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Identification of 2-substituted ethenesulfonic acid ester derivatives as novel, potent and selective inhibitors of protein tyrosine phosphatase 1B

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Sixteen 2-substituted ethenesulfonic acid ester derivatives were designed, synthesized and evaluated for the inhibitory activity against tyrosine phosphatase 1B (PTP1B) and T-Cell protein tyrosine phosphatase (TCPTP). The structural activity relationship (SAR) of these compounds demonstrated that the hydrophilic head, aromatic center and the hydrophobic tail affected the inhibitory activities against PTP1B and the selectivity over TCPTP. Most of the compounds exhibited excellent inhibitory activity against PTP1B with IC_{50} value of 1.0 μM - 31.2 μM. SAR analysis revealed that the hydrophilic head was indispensable in the maintain of inhibitory activity against PTP1B, the aromatic center significantly altered the selectivity of PTP1B over TCPTP, and the hydrophobic tail significantly altered the inhibitory activity against PTP1B.

1. Introduction

Patients suffering from obesity-induced type 2 diabetes mellitus (T2DM) are at increasing risk of cardiovascular diseases and pose a huge economic burden on healthcare services (Wild et al. 2004; Eckel et al. 2005). PTP1B acts as a negative regulator in insulin signaling pathways (Taylor et al. 1994). Studies from two independent research groups indicated that down-regulation of the PTP1B gene in mice can improve insulin sensitivity with resistance to weight gain and reduce plasma glucose on high-fat diets (Zhang and Lee 2003). Further reducing PTP1B levels by using a specific antisense oligonucleotide (ISIS-113715, Phase 2, discontinued) in db/db and ob/ob mouse reinforced the potential of this target (Gum et al. 2003). The unique combination of desired attribution has driven an intense search for PTP1B inhibitors for the treatment of both type 2 diabetes and obesity (Ripka 2000; Erbe et al. 2005; Takahashi et al. 2004).

Previously, we have identified a series of 2-substituted ethenesulfonic acid ester derivatives as novel, safe, potent and selective PTP1B inhibitors (Liu et al. 2012). These compounds structurally comprise a hydrophilic head, an aromatic center, a five or six-atom linker and a hydrophobic tail. We went further to optimize each structure component of these compounds. SAR analysis demonstrates that the length of the linker, the substitution at the aromatic center and the hydrophobic tail have remarkable effects on the inhibitory activity against PTP1B and selectivity over TCPTP (Liu et al. 2015).

To get a deeper understanding of the impact brought by each structure component of the ligands on the activity and selectivity to PTP1B, we used a strategy of fusing the active structure fragments into the molecule template and optimizing the aromatic center and hydrophobic tail of the ligand. We also introduced indole to the aromatic center to expand the variety and validate its potential as a possible ingredient of the aromatic center. Herein, we report the design, synthesis, and evaluation of 2-substituted ethenesulfonic acid ester derivatives as a novel class of potent and selective PTP1B inhibitors.

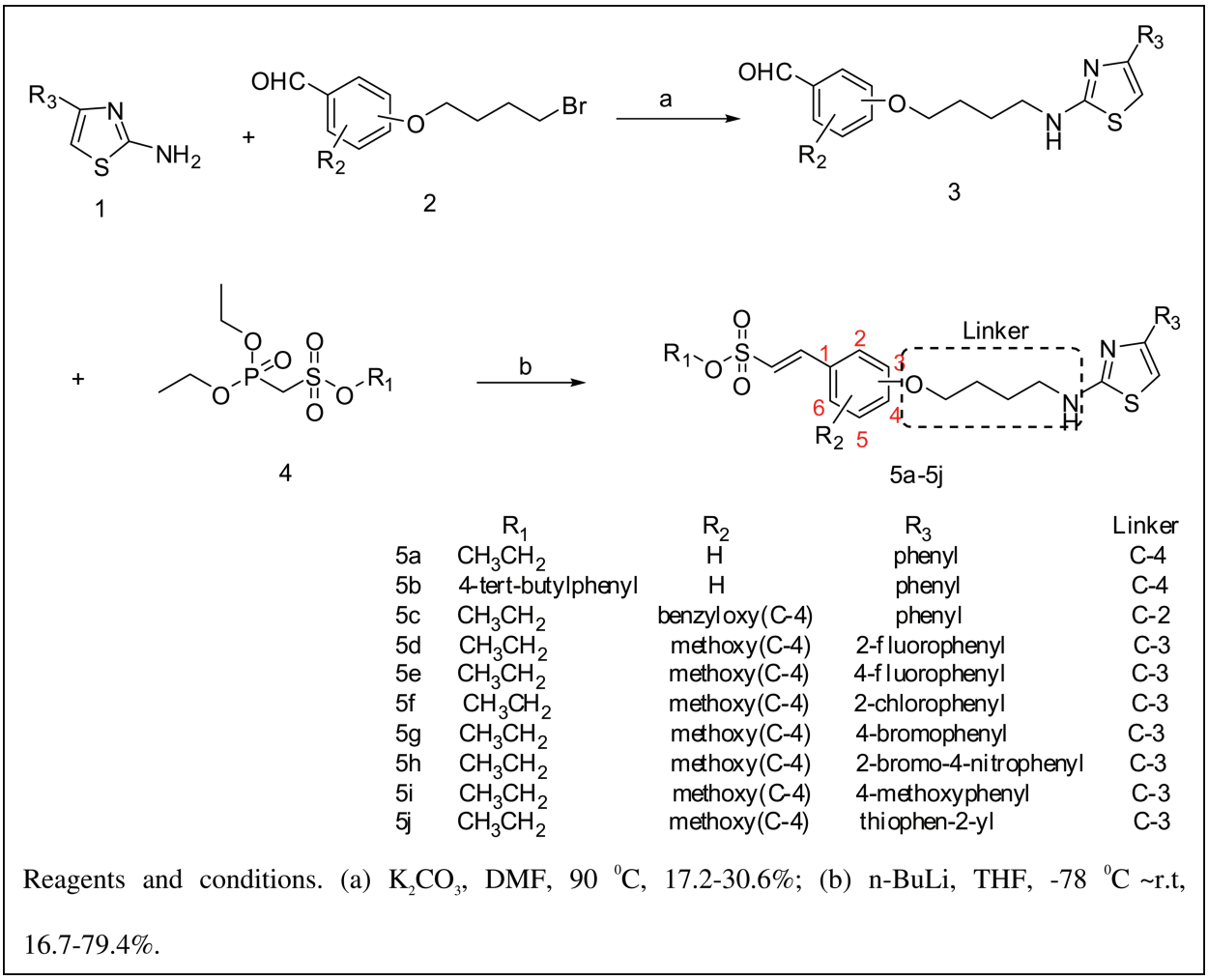
2. Investigations, results and discussion

2.1. Chemistry

The synthetic routes for the novel 2-substituted ethenesulfonic acid ester derivatives are outlined in Schemes 1 and 2. Most of the intermediates were prepared according to commonly used procedures (Tapia et al. 2003; Hargrave et al. 1983; Duan et al. 2007; Korthals and Wulff 2008). Scheme 1 describes the synthesis of the analogues **5a-5j** in two steps. Treatment of substituted thiazol-2-amine with substituted-(bromobutoxy) benzaldehyde in the presence of K_2CO_3 gave intermediate **3**, then coupling of compound **3** with (diethoxyphosphoryl) methane sulfonate by Wittig-Horner Reaction yielded **5a-5j**. Compounds **12a-12f** (Scheme 2) were synthesized according to the similar procedure depicted in Scheme 1. Reaction of 1*H*-indole-5-carbaldehyde with different length of dibromo alkanes afforded 1-(substituted)-1*H*-indole-5-carbaldehyde **8**. Then compound **8** was treated with substituted amine to yield intermediate **10**. Finally, compounds **12a**-**12f** were obtained by Wittig-Horner Reaction with intermediate **10** and ethyl (diethoxyphosphoryl) methanesulfonate. All synthesized compounds were characterized by the NMR and MS spectroscopies.

