 Seegar TC, Eller B, Tzvetkova-Robev D, et al. Tie1-Tie2 interactions mediate functional differences between angiopoietin ligands. *Mol Cell*. 2010;37:643–655.
8 Suri C, Jones PF, Patan S, et al. Requisite Role of Angiopoietin-1, a ligand for the TIE2 receptor, during embryonic angiogenesis. *Cell*. 1996;87:1171–1180.
9 Thurston G, Suri C, Smith K, et al. Leakage-resistant blood vessels in mice transgenically overexpressing angiopoietin-1. *Science*. 1999;286:2511–2514.
10 Saharinen P, Eklund L, Alitalo K. Therapeutic targeting of the angiopoietin-TIE pathway. *Nat Rev Drug Discov*. 2017;16:635.
11 Campochiaro PA, Khanani A, Singer M, et al. Enhanced benefit in diabetic macular edema from AKB-9778 Tie2 activation combined with vascular endothelial growth factor suppression. *Ophthalmology*. 2016;123:1722–1730.
12 Goel S, Gupta N, Walcott BP, et al. Effects of vascular-endothelial protein tyrosine phosphatase inhibition on breast cancer vasculature and metastatic progression. *J Natl Cancer Inst*. 2013;105:1188–1201.
13 Li-Fan Z, Ruo-Yu Z, Yunpeng B, Li W, Gunawan AM, Zhong-Yin Z. Hydroxyindole carboxylic acid-based inhibitors for receptor-type protein tyrosine protein phosphatase beta. *Antioxid & Redox Signal*. 2014;20:2130–2140.
14 Zhang ZY, Dixon JE. Active site labeling of the Yersinia protein tyrosine phosphatase: the determination of the pKa of the active site cysteine and the function of the conserved histidine 402. *Biochemistry*. 1993;32:9340–9345.
15 Jackson MD, Denu JM. Molecular reactions of protein phosphatasess insights from structure and chemistry. *Cheminform*. 2001;32:2313–2340.

16 Stanford SM, Bottini N. Targeting tyrosine phosphatases: time to end the stigma. *Trends Pharmacol Sci*. 2017;38:524–540.
17 Li LF, Bhandari A, Holmes CP, Szardenings AK. α, α-Difluoro-β-ketophosphonates as potent inhibitors of protein tyrosine phosphatase 1B. *Bio Med Chem Lett*. 2004;14:4301–4306.
18 Holmes CP, Li X, Pan Y, et al. Discovery and structure–activity relationships of novel sulfonamides as potent PTP1B inhibitors. *Bio Med Chem Lett*. 2005;15:4336–4341.
19 Holmes CP, Li X, Pan Y, et al. PTP1B inhibitors: Synthesis and evaluation of difluoromethylenephosphonate bioisosteres on a sulfonamide scaffold. *Bio Med Chem Lett*. 2008;18:2719–2724.
20 Klopfenstein SR, Evdokimov AG, Colson AO, et al. 1,2,3,4-Tetrahydroisoquinolinyl sulfamic acids as phosphatase PTP1B inhibitors. *Bio Med Chem Lett*. 2006;16:1574–1578.
21 K. Peters, G, R. Shalwitz, Compositions and methods for treating ocular edema, neovascularization and related diseases, US20120129847. Aerpio Therapeutics Inc, 2012.
22 Sankar S, Raheja RK, Newman MJ, et al. Sulfamic acids as inhibitors of human cytoplasmic protein tyrosin phosphatases, WO03082263. *Ontogen Corporation*. 2003.
23 Evdokimov AG, Pokross M, Walter R, et al. Engineering the catalytic domain of human protein tyrosine phosphatase beta for structure-based drug discovery. *Acta Crystallogr A*. 2010;62:1435–1445.
24 Zhang W, Wei Z, Feng X, Zheng Z, Li S. Synthesis and biological evaluation of (3'-amino-[1,1'-biphenyl]-4-yl) sulfamic acid derivatives as novel HPTPbeta inhibitors. *Bioorg Chem*. 2018;81:270–277.
25 Zhang L, Addla D, Ponmani J, et al. Discovery of membrane active benzimidazole quinolones-based topoisomerase inhibitors as potential DNA-binding antimicrobial agents. *Eur J Med Chem*. 2016;111:160–182.
26 Waykole LM, McKenna JJ, Bach A, Prashad M, Repič O, Blacklock TJ. Amino acids as a chiral Pool: synthesis of (S)-and (R)-2-N-carbomethoxy-5-aminoindane from (S)-and (R)-phenylalanines. *Synth Commun*. 2007;37:1445–1454.
27 Shidore M, Machhi J, Shingala K, et al. Benzylpiperidine-linked diarylthiazoles as potential anti-Alzheimer's agents-synthesis and biological evaluation. *J Med Chem*. 2016;59:5823–5846.
28 Xiang J, Ipek M, Suri V, et al. Synthesis and biological evaluation of sulfonamidooxazoles and β-keto sulfones: selective inhibitors of 11β-hydroxysteroid dehydrogenase type I. *Cheminform*. 2005;15:2865–2869.
29 Amarasinghe KKD, Evidokimov AG, Xu K, et al. Design and synthesis of potent, non-peptidic inhibitors of HPTPβ. *Bio Med Chem Lett*. 2006;16:4252–4256.
30 Zhao C, Rakesh KP, Ravidar L, Fang WY, Qin HL. Pharmaceutical and medicinal significance of sulfur (SVI)-Containing motifs for drug discovery: A critical review. *Eur J Med Chem*. 2019;162:679–734.
31 Yu ZH, Zhang ZY. Regulatory mechanisms and novel therapeutic targeting strategies for protein tyrosine phosphatases. *Chem Rev*. 2017;118.
32 Shen J, Frye M, Lee BL, et al. Targeting VE-PTP activates TIE2 and stabilizes the ocular vasculature. *J Clin Invest*. 2014;124:4564–4576.