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Design, synthesis, and biological evaluation of 2-substituted ethenesulfonic acid ester derivatives as selective PTP1B inhibitors

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Fifteen 2-substituted ethenesulfonic acid ester derivatives were designed, synthesized, and evaluated for the inhibitory activities against protein tyrosine phosphatase 1B (PTP1B) and T-Cell protein tyrosine phosphatase (TCPTP). The structural activity relationship (SAR) of these compounds are discussed to clarify the impact of the linker and the optimized tail on the inhibitory activity of PTP1B and selectivity over TCPTP. Most of the compounds exhibit excellent inhibitory activities against PTP1B with IC_{50} values of 1.5-8.9 μM. SAR analysis reveal that the substituents at the hydrophobic tail significantly alter the inhibitory activity against PTP1B and selectivity over TCPTP, e.g. compound **5d** showed excellent inhibitory activity to PTP1B with IC_{50} = 7.8 μM, and ~6-fold selectivity over TCPTP. Combined with our previous findings, we confirm that the linker length and the substituted hydrophobic tail have decisive influence on the PTP1B inhibitory activity and selectivity.

1. Introduction

Over the past decades, there has been tremendous increase in the metabolic syndrome, obesity, and diabetes all over the world (Wild et al. 2004). Insulin resistance is a major feature of type 2 diabetes mellitus (T2DM). The resistance of insulin and leptin is associated with the increased activity and expression of protein tyrosine phosphatase 1B (PTP1B) (Popov 2011). PTP1B enzyme acts as a negative regulator in insulin signaling pathways. The inhibition of PTP1B enzyme activity provides a promising solution of enhancing insulin action by prolonging the phosphorylated state of the insulin receptor (Taylor et al. 1994). Efforts directed towards the development of PTP1B inhibitors would potentially lead to novel therapeutic agents for the treatment of T2DM and obesity (Lessard et al. 2010; Ali et al. 2009). So far, only two compounds (ertiprotafib and trodusquemine) reached clinical evaluation (Ripka 2000; Erbe et al. 2005; Takahashi, et al. 2004). The major contributing factors to the failure of PTPs drug discovery relate to the intrinsic properties of the PTP active site. The highly conserved active site make it not trivial to obtain selective drugs for a special PTP. This is a common issue to most enzyme families that act upon common substrate motifs (such as pTyr for PTPs or ATP for kinases) (He et al. 2012). To address the issue of specificity, it has long been recognized that non-hydrolyzable phosphotyrosine (pTyr) alone is not sufficient for high-affinity selective binding (Vetter et al. 2000). A solution of this problem could be seen in inhibitors which simultaneously bind to the catalytic site and the allosteric site (Bhattacharya et al. 2009; Bhattarai et al. 2010; Ottana et al. 2012). In addition, specifically to PTP1B, the inhibitors should reduce the flexibility of WPD loop towards a more rigid conformation preventing the WPD loop closure and the substrate binding (Ottana et al. 2009; Kumar et al. 2010). The ideal inhibitor in the future should possess the ability to recognize distinctively cytoplasmic PTP1B and interact both with the catalytic as well as the allosteric site of PTP1B for the intervention of the insulin and leptin signaling pathways (Popov 2011).

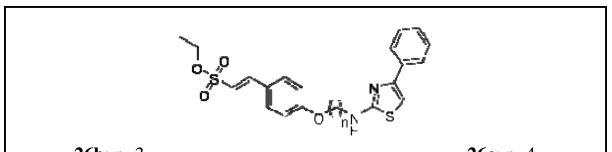
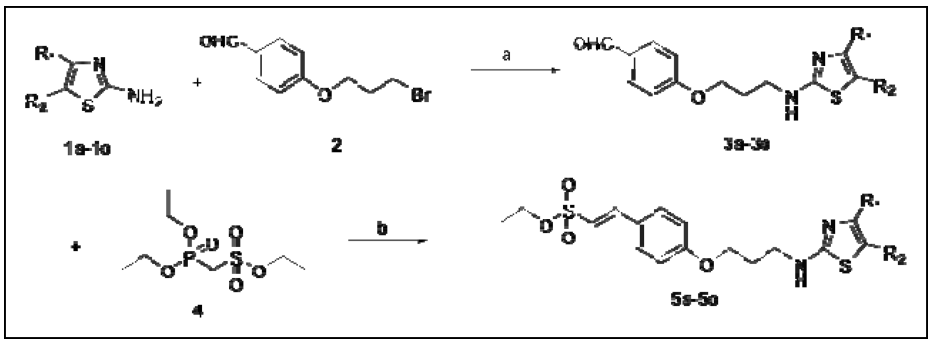


Fig. 1: Structures of our two recently published PTP1B inhibitors (Liu et al. 2012).

In a previous study (Liu et al. 2012), we identified a series of 2-substituted ethenesulfonic acid ester derivatives with an ethenesulfonic acid ethyl ester hydrophilic head, a benzene ring aromatic center, a six-atom linker and a thiazole ring hydrophobic tail, as novel, potent and selective PTP1B inhibitors. Our preliminary SAR studies demonstrated that the length of the linker, the substituent at the aromatic center and/or the hydrophobic tail remarkably affect the inhibitory activity against PTP1B and its selectivity over TCPTP. Especially, compounds with a 4-fluorophenyl (**43**) or a pyridine-2-yl (**36**) group at C-4 position of the thiazole ring at the hydrophobic tail revealed excellent inhibitory activity for PTP1B with IC_{50} values of 1.3 μM and 1.5 μM, respectively, and have 10- and 20-fold selectivity over TCPTP. Compounds **26c** (Fig. 1) with a six-atom linker and **26b** with a five-atom linker showed good inhibitory activity against PTP1B with IC_{50} values of 22.0 μM and 24.8 μM, respectively.

In this work, we initiate the project with **26b** as a lead compound, and designed a series of 2-substituted ethenesulfonic acid ester



Scheme 1: Synthesis of compounds **5a-o**, Reagents and conditions: (a) K_2CO_3, DMF, 90 °C, 8.2–53.8%; (b) n-BuLi, THF, -78 °C ~r.t, 21.5~92.7%.