2.2. Inhibition of PTP1B

As shown in the Table, most of the compounds show improved inhibitory activity against PTP1B compared to **5a**, the lead compound. The replacement of the hydrophilic head by *tert-*



	R_1	R_2	R_3	Linker
5a	CH_3CH_2	H	phenyl	C-4
5b	4-tert-butylphenyl	H	phenyl	C-4
5c	CH_3CH_2	benzyloxy(C-4)	phenyl	C-2
5d	CH_3CH_2	methoxy(C-4)	2-fluorophenyl	C-3
5e	CH_3CH_2	methoxy(C-4)	4-fluorophenyl	C-3
5f	CH_3CH_2	methoxy(C-4)	2-chlorophenyl	C-3
5g	CH_3CH_2	methoxy(C-4)	4-bromophenyl	C-3
5h	CH_3CH_2	methoxy(C-4)	2-bromo-4-nitrophenyl	C-3
5i	CH_3CH_2	methoxy(C-4)	4-methoxyphenyl	C-3
5j	CH_3CH_2	methoxy(C-4)	thiophen-2-yl	C-3

Reagents and conditions. (a) K_2CO_3, DMF, 90 ^{0}C, 17.2-30.6%; (b) n-BuLi, THF, -78 ^{0}C ~r.t, 16.7-79.4%.

Scheme 1: Synthesis of compounds **5a-5j**.

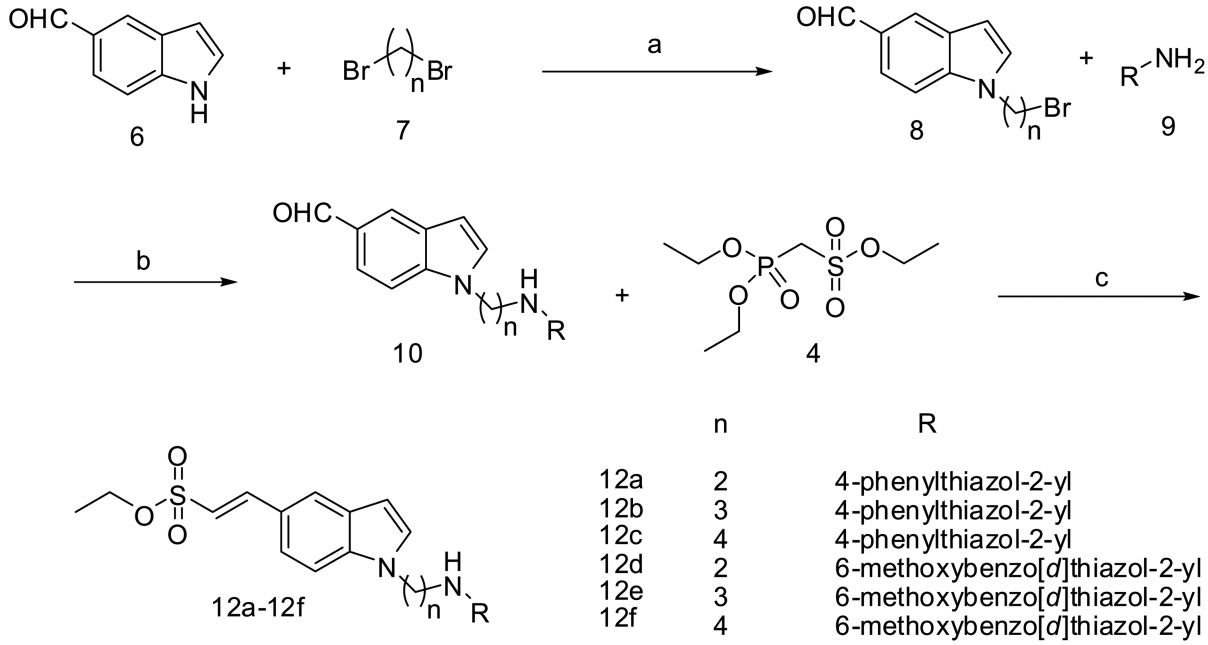
Table: In vitro inhibitory activity against two PTPs of 2-substituted ethenesulfonic acid ester derivatives

Compd.	PTP1B [a] IC_{50} (μM)	TCPTP [a] IC_{50} (μM)	Selectivity ratio[c]
5a	22.0	26.2	1.2
5b	> 100	> 100	-[d]
5c	1.1	5.2	4.7
5d	10.7	> 100	> 10
5e	2.6	5.8	2.2
5f	13.5	> 100	> 7.4
5g	1.0	14.8	14.8
5h	14.4	20.0	1.4
5i	3.6	2.5	-
5j	8.9	19.1	2.1
12a	7.2	12.4	1.7
12b	> 100	39.6	-
12c	31.2	15.1	-
12d	3.5	2.4	-
12e	16.2	8.3	-
12f	3.9	4.8	1.2
Sodium orthovanadate[b]	0.046	0.014	-

[a] IC_{50} values are means of three experiments.
[b] Positive control.
[c] Selectivity ratio means IC_{50} (TCPTP) /IC_{50}(PTP1B).
[d] No selectivity.

butylphenyl ester (**5b**) results in a total loss of PTP1B activity. It indicates that the alkane ester is a key factor maintaining the inhibitory activity against PTP1B compared to the aromatic ester. Further, we studied the influence of the substituent of the aromatic center for the inhibitory against PTP1B. The introduction of a benzyloxy or methoxy group to the phenyl center results in a boost of inhibitory activity against PTP1B (**5c – 5j**), e.g. IC_{50} value of **5d** is increased to 1.0 μM. Either the ether or the aromatic substituent on the aromatic center poses a positive impact on the inhibitory activity against PTP1B. It may suggest that the ligands bind to a pocket big enough for a side chain extension. Besides the modification of the aromatic center, different substituents on different positions of the hydrophobic tail also exert great impact on the ligand activity. The para- substitution is prior to the ortho- substitution (**5d** and **5e**, IC_{50} = 10.7 μM, 2.6 μM) which brings about 10-fold activity increase. A bromo-substitution (**5g**, IC_{50} = 1 μM) on the para-position is better than other electronic withdrawing groups (**5e**, **5 h**, IC_{50} = 2.6 μM, 14.4 μM) or an electronic donating group (**5i**, IC_{50} = 3.6 μM). Of all the candidates, **5 g** excels having the best activity which is 22 fold higher than the lead compound **5a**.

With the joyful progress brought by the substituted phenyl group, we started to validate different types of aromatic centers to seek for further improvement. Then indole was introduced (**12a-f**). This modification indeed brings up to 6-fold activity increase to the compound (**12d**, IC_{50} = 3.5 μM).



Reagents and conditions. (a) NaOH, Tetrabutyl ammonium bromide, CH_2Cl_2, reflux, 23-77.7%; (b) K_2CO_3, DMF, reflux,65.5-88.6%; (c) n-BuLi, THF, -78 ^{0}C ~r.t, 34.1-68.9%.

Scheme 2: Synthesis of compounds **12a**-**12f**.

2.3. Selectivity over TCPTP

The ligands were also tested for TCPTP inhibitory activity to explore the specificity of 2-substituted ethenesulfonic acid ester derivatives on PTPs. As shown in the Table, most compounds showed potent selectivity over TCPTP compared with **5a**. The substituted phenyl ring in the aromatic center plays a key role to determine the ligands' selectivity. Compounds **5c-5j** exhibited higher selectivity than compounds **12a – 12f**. Besides this critical factor, the substitution groups on the hydrophobic tail also attribute to the ligands selectivity. Compounds **5d** and **5 g** have more than 10 fold selectivity on PTP1B over TCPTP enzyme. Considering **5 g** is the most potent candidate, it's also the most selective ligand from the present study.

2.4. Molecular docking

Molecular docking of the most potent and selective compound (**5 g**) to PTP1B (PDB code: 2NT7) was performed on GOLD 5.1. As depicted in Fig. 2A, Compound **5 g** binds to the active site located on the surface of PTP1B with the aromatic center lies in a hydrophobic pocket comprised by Y46 and F182. The binding conformation is further stabilized by the sulfonyl group anchoring to R221 and C215 with two H-bonds, and the other H-bond formed between Q262 and the ligand. Overall, the binding conformation of **5 g** to PTP1B is in accordance with our previously model (Jingbao Liu 2015) and the reported crystal structure (Wan et al. 2007).

The docking of compound **12a**, which has an indole in the aromatic center, to PTP1B is also done to investigate the ligand-protein interactions (Fig. 2B). The binding conformation of **12a** is generally consistent with that of **5 g** with similar key interactions with PTP1B. However, owing to a more rigid conformation brought by the indole ring, **12a** occupies the PTP1B active site less than **5 g** does (Fig. 2C). This finding may give an explanation to the less potency of **12a** than **5 g**. The binding models also suggest that a longer linker is needed for the **12a** series to occupy the PTP1B active site and to achieve a higher potency.

2.5. Conclusion

In summary, we discovered a series of potent, novel 2-substituted ethenesulfonic acid ester derivatives with excellent inhibitory activity against PTP1B. Compound **5 g** is the most potent (PTP1B $IC_{50} = 1\ \mu M$) and selective one (TCPTP $IC_{50} = 14.8\ \mu M$). SAR analysis indicates that the substituent on the aromatic center or hydrophobic tail has a great help to the inhibitory activity against PTP1B and selectivity over TCPTP. Compounds with an indole also show good inhibitory activity against PTP1B, but with competitive inhibition over TCPTP. Further study shall focus on the substituted aromatic center and the hydrophobic tail to seek for more potent and more selective PTP1B inhibitors.

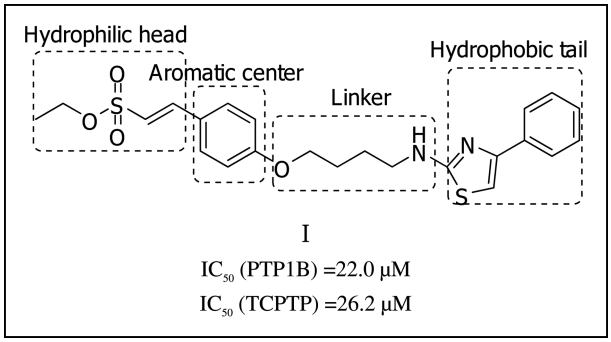


Fig. 1: Newly designed potent PTP1B inhibitor.

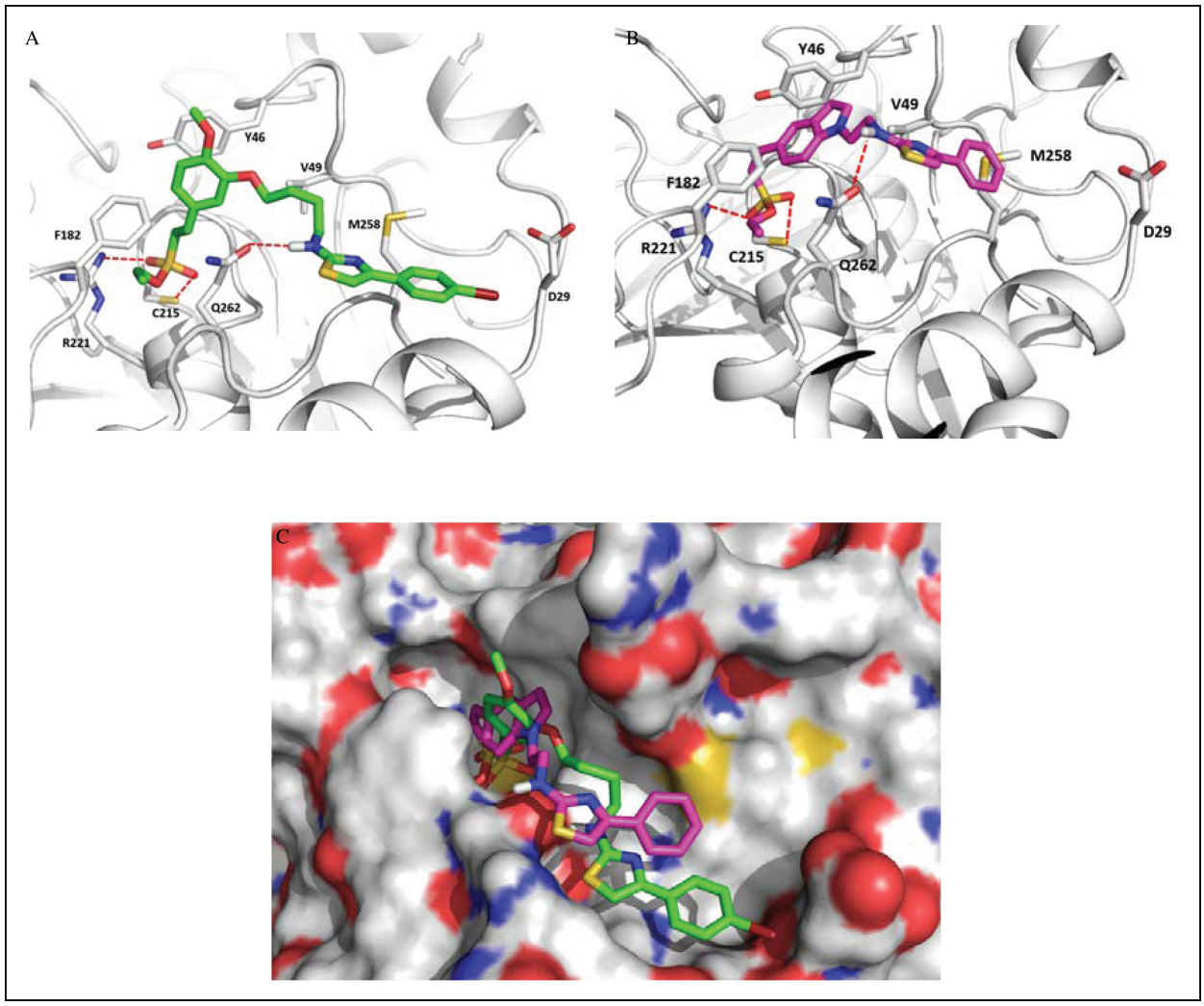


Fig. 2: Docking of **5 g** and **12a** to PTP1B. PTP1B is shown in white color, **5 g** is colored in green and **12a** is colored in violet. H-bonds are shown with red dot-lines. A) Compound **5 g** in the PTP1B active site; B) Compound **12a** in the PTP1B active site; C) Overlay of **5 g** and **12a** in the PTP1B active site.