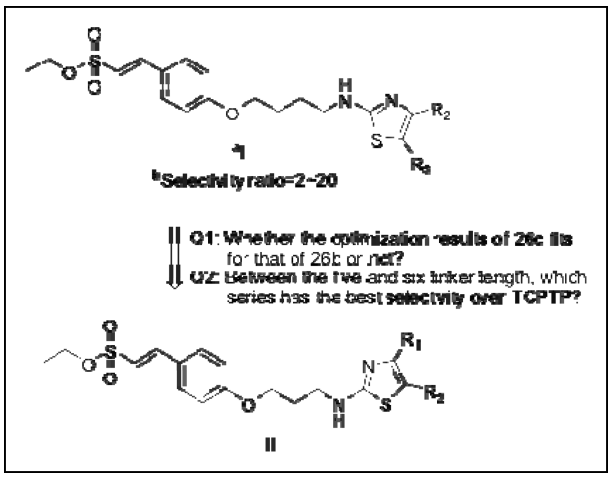


Fig. 2: Design of 2-substituted ethenesulfonic acid ester derivatives with five-atom length of hydrophobic linker as novel PTP1B inhibitors.

derivatives to study the effects of electron densities, halogen positions, substituent bulkiness and heterocyclic substituents on the inhibitory activity for the PTP1B and selectivity over TCPTP (Fig. 2). Herein, we report the design, synthesis, and evaluation of these derivatives with five-atom length of hydrophobic linker as a new class of PTP1B inhibitors.

2. Investigations and results

2.1. Chemistry

The synthesis of **5a**-**o** analogues is shown in the Scheme. Treatment of substituted thiazol-2-amines **1a-o** with 4-(3-bromopropoxy) benzaldehyde in the presence of K_2CO_3 gives the intermediates **3a**-**o.** Coupling of these intermediates with ethyl (diethoxyphosphoryl) methanesulfonate (**4**) by Wittig-Horner reaction yielded compounds **5a**-**o**. All synthesized compounds were characterized by the NMR and mass spectroscopy.

2.2. PTP1B and TCPTP inhibitory activities

The inhibitory activities of compounds **5a**-**o** against PTP1B and TCPTP were determined and their IC_{50} values are summarized in the Table.

2.3. Cytotoxicity against COS-7 (African green monkey kidney fibroblast-like cell line)

We investigated the cytotoxicity of the 2-substituted ethenesulfonic acid ester derivatives against COS-7 (African green monkey kidney fibroblast-like cell line) by MTT assay, the results are also summarized in the Table.

3. Discussion

3.1. Structure–activity relationships

As shown in the Table, compound **5a** shows moderate inhibitory activity against PTP1B with $IC_{50} = 24.8\ \mu M$. After optimization of the hydrophobic tail, most of compounds display high inhibitory activity against PTP1B. We attached halogens on ortho-, meta- and para-positions of the phenyl of R1 group, compounds **5b**, **5c**, **5d**, **5e** and **5f** all displayed excellent inhibitory activity with IC_{50} values between 2.3 and 7.8 μM. This indicates the significant influence of the position of the halogens substituent on the inhibitory activity against PTP1B. We also introduced the electron-donating and withdrawing groups on the phenyl of R1 group to investigate the electron density effect on the inhibitory activity against PTP1B. Compounds **5 g**, **5 h** and **5i** exhibit good activity with $IC_{50} = 2.0\text{-}8.0\ \mu M$, which suggests little influence of the electron density effect on the inhibitory activity. Compared to **5a** with a phenyl at the R1 group, ligands with thiophen-2-yl (**5j**), biphenyl-4-yl (**5l**), or naphthalen-1-yl (**5m**) at R1 show prominent inhibitory activity with $IC_{50} = 1.5\text{-}8.9\ \mu M$. However, the candidate with pyridin-4-yl (**5k**) has negligible activity against with $IC_{50} > 100\ \mu M$. The heterocyclic substituent at R1 shows great influence to the PTP1B inhibitory activity, and tends to be more hydrophobic to enhance the activity. We simultaneously studied the influence of the substituent of the R2 group on the inhibitory activity against PTP1B. Ligands with a methyl (**5n**) and a phenyl group (**5o**) both show excellent activity with $IC_{50} = 1.6\text{-}2.3\ \mu M$, compared to **5a** with a hydrogen, indicating positive influence to the activity of the substituent bulk of R2.

3.2. Selectivity over TCPTP

To explore the selectivity of **5a**-**o** over PTPs, the candidates were also tested for inhibitory activity against TCPTP (Table 1). When the halogen was introduced to the phenyl of R1 group, compounds **5b**, **5d**, **5e** and **5f** showed ~2-6-fold selectivity over TCPTP. Compound **5c** with a fluoro- on the para-position of the phenyl of R1 group displays competitive inhibition against TCPTP, indicating a certain influence of the position of halogen on the selectivity. Compound **5c** with a five-atom length linker between the hydrophobic tail and aromatic center showed no selectivity, compared to compound **43** from our previous study (Liu et al. 2012) with a six-atom length linker showing 10-fold selectivity over TCPTP. Such a result confirms that the linker length exerts great influence on the selectivity and that a six-atom linker length leads to better selectivity.

Table 1: ***In vitro*** **inhibitory activity against two PTPs of 2-substituted ethenesulfonic acid ester derivatives**

Compd.	R_1	R_2	[a]IC_{50} (μM) PTP1B	TCPTP	Selectivity ratio[d]	COS-7 cell
[b]**5a**	Phenyl	H	24.8	29.5	1.2	> 100
5b	2-fluorophenyl	H	5.1	10.5	2.1	> 100
5c	4-fluorophenyl	H	4.4	4.8	1.1	> 100
5d	2-chlorophenyl	H	7.8	44.9	5.8	> 100
5e	3-chlorophenyl	H	4.7	7.8	1.7	> 100
5f	4-bromophenyl	H	2.3	7.1	3.1	> 100
5g	3-methoxyphenyl	H	2.0	7.5	3.8	> 100
5h	3,4,5-trimethoxyphenyl	H	3.4	9.0	2.6	> 100
5i	4-nitrophenyl	H	8.0	9.3	1.2	> 100
5j	thiophen-2-yl	H	8.9	12.1	1.4	> 100
5k	pyridine-4-yl	H	> 100	> 100	-	> 100
5l	biphenyl-4-yl	H	4.9	7.4	1.5	> 100
5m	naphthalen-1-yl	H	1.5	3.4	2.3	> 100
5n	phenyl	CH_3	2.3	9.2	4.0	> 100
5o	phenyl	phenyl	1.6	4.1	2.6	> 100
Sodium orthovanadate[c]	0.046		0.014	0.3	-[e]	

[a] IC_{50} values are means of three experiments.
[b] **5a** is the **26b** which was published by Liu et al. (2012).
[c] Positive control.
[d] Selectivity ratio means IC_{50} (TCPTP) /IC_{50}(PTP1B).
[e] Not tested.