3. Experimental

^{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).

3.1. Synthesis of compounds 3a – 3i

*3.1.1. 4-(4-(4-Phenylthiazol-2-ylamino)butoxy)benzaldehyde (**3a**)*

To a solution of 4-(4-bromobutoxy)benzaldehyde (400.00 mg, 1.56 mmol) and 4-phenylthiazol-2-amine (275.00 mg, 1.56 mmol) in DMF (15 mL), potassium carbonate (331.80 mg, 2.34 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 yellow oil. Yield 27.4%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.922-1.964 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2NH$), 4.092-4.132 (t, 2H, $OCH_2CH_2CH_2\underline{CH_2}NH$, J = 6 Hz), 4.229-4.276 (t, 2H, $O\underline{CH_2}CH_2CH_2CH_2NH$, J = 7.05 Hz), 6.958-6.986 (d, 2H, ArH, J = 8.4 Hz), 7.314-7.407 (m, 3H, ArH), 7.801-7.880 (m, 4H, ArH), 8.638 (s, 1H, CH), 9.873 (s, 1H, CHO); MS(ESI m/z):353 $(M+H)^+$.

*3.1.2. 4-(Benzyloxy)-2-(4-(4-phenylthiazol-2-ylamino)butoxy)benzaldehyde (**3b**)*

Compound **3b** (50.00 mg, 19.20%) as a yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.931-2.055 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2NH$), 4.129-4.168 (t, 2H, $OCH_2CH_2CH_2\underline{CH_2}NH$, J = 5.85 Hz), 4.259-4.299 (t, 2H, $O\underline{CH_2}CH_2CH_2CH_2NH$, J = 6 Hz), 5.140 (s, 2H, $O\underline{CH_2}$Phenyl), 6.956-6.983 (d, 2H, ArH, J = 8.1 Hz), 7.374- 7.457 (m, 5H, ArH), 7.915-7.944 (m, 1H, ArH), 8.024 (s, 1H, CH), 10.327 (s,1H, CHO); MS(ESI m/z):459 $(M+H)^+$.

*3.1.3. 3-(4-(4-(2-Fluorophenyl)thiazol-2-ylamino)butoxy)-4-methoxybenzaldehyde(**3c**)*

Compound **3c** (81.00 mg, 28.90%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.890-1.976 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2N$), 3.948 (s, 3H, OCH_3), 4.095-4.134 (m, 4H, $O\underline{CH_2}CH_2CH_2\underline{CH_2}N$), 6.964-6.990 (m, 1H, ArH), 7.085-7.211 (m, 2H, ArH), 7.400-7.473 (m, 2H, ArH), 8.074 (s, 1H, ArH), 8.248 (s, 1H, CH), 9.845 (s, 1H, CHO); MS(ESI m/z):401 $(M+H)^+$.

*3.1.4. 3-(4-(4-(4-Fluorophenyl)thiazol-2-ylamino)butoxy)-4-methoxybenzaldehyde (**3d**)*

Compound **3d** (48.00 mg, 17.20%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.874-1.979 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2N$), 3.945 (s, 3H, OCH_3), 4.089-4.130 (t, 2H, $OCH_2CH_2CH_2\underline{CH_2}N$, J = 6.15 Hz), 4.243-4.283 (t, 2H, $O\underline{CH_2}$ $CH_2CH_2CH_2N$, J = 6 Hz), 6.594 (s, 1H, ArH), 6.962-6.989 (d, 2H, ArH, J = 8.1 Hz), 7.049-7.086 (m, 1H, ArH), 7.441-7.471 (d, 2H, ArH, J = 9 Hz), 7.728- 7.781 (m, 1H, ArH), 8.072 (s, 1H, CH), 9.842 (s, 1H, CHO); MS(ESI m/z):401 $(M+H)^+$.

*3.1.5. 3-(4-(4-(2-Chlorophenyl)thiazol-2-ylamino)butoxy)-4-methoxybenzaldehyde (**3e**)*

Compound **3e** (89.00 mg, 30.60%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.877-1.985 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2N$), 3.964 (s, 3H, OCH_3), 4.095-4.133 (m, 4H, $O\underline{CH_2}CH_2CH_2\underline{CH_2}N$), 6.970-6.997 (m, 1H, ArH), 7.294-7.318 (m, 2H, ArH), 7.397- 7.474 (m, 3H, ArH), 7.935-7.967 (dd, 1H, ArH, J = 1.8 Hz, J = 1.8 Hz), 8.274 (s, 1H, CH), 9.847 (s, 1H, CHO); MS(ESI m/z):417 $(M+H)^+$.

*3.1.6. 3-(4-(4-(2-Bromophenyl)thiazol-2-ylamino)butoxy)-4-methoxybenzaldehyde (**3f**)*

Compound **3f** (85.00 mg, 26.40%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.910-2.086 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2N$), 3.947 (s, 3H, OCH_3), 4.092-4.184 (m, 4H, $O\underline{CH_2}CH_2CH_2\underline{CH_2}N$), 6.965-6.992 (d, 2H, ArH, J = 8.1 Hz), 7.395-7.471 (m, 2H, ArH), 7.573-7.598 (d, 1H, ArH, J = 7.5 Hz), 7.794-7.821 (d, 2H, ArH, J = 8.1 Hz), 8.072 (s, 1H, CH), 9.842 (s, 1H, CHO); MS(ESI m/z):461 $(M + H)^+$.

*3.1.7. 3-(4-(4-(2-Bromo-4-nitrophenyl)thiazol-2-ylamino)butoxy)-4-methoxybenzaldehyde (**3 g**)*

Compound **3 g** (61.00 mg, 17.30%) as a yellow solid; m.p.:168-170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.071-2.113 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2N$), 3.933 (s, 3H, OCH_3), 4.119-4.203 (m, 4H, $O\underline{CH_2}CH_2CH_2\underline{CH_2}N$), 6.953-6.988 (m, 1H, ArH), 7.208 (s, 1H, ArH), 7.396-7.464 (m, 2H, ArH), 8.022-8.051 (d, 2H, ArH, J = 8.7 Hz), 8.227 (s, 1H, CH), 9.847 (s, 1H, CHO); MS(ESI m/z):506 $(M + H)^+$.

*3.1.8. 4-Methoxy-3-(4-(4-(4-methoxyphenyl)thiazol-2-ylamino)butoxy)benzal-dehyde (**3 h**)*

Compound **3 h** (85.00 mg, 29.50%) as a yellow oil; ^{1}H NMR(300 MHz, $CDCl_3$) δ 1.944-2.037 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2N$), 3.834 (s, 6H, $2OCH_3$), 4.062-4.104 (m, 4H, $O\underline{CH_2}CH_2CH_2\underline{CH_2}N$), 6.553 (s, 1H, ArH), 6.883-6.974 (m, 3H, ArH), 7.421- 7.448 (d, 2H, ArH, J = 8.1 Hz), 7.666-7.715 (m, 1H, ArH), 8.248 (s, 1H, CH), 9.830 (s, 1H, CHO); MS(ESI m/z):413 $(M + H)^+$.

*3.1.9. 4-Methoxy-3-(4-(4-(thiophen-2-yl)thiazol-2-ylamino)butoxy) benzaldehyde (**3i**)*

Compound **3i** (65.00 mg, 23.90%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.892-1.995 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2N$), 3.982 (s, 3H, OCH_3), 4.095-4.186 (m, 4H, $O\underline{CH_2}CH_2CH_2\underline{CH_2}N$), 6.853 (s, 1H, ArH), 6.977-7.037 (m, 2H, 2CH), 7.205-7.222 (d, 1H, ArH, J = 5.1 Hz), 7.393-7.474 (m, 2H, ArH), 8.259 (s, 1H, CH), 9.846 (s, 1H, CHO); MS(ESI m/z):389 $(M + H)^+$.

3.2. Synthesis of compounds 5a – 5j

*3.2.1. 3.2.1. (E)-Ethyl2-(4-(4-(4-phenylthiazol-2-ylamino)butoxy)phenyl)ethenesulfonate (**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 hexane) dropwise under N_2 atmosphere. The mixture was stirred for 15 min, and then 4-(4-(4-phenylthiazol-2-ylamino)butoxy) benzaldehyde (67.00 mg, 0.19 mmol) was added dropwise. The reaction mixture was stirred at r.t. 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 yellow oil. Yield 79.40%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.357-1.405 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.2 Hz), 1.897-1.944 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2NH$), 4.041-4.081 (t, 2H, $OCH_2CH_2CH_2\underline{CH_2}NH$, J = 6 Hz), 4.162-4.233 (q, 2H, $O\underline{CH_2}CH_3$, J = 7.2 Hz, 7.2 Hz), 4.333-4.397 (t, 2H, $O\underline{CH_2}CH_2CH_2CH_2NH$, J = 7.05 Hz), 6.548-6.600 (d, 1H, CH = CH, J = 15.6 Hz), 6.879-6.908 (d, 2H, ArH, J = 8.7 Hz), 7.359-7.439 (m, 5H, ArH), 7.502-7.554 (d, 1H, CH = CH, J = 15.6 Hz), 7.836-7.879 (m, 2H, ArH), 8.629 (s, 1H, CH); MS(ESI m/z):459 $(M + H)^+$.

*3.2.2. (E)-4-tert-Butylphenyl-2-(4-(4-(4-phenylthiazol-2-ylamino)butoxy)phenyl)ethenesulfonate (**5b**)*

Compound **5b** (16.00 mg, 16.70%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.248 (s, 9H, $3CH_3$), 1.927-2.012 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2N$), 4.081-4.130 (m, 4H, $O\underline{CH_2}CH_2CH_2\underline{CH_2}N$), 6.906-6.991 (m, 5H, 4ArH, CH = CH), 7.340-7.458 (m, 5H, ArH), 7.779-7.857 (m, 5H, 4ArH, CH = CH), 8.016 (s, 1H, CH); MS(ESI m/z):561 $(M-H)^-$.

*3.2.3. (E)-Ethyl 2-(4-(benzyloxy)-2-(4-(4-phenylthiazol-2-ylamino)butoxy)phenyl)ethenesulfonate (**5c**)*

Compound **5c** (23.00 mg, 46.60%) 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), 1.941-2.042 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2N$), 3.851-3.890 (t, 2H, $OCH_2CH_2CH_2\underline{CH_2}N$, J = 5.85 Hz), 4.103-4.140 (t, 2H, $O\underline{CH_2}CH_2\ CH_2CH_2N$, J = 5.55 Hz), 4.174-4.245 (q, 2H, $O\underline{CH_2}CH_3$, J = 7.2 Hz, J = 6.9 Hz), 5.109 (s, 2H, OCH_2Phenyl), 6.558-6.610 (d, 1H, CH = CH, J = 15.6 Hz), 6.950-6.985 (m, 2H, ArH), 7.378-7.426 (m, 9H, ArH), 7.492-7.543 (m, 1H, CH = CH, J = 15.3 Hz), 7.885- 7.909 (m, 2H, ArH), 8.861 (s, 1H, CH); MS(ESI m/z):566$(M + H)^+$.

*3.2.4. (E)-Ethyl-2-(3-(4-(4-(2-fluorophenyl)thiazol-2-ylamino)butoxy)-4-methoxyphenyl)ethenesulfonate (**5d**)*

Compound **5d** (27.00 mg, 42.70%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.370-1.409 (t, 3H, $OCH_2\underline{CH_3}$, J = 5.85 Hz), 2.020-2.083 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}\ CH_2NH$), 3.902 (s, 3H, OCH_3), 4.102-4.236 (m, 6H, $O\underline{CH_2}CH_2CH_2\underline{CH_2}NH$, $O\underline{CH_2}CH_3$), 6.547-6.602 (d, 1H, CH = CH, J = 16.5 Hz), 6.866-6.939 (m, 1H, ArH), 7.095-7.105 (m, 2H, ArH), 7.133-7.227 (m, 2H, ArH), 7.482-7.535 (d, 1H, CH = CH, J = 15.9 Hz), 8.197-8.247 (m, 2H, ArH), 8.398 (s, 1H, CH); MS(ESI m/z):507 $(M + H)^+$.

*3.2.5. (E)-Ethyl-2-(3-(4-(4-(4-fluorophenyl)thiazol-2-ylamino)butoxy)-4-methoxyphenyl)ethenesulfonate (**5e**)*

Compound **5e** (10.00 mg, 19.70%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.373-1.420 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.05 Hz), 2.026-2.093 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}\ CH_2NH$), 3.905 (s, 3H, OCH_3), 4.103-4.238 (m, 6H, $O\underline{CH_2}CH_2CH_2\ \underline{CH_2}NH$, $O\underline{CH_2}CH_3$), 6.557 (s, 1H, ArH), 6.605-6.656 (d, 1H, CH = CH, J = 15.3 Hz), 6.876-6.901 (d, 2H, ArH, J = 7.5 Hz), 7.030-7.148 (m, 2H, ArH), 7.485-7.537 (d, 1H, CH = CH, J = 15.6 Hz), 7.712-7.736 (d, 2H, ArH, J = 7.2 Hz), 8.604 (s, 1H, CH); MS(ESI m/z):507 $(M + H)^+$.

*3.2.6. (E)-Ethyl-2-(3-(4-(4-(2-chlorophenyl)thiazol-2-ylamino)butoxy)-4-methoxyphenyl)ethenesulfonate (**5f**)*

Compound **5f** (43.00 mg, 68.60%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.363-1.410 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.05 Hz), 1.847-1.972 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}\ CH_2NH$), 3.916 (s, 3H, OCH_3), 4.060-4.218 (m, 6H, $O\underline{CH_2}CH_2CH_2\underline{CH_2}NH$, $O\underline{CH_2}CH_3$), 6.556-6.609 (d, 1H, CH = CH, J = 15.9 Hz), 6.867-6.901 (m, 1H, ArH), 7.003 (s, 1H, ArH), 7.264-7.301 (m, 2H, ArH), 7.403-7.432 (m, 2H, ArH), 7.489-7.540 (d, 1H, CH = CH, J = 15.3 Hz), 7.937-7.963 (d, 1H, ArH, J = 7.8 Hz), 8.262 (s, 1H, CH); MS(ESI m/z):523 $(M + H)^+$.