The electron withdrawing group on the phenyl of R1 group, as compound **5i** with a nitro on the para-position of phenyl of R1 group, shows competitive inhibition against TCPTP. And **5 g** and **5 h** with electron-donating groups on the phenyl of R1 group resulted in ∼3-4 fold selectivity over TCPTP, indicating that an electron-donating effect has a positive effect on the selectivity. As the heterocyclic substituent was introduced to the R1 group, the **5j** with a thiophen-2-yl exhibits competitive inhibition against TCPTP, and **5k** with a pyridine-4-yl has no activity on the PTP1B or TCPTP, which suggests that the heterocyclic substituent is unable to strengthen the selectivity over TCPTP. By increasing the number of phenyls on the R1 group, **5l** with a biphenyl-4-yl and **5m** with naphthalen-1-yl both show ∼2-fold selectivity over TCPTP. Compared to the results of our previous study, compound **34** with a six-atom length linker showed ∼8 fold selectivity over TCPTP, which also confirms that the linker length has a positive influence on selectivity. As the substituent bulk of R2 is changed, **5n** with a methyl and **5o** with a phenyl display ∼3-4-fold selectivity over TCPTP. By comparing to **5a** with hydrogen which shows competitive inhibition, bulky substituent groups have positive impact on the ligand selectivity.

3.3. Binding models

To obtain information for further structural optimization studies, we constructed the 3D binding model of compound **5d** binding to PTP1B in open conformation based on the docking simulation (Fig. 3) (Ye et al. 2010). The sulfonyl acid ester group of **5d** forms an H-bond network with ARG221, ASP181, LYS116, ASN111 and GLU115 at the active site of PTP1B. Additionally, **5d** also forms a H-bond with the key residue THR263. Furthermore, the phenyl ring of the ligand lies in a hydrophobic pocket constructed by the surrounding amino acid (PHE182, GLN262, ASP48, ARG24 and MET258). We believe due to these multiple interactions, that **5d** displays an excellent inhibitory activity against PTP1B and serves as a potent inhibitor.

In conclusion, we designed and synthesized fifteen novel 2-substituted ethenesulfonic acid ester derivatives with a five-atom hydrophobic linker between the hydrophobic tail and the aromatic center and further optimized the functional groups of the hydrophobic tail. Most of the compounds exhibit outstanding inhibitory activity against PTP1B with IC_{50} = 1.5-8.9 μM, and lower cytotoxicity with IC_{50} values > 100 μM. A preliminary SAR discussion indicates that the hydrophobic tail is essential to the inhibitory activity against PTP1B. Ligands with electron-withdrawing or donating groups or a heterocyclic substituent at R1 group all strengthened the inhibitory activity against PTP1B. Moreover, substituents on the hydrophobic tail resulted in a wide range of selectivities over TCPTP. Most of the ligands display ∼2-4-fold selectivity over TCPTP, specifically compound **5d** with a meta-positioned chloro substituent at the phenyl of R1 group, displayed ∼6-fold selectivity over TCPTP. In this work, we further confirmed that the linker length has a decisive effect on the inhibitory activity against PTP1B and selectivity over TCPTP and six-atom linkers yield the best activity.

4. Experimental

4.1. Chemistry

^{1}H NMR was recorded on either a Brucker 300 MHz Avance DPX Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Chemical shift values are given in parts per million and coupling constants (J) in Hertz. High resolution mass spectroscopy was conducted using Micromass LCT system. All reactions were followed by TLC (silica gel, aluminum sheets 60 F254).

*4.1.1. 4-(3-(4-Phenylthiazol-2-ylamino)propoxy)benzaldehyde (***3a***)*

To a solution of 4-(3-bromopropoxy)benzaldehyde (200.00 mg, 0.82 mmol) and 4-phenylthiazol-2-amine (144.50 mg, 0.82 mmol) in DMF (15 mL), potassium carbonate (170.00 mg, 1.23 mmol) was added. The reaction mixture was refluxed for 12 h. The reaction mixture was quenched with water, and extracted with toluene (20 mL*3). The combined organic layer was washed with brine, dried with anhydrous sodium sulphate, concentrated under vacuum, then purified by flash chromatography (petroleum ether: ethyl acetate = 3:1) to afford a colorless solid. Yield 32.3%; m.p.: 90-92 °C; ^{1}H NMR (300 MHz, CDCl3) δ 2.452-2.509 (m, 2H, OCH2CH2CH2NH), 4.130-4.167 (t, 2H, OCH2CH2CH2NH, J = 5.55 Hz), 4.377-4.420 (t, 2H, OCH2CH2CH2 NH, J = 6.45 Hz), 6.984-7.013 (d, 2H, ArH, J = 8.7 Hz), 7.327-7.434 (m, 3H, ArH), 7.816-7.885 (m, 4H, ArH), 8.597 (s, 1H, CH), 9.885 (s, 1H, CHO); MS(ESI m/z):339 (M + H)+.

The procedure described for the synthesis of compound **3a** can also be applied to the synthesis of compounds **3b**-**o**.

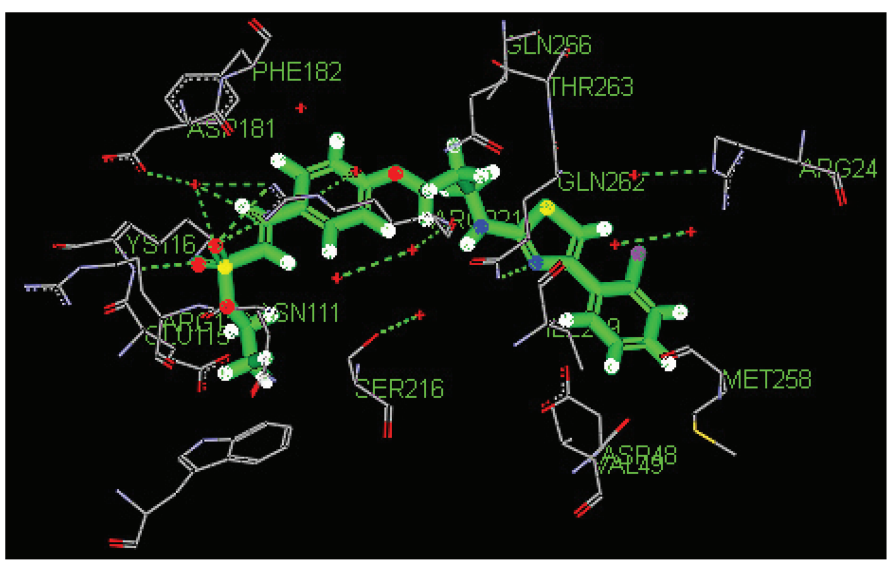


Fig. 3: Binding mode of compound **5d** to PTP1B derived from docking simulation. **5d** and the key residues of PTP1B are shown in a capped stick representation. Carbon is in green for ligand and gray for PTP1B, oxygen is in red, nitrogen is in blue, sulfur is in yellow, hydrogen is in white and chlorine is in purple.

*4.1.2. 4-(3-(4-(2-Fluorophenyl)thiazol-2-ylamino) propoxy)benzaldehyde (**3b**)*

Compound **3b** (75.00 mg, 25.50%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.171-2.211 (m, 2H, $OCH_2CH_2CH_2N$), 3.521-3.567 (t, 2H, $OCH_2CH_2CH_2N$, J = 6.9 Hz), 4.146-4.181 (t, 2H, $OCH_2CH_2CH_2N$, J = 5.25 Hz), 6.981-7.007 (d, 2H, ArH, J = 7.8 Hz), 7.093-7.231 (m, 4H, ArH), 7.816-7.843 (d, 2H, ArH, J = 8.1 Hz), 8.241 (s, 1H, CH), 9.885 (s, 1H, CHO); MS(ESI m/z):357 (M + H)+.

*4.1.3. 4-(3-(4-(4-Fluorophenyl)thiazol-2-ylamino) propoxy)benzaldehyde (**3c**)*

Compound **3c** (59.00 mg, 20.00%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.172-2.233 (m, 2H, $OCH_2CH_2CH_2N$), 3.547-3.587 (t, 2H, $OCH_2CH_2CH_2N$, J = 6 Hz), 4.166-4.205 (t, 2H, $OCH_2CH_2CH_2N$, J = 5.85 Hz), 7.029-7.087 (d, 4H, ArH, J = 8.7 Hz), 7.824-7.853 (d, 4H, ArH, J = 8.7 Hz), 8.258 (s, 1H, CH), 9.889 (s, 1H, CHO); MS(ESI m/z):357 (M + H)+.

*4.1.4. 4-(3-(4-(2-Chlorophenyl)thiazol-2-ylamino)propoxy) benzaldehyde (**3d**)*

Compound **3d** (71.00 mg, 23.10%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.953-1.995 (m, 2H, $OCH_2CH_2CH_2N$), 3.360-3.412 (t, 2H, $OCH_2CH_2CH_2N$, J = 7.8 Hz), 3.988-4.027 (t, 2H, $OCH_2CH_2CH_2N$, J = 5.85 Hz), 6.923-6.951 (d, 2H, ArH, J = 8.4 Hz), 7.233-7.356 (m, 1H, ArH), 7.403-7.448 (m, 2H, ArH), 7.796-7.824 (d, 2H, ArH, J = 8.4 Hz), 8.246 (s, 1H, CH), 9.872 (s, 1H, CHO); MS(ESI m/z):372 (M + H)+.

*4.1.5. 4-(3-(4-(3-Chlorophenyl)thiazol-2-ylamino)propoxy) benzaldehyde (**3e**)*

Compound **3e** (85.00 mg, 27.60%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.119-2.207 (m, 2H, $OCH_2CH_2CH_2N$), 3.263-3.306 (t, 2H, $OCH_2CH_2CH_2N$, J = 6.45 Hz), 4.111-4.153 (t, 2H, $OCH_2CH_2CH_2N$, J = 6.3 Hz), 6.971-6.995 (d, 2H, ArH, J = 7.2 Hz), 7.248-7.315 (m, 2H, ArH), 7.771-7.843 (m, 4H, ArH), 8.251 (s, 1H, CH), 9.874 (s, 1H, CHO); MS(ESI m/z):373 (M + H)+.

*4.1.6. 4-(3-(4-(4-Bromophenyl)thiazol-2-ylamino)propoxy) benzaldehyde (**3f**)*

Compound **3f** (61.00 mg, 17.70%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.139-2.194 (m, 2H, $OCH_2CH_2CH_2N$), 3.523-3.541 (t, 2H, $OCH_2CH_2CH_2N$, J = 5.4 Hz), 4.112-4.150 (t, 2H, $OCH_2CH_2CH_2N$, J = 5.7 Hz), 6.956-6.985 (d, 2H, ArH, J = 8.7 Hz), 7.460-7.488 (d, 2H, ArH, J = 8.4 Hz), 7.626-7.655 (d, 2H, ArH, J = 8.7 Hz), 7.805- 7.834 (d, 2H, ArH, J = 8.7 Hz), 8.228 (s, 1H, CH), 9.878 (s, 1H, CHO); MS(ESI m/z):417 (M + H)+.

*4.1.7. 4-(3-(4-(3-Methoxyphenyl)thiazol-2-ylamino)propoxy) benzaldehyde (**3 g**)*

Compound **3 g** (74.00 mg, 24.30%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.096-2.214 (m, 2H, $OCH_2CH_2CH_2N$), 3.786-3.848 (m, 5H, $OCH_2CH_2CH_2N$, OCH_3), 4.122-4.161 (t, 2H, $OCH_2CH_2CH_2N$, J = 5.85 Hz), 6.679 (s, 1H, ArH), 6.969- 6.997 (d, 2H, ArH, J = 8.4 Hz), 7.331-7.355 (d, 2H, ArH, J = 7.2 Hz), 7.800-7.849 (m, 2H, ArH), 8.244 (s, 1H, CH), 9.875 (s, 1H, CHO); MS(ESI m/z):369 (M + H)+.

*4.1.8. 4-(3-(4-(3,4,5-Trimethoxyphenyl)thiazol-2-ylamino)propoxy) benzaldehyde (**3 h**)*

Compound **3 h** (70.00 mg, 19.70%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.058-2.185 (m, 2H, $OCH_2CH_2CH_2N$), 3.263-3.306 (t, 2H, $OCH_2CH_2CH_2N$, J = 6.45 Hz), 3.912 (s, 9H, $3OCH_3$), 4.098-4.134 (t, 2H, $OCH_2CH_2CH_2N$, J = 5.4 Hz), 6.933- 7.017 (m, 4H, ArH), 7.795-7.820 (d, 2H, ArH, J = 7.5 Hz), 8.012 (s, 1H, CH), 9.876 (s, 1H, CHO); MS(ESI m/z):429 (M + H)+.

*4.1.9. 4-(3-(4-(4-Nitrophenyl)thiazol-2-ylamino) propoxy)benzaldehyde (**3i**)*

Compound **3i** (43.00 mg, 13.60%) as a yellow solid; m.p.: 108-110 °C; 1H NMR (300 MHz, $CDCl_3$) δ 2.045-2.131 (m, 2H, $OCH_2CH_2CH_2N$), 3.616-3.657 (t, 2H, $OCH_2CH_2CH_2N$, J = 6.15 Hz), 4.130-4.169 (t, 2H, $OCH_2CH_2CH_2N$, J = 5.85 Hz), 7.059-7.087 (d, 2H, ArH, J = 8.4 Hz), 7.833-7.861 (d, 2H, ArH, J = 8.4 Hz), 7.915-7.944 (d, 2H, ArH, J = 8.7 Hz), 8.320-8.349 (d, 2H, ArH, J = 8.7 Hz), 8.725 (s, 1H, CH), 9.889 (s, 1H, CHO); MS(ESI m/z):419 (M + 39)+.