*3.2.7. (E)-Ethyl-2-(3-(4-(4-(4-bromophenyl)thiazol-2-ylamino)butoxy)-4-methoxyphenyl)ethenesulfonate (**5 g**)*

Compound **5 g** (32.00 mg, 52.00%) as a yellow solid; m.p.: 122-124 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.369-1.416 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.05 Hz), 2.006-2.090 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2NH$), 3.889 (s, 3H, OCH_3), 4.089-4.242 (m, 6H, $O\underline{CH_2}CH_2CH_2\ \underline{CH_2}NH$, $O\underline{CH_2}CH_3$), 6.564-6.615 (d, 1H, CH = CH, J = 15.3 Hz), 6.873-6.900 (d, 2H, ArH, J = 8.1 Hz), 6.943 (s, 1H, ArH), 7.486-7.537 (d, 1H, CH = CH, J = 15.3 Hz), 7.544-7.601 (m, 2H, ArH), 7.799-7.828 (d, 2H, ArH, J = 8.7 Hz), 8.023 (s, 1H, CH); MS(ESI m/z):567 $(M + H)^+$.

*3.2.8. (E)-Ethyl-2-(3-(4-(4-(2-bromo-4-nitrophenyl)thiazol-2-ylamino)butoxy)-4-methoxyphenyl)ethenesulfonate (**5 h**)*

Compound **5 h** (41.00 mg, 67.80%) as a yellow solid; m.p.: 188-190 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.373-1.420 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.05 Hz), 1.902-2.041 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2NH$), 3.892 (s, 3H, OCH_3), 4.137-4.224 (m, 6H, $O\underline{CH_2}CH_2\ \underline{CH_2}\underline{CH_2}NH$, $O\underline{CH_2}CH_3$), 6.545-6.598 (d, 1H, CH = CH, J = 15.9 Hz), 6.877-6.905 (d, 1H, ArH, J = 8.4 Hz), 6.963-7.020 (m, 2H, ArH), 7.087-7.116 (d, 1H, ArH, J = 7.2 Hz), 7.491-7.543 (d, 1H, CH = CH, J = 15.6 Hz), 7.926-7.955 (m, 2H, ArH), 8.293 (s, 1H, CH); MS(ESI m/z):639 $(M + 23)^+$.

*3.2.9. (E)-Ethyl-2-(4-methoxy-3-(4-(4-(4-methoxyphenyl)thiazol-2-ylamino)butoxy)phenyl)ethenesulfonate (**5i**)*

Compound **5i** (44.00 mg, 70.00%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.364-1.410 (t, 3H, $OCH_2\underline{CH_3}$, J = 6.9 Hz), 1.802-1.991 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2NH$), 3.894 (s, 3H, OCH_3), 4.055-4.241 (m, 6H, $O\underline{CH_2}CH_2CH_2\underline{CH_2}NH$, $O\underline{CH_2}CH_3$), 6.560- 6.612 (d, 1H, CH = CH, J = 15.6 Hz), 6.864-6.891 (d, 2H, ArH, J = 8.1 Hz), 6.954-7.007 (m, 2H, ArH), 7.078-7.104 (d, 2H, ArH, J = 7.8 Hz), 7.399 (s, 1H, ArH), 7.481-7.533 (d, 1H, CH = CH, J = 15.6 Hz), 8.021 (s, 1H, CH); MS(ESI m/z):519 $(M + H)^+$.

*3.2.10. (E)-Ethyl-2-(4-methoxy-3-(4-(4-(thiophen-2-yl)thiazol-2-ylamino)butoxy)phenyl)ethenesulfonate (**5j**)*

Compound **5j** (31.00 mg, 48.70%) as a yellow solid; m.p.: 116-118 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.374-1.416 (t, 3H, $OCH_2\underline{CH_3}$, J = 6.3 Hz), 1.949-2.096 (m, 4H, $OCH_2\underline{CH_2}\underline{CH_2}CH_2NH$), 3.890 (s, 3H, OCH_3), 4.065-4.245 (m, 6H, $O\underline{CH_2}CH_2\ CH_2\ \underline{CH_2}NH$, $O\underline{CH_2}CH_3$), 6.549-6.601 (d, 1H,

CH = CH, J = 15.6 Hz), 6.815 (s, 1H, ArH), 6.877-6.904 (m, 1H, CH), 7.024-7.040 (m, 1H, CH), 7.090-7.117 (m, 2H, ArH), 7.489-7.539 (d, 1H, CH = CH, J = 15 Hz), 7.637-7.671 (m, 1H, CH), 8.105 (s, 1H, CH); MS(ESI m/z):494 $(M + H)^+$.

3.3. Synthesis of compounds 8a– 8c

*3.3.1. 1-(2-Bromoethyl)-1H-indole-5-carbaldehyde (**8a**)*

A mixture of 1*H*-indole-5-carbaldehyde (50.00 mg, 0.34 mmol), 1,2-dibromoethane (0.50 mL), NaOH (54.40 mg, 1.36 mmol) and tetrabutyl ammonium bromide (21.60 mg, 0.07 mmol) in CH_2Cl_2 (15 mL) was heated to reflux for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, and extracted with CH_2Cl_2 (20 mL*3). The combined organic layer was washed with brine, dried with anhydrous sodium sulphate, concentrated under vacuum, then purified by flash chromatography (dichloromethane:ethyl acetate = 30:1) to afford a yellow oil. Yield 23.00%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.648-3.708 (t, 2H, NCH_2CH_2Br, J = 4.5 Hz), 4.541-4.606 (t, 2H, NCH_2CH_2Br, J = 4.87 Hz), 6.700-6.710 (d, 1H, CHCH, J = 3 Hz), 7.259-7.269 (d, 1H, CHCH, J = 3 Hz), 7.804-7.876 (m, 2H, ArH), 8.111 (s, 1H, ArH), 10.043 (s, 1H, CHO); MS(ESI m/z):253 $(M + H)^+$.

*3.3.2. 1-(3-Bromopropyl)-1H-indole-5-carbaldehyde (**8b**)*

Compound **8b** (0.23 g, 62.70%) as a yellow oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.235-2.324 (m, 2H, $NCH_2CH_2CH_2Br$), 3.385-3.429 (t, 2H, $NCH_2CH_2CH_2Br$, J = 6.6 Hz), 4.317-4.362 (t, 2H, $NCH_2CH_2CH_2Br$, J = 6.75 Hz), 6.676-6.686 (d, 1H, CHCH, J = 3 Hz), 7.530-7.541 (d, 1H, CHCH, J = 3.3 Hz), 7.660 (s, 2H, ArH), 8.165 (s, 1H, ArH), 9.955 (s, 1H, CHO); MS(ESI m/z):267 $(M + H)^+$.