*4.1.10. 4-(3-(4-(Thiophen-2-yl)thiazol-2-ylamino)propoxy) benzaldehyde (**3j**)*

Compound **3j** (58.00 mg, 25.50%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.064-2.203 (m, 2H, $OCH_2CH_2CH_2N$), 3.515-3.553 (t, 2H, $OCH_2CH_2CH_2N$, J = 5.7 Hz), 4.148-4.187 (t, 2H, $OCH_2CH_2CH_2N$, J = 5.85 Hz), 6.855 (s, 1H, CH), 7.011-7.035 (d, 2H, ArH, J = 7.2 Hz), 7.204-7.221 (d, 1H, CH, J = 5.1 Hz), 7.390-7.402 (d, 1H, CH, J = 3.6 Hz), 7.819-7.847 (d, 2H, ArH, J = 8.4 Hz), 8.252 (s, 1H, CH), 9.887 (s, 1H, CHO); MS(ESI m/z):345 (M + H)+.

*4.1.11. 4-(3-(4-(Pyridin-4-yl)thiazol-2-ylamino)propoxy) benzaldehyde (**3k**)*

Compound **3k** (23.00 mg, 8.20%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.194-2.281 (m, 2H, $OCH_2CH_2CH_2N$), 4.134-4.181 (m, 4H, $OCH_2CH_2CH_2N$), 6.995- 7.018 (d, 4H, ArH, J = 6.9 Hz), 7.834-7.860 (d, 4H, ArH, J = 7.8 Hz), 8.404 (s, 1H, CH), 9.894 (s, 1H, CHO); MS(ESI m/z):340 (M + H)+.

*4.1.12. 4-(3-(4-(Biphenyl-4-yl)thiazol-2-ylamino)propoxy) benzaldehyde (**3l**)*

Compound **3l** (114.00 mg, 33.30%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.057-2.097 (m, 2H, $OCH_2CH_2CH_2N$), 3.853-3.893 (t, 2H, $OCH_2CH_2CH_2N$, J = 6 Hz), 4.180-4.220 (t, 2H, $OCH_2CH_2CH_2N$, J = 6 Hz), 6.985-7.014 (d, 4H, ArH, J = 8.7 Hz), 7.360-7.467 (m, 2H, ArH), 7.592-7.690 (m, 3H, ArH), 7.809-7.838 (d, 4H, ArH, J = 8.7 Hz), 8.023 (s, 1H, CH), 9.873 (s, 1H, CHO); MS(ESI m/z):415 (M + H)+.

*4.1.13. 4-(3-(4-(Naphthalen-1-yl)thiazol-2-ylamino)propoxy) benzaldehyde (**3m**)*

Compound **3m** (80.00 mg, 24.90%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.988-2.048 (m, 2H, $OCH_2CH_2CH_2N$), 3.360-3.412 (t, 2H, $OCH_2CH_2CH_2N$, J = 7.8 Hz), 4.017-4.056 (t, 2H, $OCH_2CH_2CH_2N$, J = 5.85 Hz), 6.597 (s, 1H, ArH), 6.955- 6.984 (d, 2H, ArH, J = 8.7 Hz), 7.461-7.509 (m, 2H, ArH), 7.622-7.688 (m, 2H, ArH), 7.812-7.878 (m, 3H, ArH), 8.262-8.336 (m, 1H, ArH), 8.392 (s, 1H, CH), 9.886 (s, 1H, CHO); MS(ESI m/z):389 (M + H)+.

*4.1.14. 4-(3-(5-Methyl-4-phenylthiazol-2-ylamino)propoxy) benzaldehyde (**3n**)*

Compound **3n** (85.00 mg, 29.20%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.230-2.278 (m, 2H, $OCH_2CH_2CH_2N$), 2.041 (s, 3H, CH3), 4.080-4.411 (m, 4H, $OCH_2CH_2CH_2N$), 7.032-7.061 (d, 2H, ArH, J = 8.7 Hz), 7.404-7.525 (m, 5H, ArH), 7.823-7.851 (d, 2H, ArH, J = 8.4 Hz), 9.882 (s, 1H, CHO); MS(ESI m/z):353(M + H)+.

*4.1.15. 4-(3-(4,5-Diphenylthiazol-2-ylamino)propoxy)benzaldehyde (**3o**)*

Compound **3o** (184.00 mg, 53.80%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.090-2.131 (m, 2H, $OCH_2CH_2CH_2N$), 3.468-3.506 (t, 2H, $OCH_2CH_2CH_2N$, J = 5.7 Hz), 4.096-4.135 (t, 2H, $OCH_2CH_2CH_2N$, J = 5.7 Hz), 6.972-7.001 (d, 2H, ArH, J = 8.7 Hz), 7.230-7.281 (m, 10H, ArH), 7.812-7.841 (d, 2H, ArH, J = 8.7 Hz), 9.882 (s, 1H, CHO); MS(ESI m/z):415 (M + H)+.

*4.1.16. (E)-Ethyl 2-(4-(3-(4-phenylthiazol-2-ylamino)propoxy)phenyl) ethanesulfonate (**5a**)*

The ethyl (diethoxyphosphoryl)methanesulfonate (50.00 mg, 0.19 mmol) was dissolved in THF (15 mL), and the solution was cooled to -78 °C, then added n-BuLi (0.18 mL, 0.29 mmol, 2.2 M in hexanes) dropwise under N2 atmosphere. The mixture was stirred for 15 min, and then 4-(3-(4-phenylthiazol-2-ylamino)propoxy) benzaldehyde (64.00 mg, 0.19 mmol) was added dropwise. The reaction mixture was stirred at rt for 4 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, and extracted with ethyl acetate (20 mL*3). The combined organic layer was washed with brine, dried with anhydrous sodium sulphate, concentrated under vacuum, then purified by flash chromatography (petroleum ether: ethyl acetate = 3:1) to afford a colorless solid. Yield 46.80%; m.p.: 112-114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.389-1.436 (t, 3H, OCH_2CH_3, J = 7.05 Hz), 2.468-2.507 (m, 2H, $OCH_2CH_2CH_2NH$), 4.096-4.132 (t, 2H, $OCH_2CH_2CH_2NH$, J = 5.4 Hz), 4.192-4.264 (q, 2H, OCH_2CH_3, J = 7.2 Hz, 7.2 Hz), 4.384-4.427 (t, 2H, $OCH_2CH_2CH_2NH$, J = 6.45 Hz), 6.576-6.627 (d, 1H, CH = CH, J = 15.3 Hz), 6.926-6.953 (d, 2H, ArH, J = 8.1 Hz), 7.274-7.473 (m, 5H, ArH), 7.526-7.578 (d, 1H, CH = CH, J = 15.6 Hz), 7.878-7.905 (d, 2H, ArH, J = 8.1 Hz), 8.601 (s, 1H, CH); MS(ESI m/z):445 (M + H)+.
The procedure for the synthesis of compound **5a** can also be applied to the synthesis of compounds **5b–o**.

*4.1.17. (E)-Ethyl2-(4-(3-(4-(2-fluorophenyl)thiazol-2-ylamino) propoxy)phenyl) ethenesulfonate (**5b**)*

Compound **5b** (42.00 mg, 64.70%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.365-1.412 (t, 3H, OCH2CH3, J = 7.05 Hz), 2.275-2.308 (m, 2H, OCH2CH2CH2NH), 4.179-4.239 (m, 6H, OCH2CH2CH2NH, OCH2CH3), 6.558-6.610 (d, 1H, CH = CH, J = 15.6 Hz), 6.970-7.000 (d, 2H, ArH, J = 9 Hz), 7.116-7.232 (m, 4H, ArH), 7.438- 7.468 (d, 2H, ArH, J = 9 Hz), 7.505-7.556 (d, 1H, CH = CH, J = 15.3 Hz), 8.257 (s, 1H, CH); MS(ESI m/z):463 (M + H)+.

*4.1.18. (E)-Ethyl2-(4-(3-(4-(4-fluorophenyl)thiazol-2-ylamino) propoxy)phenyl) ethenesulfonate (**5c**)*

Compound **5c** (42.00 mg, 64.70%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.364-1.411 (t, 3H, OCH_2CH_3, J = 7.05 Hz), 2.261-2.301 (m, 2H, $OCH_2CH_2CH_2NH$), 4.097-4.215 (m, 6H, $OCH_2CH_2CH_2NH$, OCH_2CH_3), 6.557-6.609 (d, 1H, CH = CH, J = 15.6 Hz), 6.924-6.949 (d, 2H, ArH, J = 7.5 Hz), 7.101-7.129 (d, 2H, ArH, J = 8.4 Hz), 7.435-7.464 (d, 2H, ArH, J = 8.7 Hz), 7.501-7.553 (d, 1H, CH = CH, J = 15.6 Hz), 7.894- 7.921 (d, 2H, ArH, J = 8.1 Hz), 8.907 (s, 1H, CH); MS(ESI m/z):463 (M + H)+.

*4.1.19. (E)-Ethyl2-(4-(3-(4-(2-chlorophenyl)thiazol-2-ylamino)propoxy) phenyl) ethenesulfonate (**5d**)*

Compound **5d** (47.00 mg, 73.20%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.367-1.414 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.05 Hz), 2.246-2.285 (m, 2H, $OCH_2\underline{CH_2}CH_2NH$), 4.106-4.244 (m, 6H, $O\underline{CH_2}CH_2\underline{CH_2}NH$, $O\underline{CH_2}CH_3$), 6.562-6.614 (d, 1H, $\underline{CH}$ = CH, J = 15.6 Hz), 6.959-6.987 (d, 2H, ArH, J = 8.4 Hz), 7.431-7.505 (m, 3H, 2ArH, CH = $\underline{CH}$), 7.641-7.774 (m, 2H, ArH), 7.878-7.920 (m, 2H, ArH), 8.765 (s, 1H, CH); MS(ESI m/z):478 $(M + H)^+$.

4.1.20. (E)-Ethyl2-(4-(3-(4-(3-chlorophenyl)thiazol-2-ylamino)propoxy)phenyl)

ethenesulfonate (**5e**)
Compound **5e** (18.00 mg, 28.00%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.364-1.411 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.05 Hz), 2.196-2.362 (m, 2H, $OCH_2\underline{CH_2}CH_2NH$), 4.168-4.215 (m, 6H, $O\underline{CH_2}CH_2\underline{CH_2}NH$, $O\underline{CH_2}CH_3$), 6.558-6.609 (d, 1H, $\underline{CH}$ = CH, J = 15.3 Hz), 7.015 (s, 1H, ArH), 7.263-7.332 (m, 2H, ArH), 7.434-7.461 (d, 2H, ArH, J = 8.1 Hz), 7.501-7.553 (d, 1H, CH = $\underline{CH}$, J = 15.6 Hz), 7.771-7.794 (d, 2H, ArH, J = 6.9 Hz), 8.719 (s, 1H, CH); MS(ESI m/z):479 $(M + H)^+$.

*4.1.21. (E)-Ethyl2-(4-(3-(4-(4-bromophenyl)thiazol-2-ylamino)propoxy) phenyl) ethenesulfonate (**5f**)*

Compound **5f** (32.00 mg, 51.00%) as a yellow solid; m.p.:108-110 ^{0}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.367-1.415 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.2 Hz), 2.266-2.302 (m, 2H, $OCH_2\underline{CH_2}CH_2NH$), 4.171-4.219 (m, 6H, $O\underline{CH_2}CH_2\underline{CH_2}NH$, $O\underline{CH_2}CH_3$), 6.559-6.612 (d, 1H, $\underline{CH}$ = CH, J = 15.9 Hz), 6.971-7.000 (d, 2H, ArH, J = 8.7 Hz), 7.176-7.204 (d, 2H, ArH, J = 8.4 Hz), 7.436-7.464 (d, 2H, ArH, J = 8.4 Hz), 7.438-7.585 (m, 3H, CH = $\underline{CH}$, 2ArH), 8.461 (s, 1H, CH); MS(ESI m/z):520 $(M-H)^-$.

*4.1.22. (E)-Ethyl2-(4-(3-(4-(3-methoxyphenyl)thiazol-2-ylamino)propoxy) phenyl) ethenesulfonate (**5 g**)*

Compound **5 g** (25.00 mg, 38.80%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.369-1.416 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.05 Hz), 2.263-2.309 (m, 2H, $OCH_2\underline{CH_2}CH_2NH$), 3.888 (s, 3H, OCH_3), 4.102-4.222 (m, 6H, $O\underline{CH_2}CH_2\underline{CH_2}NH$, $O\underline{CH_2}CH_3$), 6.561- 6.613 (d, 1H, $\underline{CH}$ = CH, J = 15.6 Hz), 6.880-6.972 (m, 2H, ArH), 6.981-6.008 (d, 2H, ArH, J = 8.1 Hz), 7.358-7.468 (m, 3H, ArH), 7.505-7.555 (d, 1H, CH = $\underline{CH}$, J = 15 Hz), 7.634 (s, 1H, ArH), 8.274 (s, 1H, CH); MS(ESI m/z):475 $(M + H)^+$.