*3.3.3. 1-(4-Bromobutyl)-1H-indole-5-carbaldehyde (**8c**)*

Compound **8c** (0.30 g, 77.70%) as a yellow oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.694-1.765 (m, 2H, $NCH_2CH_2CH_2CH_2Br$), 1.814-1.886 (m, 2H, $NCH_2CH_2CH_2$ CH_2Br), 3.485-3.529 (t, 2H, $NCH_2CH_2CH_2CH_2Br$, J = 6.6 Hz), 4.240-4.285 (t, 2H, $NCH_2CH_2CH_2CH_2Br$, J = 6.75 Hz), 6.659-6.669 (d, 1H, CHCH, J = 3 Hz), 7.536-7.546 (d, 1H, CHCH, J = 3 Hz), 7.658 (s, 2H, ArH), 8.160 (s, 1H, ArH), 9.954 (s, 1H, CHO); MS(ESI m/z):281 $(M + H)^+$.

3.4. Synthesis of Compound 10a – 10f

*3.4.1. 1-(2-(4-Phenylthiazol-2-ylamino)ethyl)-1H-indole-5-carbaldehyde (**10a**)*

To the solution of 1-(2-bromoethyl)-1*H*-indole-5-carbaldehyde (120.00 mg, 0.48 mmol) and 4-phenylthiazol-2-amine (91.60 mg, 0.52 mmol) in DMF (15 mL), was added potassium carbonate (99.50 mg, 0.72 mmol). 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 red oil. Yield 24.8%; ^{1}H NMR(300 MHz, $CDCl_3$) δ 3.962-3.997 (t, 2H, NCH_2CH_2N, J = 5.25 Hz), 4.287- 4.322 (t, 2H, NCH_2CH_2N, J = 5.25 Hz), 6.633-6.704 (m, 2H, ArH), 7.143-7.154 (d, 1H, CHCH, J = 3.3 Hz), 7.222-7.233 (d, 1H, CHCH, J = 3.3 Hz), 7.308 (s, 1H, CH), 7.347-7.447 (m, 4H, ArH), 7.747-7.824 (m, 2H, ArH), 9.996 (s, 1H, CHO); MS(ESI m/z):348 $(M + H)^+$.

*3.4.2. 1-(3-(4-Phenylthiazol-2-ylamino)propyl)-1H-indole-5-carbaldehyde (**10b**)*

Compound **10b** (67.00 mg, 24.70%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.049-2.091 (m, 2H, $NCH_2CH_2CH_2N$), 3.592-3.630 (t, 2H, $NCH_2CH_2CH_2N$, J = 5.7 Hz), 4.120-4.160 (t, 2H, $NCH_2CH_2CH_2N$, J = 6 Hz), 6.655-6.711 (m, 2H, ArH), 7.146 (s, 1H, CH), 7.184-7.194 (d, 1H, CHCH, J = 3 Hz), 7.223-7.233 (d, 1H, CHCH, J = 3 Hz), 7.351-7.428 (m, 4H, ArH), 7.755-7.778 (m, 2H, ArH), 10.015 (s, 1H, CHO); MS(ESI m/z):362 $(M + H)^+$.

*3.4.3. 1-(4-(4-Phenylthiazol-2-ylamino)butyl)-1H-indole-5-carbaldehyde (**10c**)*

Compound **10c** (62.00 mg, 15.40%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.893-1.959 (m, 4H, $NCH_2CH_2CH_2CH_2N$), 3.626-3.668 (t, 2H, $NCH_2CH_2CH_2CH_2N$, J = 6.3 Hz), 4.164-4.199 (t, 2H, $NCH_2CH_2CH_2CH_2N$, J = 5.25 Hz), 6.656-6.667 (m, 2H, ArH), 6.975 (s, 1H, CH), 7.184-7.194 (d, 1H, CHCH, J = 3 Hz), 7.223-7.233 (d, 1H, CHCH, J = 3 Hz), 7.374-7.420 (m, 4H, ArH), 7.749-7.865 (m, 2H, ArH), 10.016 (s, 1H, CHO); MS(ESI m/z):376 $(M + H)^+$.

*3.4.4. 1-(2-(6-Methoxybenzo[d]thiazol-2-ylamino)ethyl)-1H-indole-5-carbaldehyde (**10d**)*

Compound **10d** (17.00 mg, 66.20%) as a yellow oil; ^{1}H NMR(300 MHz, $CDCl_3$) δ 3.893 (s, 3H, OCH_3), 3.925-3.954 (t, 2H, $NHCH_2CH_2N$, J = 4.35 Hz), 4.574-4.611 (t, 2H, $NHCH_2CH_2N$, J = 5.55 Hz), 6.705-6.715 (d, 1H, CHCH, J = 3 Hz), 6.965-7.003 (dd, 1H, ArH, J = 2.4 Hz, J = 2.4 Hz), 7.183 (s, 1H, ArH), 7.229-7.239 (d, 1H, CHCH, J = 3 Hz), 7.462-7.559 (m, 2H, ArH), 7.787-7.815 (d, 2H, ArH, J = 8.4 Hz), 8.184 (s, 1H, ArH), 10.060 (s, 1H, CHO); MS(ESI m/z):458 $(M + H)^+$.

*3.4.5. 1-(3-(6-Methoxybenzo[d]thiazol-2-ylamino)propyl)-1H-indole-5-carbaldehyde (**10e**)*

Compound **10e** (22.00 mg, 65.50%) as a yellow oil; ^{1}H NMR(300 MHz, $CDCl_3$) δ 1.941-1.992 (m, 2H, $NCH_2CH_2CH_2Br$), 3.400-3.445 (t, 2H, $NCH_2CH_2CH_2Br$, J = 6.75 Hz), 3.819 (s, 3H, OCH_3), 4.208-4.253 (t, 2H, $NCH_2CH_2CH_2Br$, J = 6.75 Hz), 6.650-6.659 (d, 1H, CHCH, J = 2.7 Hz), 6.892-6.929 (dd, 1H, ArH, J = 2.4 Hz, J = 2.4 Hz), 7.100-7.108 (d, 1H, ArH, J = 2.4 Hz), 7.192-7.201 (d, 1H, CHCH, J = 2.4 Hz), 7.395- 7.442 (m, 2H, ArH), 7.751-7.779 (m, 1H, ArH), 8.143 (s, 1H, ArH), 10.015 (s, 1H, CHO); MS(ESI m/z):472 $(M + H)^+$.

*3.4.6. 1-(4-(6-Methoxybenzo[d]thiazol-2-ylamino)butyl)-1H-indole-5-carbaldehyde (**10f**)*

Compound **10f** (34.00 mg, 88.60%) as a yellow oil; ^{1}H NMR(300 MHz, $CDCl_3$) δ 1.877-1.948 (m, 2H, $NCH_2CH_2CH_2CH_2Br$), 2.302-2.259 (m, 2H, NCH_2CH_2 CH_2CH_2Br), 3.388-3.432 (t, 2H, $NCH_2CH_2CH_2CH_2Br$, J = 6.6 Hz), 3.820 (s, 3H, OCH_3), 4.320-4.363 (t, 2H, $NCH_2CH_2CH_2CH_2Br$, J = 6.45 Hz), 6.678 (s, 1H, ArH), 6.903-6.933 (d, 1H, CHCH, J = 9 Hz), 7.099-7.107 (d, 1H, CHCH, J = 2.4 Hz), 7.415- 7.456 (m, 2H, ArH), 7.738-7.767 (m, 1H, ArH), 8.156 (s, 1H, ArH), 10.013 (s, 1H, CHO); MS(ESI m/z):486 $(M + H)^+$.