*4.1.23. (E)-Ethyl2-(4-(3-(4-(3,4,5-trimethoxyphenyl)thiazol-2-ylamino)propoxy)-phenyl)ethenesulfonate (**5 h**)*

Compound **5 h** (28.00 mg, 44.90%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.369-1.416 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.05 Hz), 2.147-2.185 (m, 2H, $OCH_2\underline{CH_2}CH_2NH$), 3.936 (s, 9H, $3OCH_3$), 4.082-4.224 (m, 6H, $O\underline{CH_2}CH_2\underline{CH_2}NH$, $O\underline{CH_2}CH_3$), 6.562- 6.614 (d, 1H, $\underline{CH}$ = CH, J = 15.6 Hz), 6.876-6.943 (m, 4H, ArH), 7.436-7.459 (d, 2H, ArH, J = 6.9 Hz), 7.507-7.559 (d, 1H, CH = $\underline{CH}$, J = 15.6 Hz), 8.783 (s, 1H, CH); MS (ESI m/z):535 $(M + H)^+$.

*4.1.24. (E)-Ethyl2-(4-(3-(4-(4-nitrophenyl)thiazol-2-ylamino) propoxy)phenyl) ethenesulfonate (**5i**)*

Compound **5i** (20.00 mg, 52.20%) as a yellow solid; m.p.: 106-108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.372-1.420 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.2 Hz), 2.294-2.330 (m, 2H, $OCH_2\underline{CH_2}CH_2NH$), 4.202-4.250 (m, 6H, $O\underline{CH_2}CH_2\underline{CH_2}NH$, $O\underline{CH_2}CH_3$), 6.568-6.619 (d, 1H, $\underline{CH}$ = CH, J = 15.3 Hz), 6.991-7.019 (d, 2H, ArH, J = 8.4 Hz), 7.450-7.476 (d, 2H, ArH, J = 7.8 Hz), 7.508-7.559 (d, 1H, CH = $\underline{CH}$, J = 15.3 Hz), 7.952-7.992 (d, 2H, ArH, J = 6 Hz), 8.315-8.342 (d, 2H, ArH, J = 8.1 Hz), 8.613 (s, 1H, CH); MS(ESI m/z):490 $(M + H)^+$.

*4.1.25. (E)-Ethyl2-(4-(3-(4-(thiophen-2-yl)thiazol-2-ylamino)propoxy)phenyl) ethenesulfonate (**5j**)*

Compound **5j** (16.00 mg, 30.60%) as a yellow solid; m.p.: 118-120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.364-1.412 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.2 Hz), 2.274-2.290 (m, 2H, $OCH_2\underline{CH_2}CH_2NH$), 4.103-4.238 (m, 6H, $O\underline{CH_2}CH_2\underline{CH_2}NH$, $O\underline{CH_2}CH_3$), 6.557-6.610 (d, 1H, $\underline{CH}$=CH, J = 15.9 Hz), 6.923-7.003 (m, 1H, CH), 7.061-7.087 (d, 2H, ArH, J = 7.8 Hz), 7.346-7.360 (m, 1H, CH), 7.430-7.456 (d, 2H, ArH, J = 7.8 Hz), 7.503- 7.554 (d, 1H, CH=$\underline{CH}$, J = 15.3 Hz), 7.889-7.900 (m, 1H, CH), 8.017 (s, 1H, CH); MS(ESI m/z):451 $(M+H)^+$.

*4.1.26. (E)-Ethyl2-(4-(3-(4-(pyridin-4-yl)thiazol-2-ylamino)propoxy)phenyl) ethenesulfonate (**5k**)*

Compound **5k** (13.00 mg, 49.40%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.725-1.766 (t, 3H, $OCH_2\underline{CH_3}$, J = 6.15 Hz), 2.166-2.241 (m, 2H, $OCH_2\underline{CH_2}CH_2NH$), 4.380-4.516 (m, 6H, $O\underline{CH_2}CH_2\underline{CH_2}NH$, $O\underline{CH_2}CH_3$), 6.555-6.607 (d, 1H, $\underline{CH}$=CH, J = 15.6 Hz), 6.920-6.942 (d, 4H, ArH, J = 6.6 Hz), 7.441-7.463 (d, 4H, ArH, J = 6.6 Hz), 7.508-7.558 (d, 1H, CH=$\underline{CH}$, J = 15 Hz), 8.342 (s, 1H, CH); MS (ESI m/z):446 $(M+H)^+$.

*4.1.27. (E)-Ethyl2-(4-(3-(4-(biphenyl-4-yl)thiazol-2-ylamino)propoxy)phenyl) ethenesulfonate (**5l**)*

Compound **5l** (38.00 mg, 60.50%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.366-1.413 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.05 Hz), 2.046-2.082 (m, 2H, $OCH_2\underline{CH_2}CH_2NH$), 4.162-4.214 (m, 6H, $O\underline{CH_2}CH_2\underline{CH_2}NH$, $O\underline{CH_2}CH_3$), 6.555-6.607 (d, 1H, $\underline{CH}$=CH, J = 15.6 Hz), 6.919-6.948 (d, 2H, ArH, J = 8.7 Hz), 6.992-7.020 (d, 2H, ArH, J = 8.4 Hz), 7.434-7.509 (m, 6H, 5ArH, CH=$\underline{CH}$), 7.678-7.706 (d, 2H, ArH, J = 8.4 Hz), 7.815- 7.842 (d, 2H, ArH, J = 8.1 Hz), 8.045 (s, 1H, CH); MS(ESI m/z):521 $(M+H)^+$.

*4.1.28. (E)-ethyl2-(4-(3-(4-(naphthalen-1-yl)thiazol-2-ylamino)propoxy)phenyl) ethanesulfonate (**5m**)*

Compound **5m** (60.00 mg, 94.30%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.368-1.415 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.05 Hz), 2.286-2.344 (m, 2H, $OCH_2\underline{CH_2}CH_2NH$), 3.579-3.621 (t, 2H, $OCH_2CH_2\underline{CH_2}NH$, J = 6.3 Hz), 4.108-4.221 (m, 4H, $O\underline{CH_2}CH_2CH_2$ NH, $O\underline{CH_2}CH_3$), 6.569-6.621 (d, 1H, $\underline{CH}$=CH, J = 15.6 Hz), 6.758 (m, 1H, ArH), 6.988 -7.017 (d, 2H, ArH, J = 8.7 Hz), 7.451-7.584 (m, 5H, 4ArH, CH=$\underline{CH}$), 7.907-8.018 (m, 2H, ArH), 8.032-8.098 (m, 2H, ArH), 8.235 (s, 1H, CH); MS(ESI m/z):494 $(M+H)^+$.

*4.1.29. (E)-Ethyl2-(4-(3-(5-methyl-4-phenylthiazol-2-ylamino)propoxy)phenyl) ethenesulfonate (**5n**)*

Compound **5n** (29.00 mg, 44.60%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.368-1.416 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.2 Hz), 2.242-2.297 (m, 2H, $OCH_2\underline{CH_2}CH_2NH$), 2.380 (s, 3H, CH_3), 4.079-4.243 (m, 6H, $O\underline{CH_2}CH_2\underline{CH_2}NH$, $O\underline{CH_2}CH_3$), 6.562-6.614 (d, 1H, $\underline{CH}$=CH, J = 15.6 Hz), 6.976-7.005 (d, 2H, ArH, J = 8.7 Hz), 7.368-7.562 (m, 8H, 7ArH, CH=$\underline{CH}$), 8.535 (s, 1H, CH); MS(ESI m/z):459 $(M+H)^+$.

*4.1.30. (E)-Ethyl2-(4-(3-(4,5-diphenylthiazol-2-ylamino)propoxy)phenyl) ethenesulfonate (**5o**)*

Compound **5o** (54.00 mg, 85.90%) as a yellow solid; m.p.:68-70 ^{0}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.372-1.419 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.05 Hz), 2.050-2.106 (m, 2H, $OCH_2\underline{CH_2}CH_2NH$), 4.070-4.222 (m, 6H, $O\underline{CH_2}CH_2\underline{CH_2}NH$, $O\underline{CH_2}CH_3$), 6.560-6.611 (d, 1H, $\underline{CH}$=CH, J = 15.3 Hz), 6.906-6.933 (d, 2H, ArH, J = 8.1 Hz), 7.237-7.261 (m,10H, ArH), 7.518-7.568 (d, 1H, CH=$\underline{CH}$, J = 15 Hz), 7.819-7.846 (d, 2H, ArH, J = 8.1 Hz), 8.315-8.342 (d, 2H, ArH, J = 8.1 Hz), 8.297 (s, 1H, CH); MS(ESI m/z):521 $(M+H)^+$.

4.2. Biological assays

4.2.1. PTP1B and TCPTP inhibition assays

The assay was developed according to our published procedure (Liu et al. 2012).

4.2.2. Cytotoxicity against COS-7 (African green monkey kidney fibroblast-like cell line)

The assay was developed according to our published procedure (Liu et al. 2012).

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References

Ali MI, Ketsawatsomkron P, Belin de Chantemele EJ, Mintz JD, Muta K, Salet C, Black SM, Tremblay ML, Fulton DJ, Marrero MB, Stepp DW (2009) Deletion of protein tyrosine phosphatase 1b improves peripheral insulin resistance and vascular function in obese, leptin-resistant mice via reduced oxidant tone. Circulation Res 105: 1013-1022.

Bhattacharya AK, Rana KC, Mujahid M, Sehar I, Saxena AK (2009) Synthesis and *in vitro* study of 14-aryl-14H-dibenzo[a.j]xanthenes as cytotoxic agents. Bioorgan Med Chem Lett 19: 5590–5593.

Bhattarai BR, Kafle B, Hwang JS, Ham SW, Lee KH, Park H, Han IO, Cho H (2010) Novel thiazolidinedione derivatives with anti-obesity effects: Dual action as PTP1B inhibitors and PPAR-gamma activators. Bioorgan Med Chem Lett 20: 6758–6763.

Erbe DV, Wang SY, Zhang YL, Harding K, Kung L, Tam M, Stolz L, Xing YZ, Furey S, Qadri A, Klaman LD, Tobin JF (2005) Ertiprotafib improves glycemic control and lowers lipids via multiple mechanisms. Mol Pharmacol. 67: 69–77.

He YT, Zeng LF, Yu ZH, He RJ, Liu SJ, Zhang ZY (2012) Bicyclic benzofuran and indole-based salicylic acids as protein tyrosine phosphatase inhibitors. Bioorgan Med Chem 20: 1940–1946.

Kumar R, Shinde RN, Ajay D, Sobhia ME (2010) Probing interaction requirements in PTP1B inhibitors: a comparative molecular dynamics study. J Chem Inf Model 50: 1147–1158.

Lessard L, Stuible M, Tremblay ML (2010) The two faces of PTP1B in cancer. Biochim Biophys Acta 1804: 613–619.

Liu J, Jiang F, Jin Y, Zhang Y, Liu J, Liu W, Fu L (2012) Design, synthesis, and evaluation of 2-substituted ethenesulfonic acid ester derivatives as protein tyrosine phosphatase 1B inhibitors. Eur J Med Chem 57: 10–20.

Ottana R, Maccari R, Amuso A, Wolber G, Schuster D, Herdlinger S, Manao G, Camici G, Paoli P (2012) New 4-[(5-arylidene-2-arylimino-4-oxo-3-thiazolidinyl)methyl]benzoic acids active as protein tyrosine phosphatase inhibitors endowed with insulinomimetic effect on mouse C2C12 skeletal muscle cells. Eur J Med Chem 50: 332–343.

Ottana R, Maccari R, Ciurleo R, Paoli P, Jacomelli M, Manao G, Camici G, Laggner C, Langer T (2009) 5-Arylidene-2-phenylimino-4-thiazolidinones as PTP1B and LMW-PTP inhibitors. Bioorgan Med Chem 17: 1928–1937.

Popov D (2011) Novel protein tyrosine phosphatase 1B inhibitors: interaction requirements for improved intracellular efficacy in type 2 diabetes mellitus and obesity control. Biochemical and biophysical research communications. 410: 377–381.

Ripka RC (2000) Protein tyrosine phosphatase inhibition. Annu Rep Med Chem 35: 231–250.

Takahashi N, Qi Y, Patel HR, Ahima RS (2004) A novel aminosterol reverses diabetes and fatty liver disease in obese mice. J Hepatol 41: 391–398.

Taylor SI, Accili D, Imai Y (1994) Insulin resistance or insulin deficiency. Which is the primary cause of NIDDM? Diabetes 43: 735–740.

Vetter SW, Keng YF, Lawrence DS, Zhang ZY (2000) Assessment of protein-tyrosine phosphatase 1B substrate specificity using "inverse alanine scanning". J Biol Chem 275: 2265–2268.

Wild S, Roglic G, Green A, Sicree R, King H (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 27: 1047–1053.

Ye D, Zhang Y, Wang F, Zheng M, Zhang X, Luo X, Shen X, Jiang H, Liu H (2010) Novel thiophene derivatives as PTP1B inhibitors with selectivity and cellular activity. Bioorg Med Chem 18: 1773–1782.