3.5. Synthesis of compounds 12a-f

*3.5.1. (E)-Ethyl-2-(1-(2-(4-phenylthiazol-2-ylamino)ethyl)-1H-indol-5-yl)ethenesulfonate (**12a**)*

The ethyl (diethoxyphosphoryl)methanesulfonate (40.00 mg, 0.12 mmol) was dissolved in THF (15 mL), and the solution was cooled to -78 °C, then added n-BuLi (78.40 uL, 0.17 mmol, 2.2 M in hexanes) dropwise under N_2 atmosphere. The mixture was stirred for 15 min, and then 1-(2-(4-phenylthiazol-2-ylamino) ethyl)-1*H*-indole-5-carbaldehyde (31.20 mg, 0.12 mmol) was added dropwise. The reaction mixture was stirred at r.t. 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 yellow oil. Yield 68.90%; ^{1}H NMR(300 MHz, $CDCl_3$) δ 1.375-1.417 (t, 3H, OCH_2CH_3, J = 6.3 Hz), 3.988-4.035 (t, 2H, NCH_2CH_2NH, J = 7.05 Hz), 4.162-4.233 (q, 2H, OCH_2CH_3, J = 7.2 Hz, 7.2 Hz), 4.275-4.325 (t, 2H, NCH_2CH_2NH, J = 7.5 Hz), 6.514-6.691 (m, 3H, CH = CH, 2ArH), 7.143-7.154 (d, 1H, CHCH, J = 3.3 Hz), 7.222-7.233 (d, 1H, CHCH, J = 3.3 Hz), 7.397-7.401 (m, 4H, ArH), 7.695-7.747 (d, 1H, CH = CH, J = 15.6 Hz), 7.755-7.781 (m, 2H, ArH), 8.153 (s, 1H, CH); MS(ESI m/z):454 $(M + H)^+$.

*3.5.2. (E)-Ethyl-2-(1-(3-(4-phenylthiazol-2-ylamino)propyl)-1H-indol-5-yl)ethenesulfonate (**12b**)*

Compound **12b** (30.00 mg, 46.40%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.368-1.415 (t, 3H, OCH_2CH_3, J = 7.05 Hz), 2.047-2.100 (m, 2H, $NCH_2CH_2CH_2N$), 3.619-3.669 (t, 2H, $NCH_2CH_2CH_2NH$, J = 7.5 Hz), 4.180-4.251 (q, 2H, OCH_2CH_3, J = 7.2 Hz, 6.9 Hz), 4.289-4.338 (t, 2H, $NCH_2CH_2CH_2NH$, J = 7.35 Hz), 6.552 (s, 1H, ArH), 6.632-6.683 (m, 2H, CH = CH, 1ArH), 7.181-7.191 (d, 1H, CHCH, J = 3 Hz), 7.227-7.238 (d, 1H, CHCH, J = 3.3 Hz), 7.359-7.432 (m, 4H, ArH), 7.696-7.747 (d, 1H, CH = CH, J = 15.3 Hz), 7.774-7.789 (m, 2H, ArH), 8.150 (s, 1H, CH); MS (ESI m/z):468 $(M + H)^+$.

*3.5.3. (E)-Ethyl-2-(1-(4-(4-phenylthiazol-2-ylamino)butyl)-1H-indol-5-yl)ethenesulfonate (**12c**)*

Compound **12c** (27.00 mg, 42.10%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.371-1.418 (t, 3H, OCH_2CH_3, J = 7.05 Hz), 1.951-1.969 (m, 4H, $NCH_2CH_2CH_2CH_2N$), 3.659-3.709 (t, 2H, $NCH_2CH_2CH_2CH_2NH$, J = 7.5 Hz), 4.167-4.230 (m, 4H, OCH_2CH_3, $NCH_2CH_2CH_2CH_2NH$), 6.550 (s, 1H, ArH), 6.635-6.687 (m, 2H, CH = CH, 1ArH), 7.158-7.163 (d, 1H, CHCH, J = 1.5 Hz), 7.204-7.209 (d, 1H, CHCH, J = 1.5 Hz), 7.372-7.441

(m, 4H, ArH), 7.698-7.751 (d, 1H, CH = CH, J = 15.9 Hz), 7.751-7.777 (m, 2H, ArH), 8.150 (s, 1H, CH); MS(ESI m/z):482 $(M + H)^+$.

*3.5.4. (E)-Ethyl-2-(1-(2-(6-methoxybenzo[d]thiazol-2-ylamino)ethyl)-1H-indol-5-yl)ethenesulfonate (***12d***)*

Compound **12d** (17.00 mg, 11.40%) as a yellow oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.231-1.282 (t, 3H, OCH_2CH_3, J = 7.65 Hz), 3.519-3.563 (t, 2H, $NHCH_2$ CH_2N, J = 6.6 Hz), 3.705 (s, 3H, OCH_3), 4.967-4.038 (q, 2H, OCH_2CH_3, J = 6.9 Hz, J = 7.2 Hz), 4.379-4.416 (t, 2H, $NHCH_2CH_2N$, J = 5.55 Hz), 6.433-6.495 (dd, 1H, ArH, J = 3 Hz, J = 3 Hz), 6.751-6.759 (d, 1H, CHCH, J = 2.4 Hz), 7.194-7.248 (d, 1H, CH = CH, J = 16.2 Hz), 7.292 (s, 1H, ArH), 7.424-7.414 (d, 1H, CHCH, J = 3 Hz), 7.486-7.547 (m, 3H, ArH), 7.582 (s, 1H, ArH), 7.893-7.940 (d, 1H, CH = CH, J = 14.1 Hz); MS(ESI m/z):458 $(M + H)^+$.

*3.5.5. (E)-Ethyl-2-(1-(3-(6-methoxybenzo[d]thiazol-2-ylamino)propyl)-1H-indol-5-yl)ethenesulfonate (***12e***)*

Compound **12e** (22.00 mg, 34.10%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.371-1.418 (t, 3H, OCH_2CH_3, J = 7.05 Hz), 2.225-2.266 (m, 2H, $NCH_2CH_2CH_2N$), 3.395-3.433 (t, 2H, $NCH_2CH_2CH_2N$, J = 5.7 Hz), 3.819 (s, 3H, OCH_3), 4.184-4.256 (q, 2H, OCH_2CH_3, J = 7.5 Hz, J = 6.9 Hz), 4.263-4.310 (t, 2H, $NCH_2CH_2CH_2N$, J = 7.05 Hz), 6.653-6.573 (d, 1H, CHCH, J = 3 Hz), 6.624-6.675 (d, 1H, CH = CH, J = 15.3 Hz), 6.878-6.915 (dd, 1H, ArH, J = 2.4 Hz, J = 2.4 Hz), 7.111-7.118 (d, 1H, ArH, J = 2.1 Hz), 7.175-7.185 (d, 1H, CHCH, J = 3 Hz), 7.340 (s, 2H, ArH), 7.409-7.438 (d, 1H, ArH, J = 8.7 Hz), 7.685-7.736 (d, 1H, CH = CH, J = 15.3 Hz), 7.772 (s, 1H, ArH); MS(ESI m/z):473 $(M + H)^+$.

3.6. PTP1B and TCPTP inhibition assays

The inhibitory activities of 2-substituted ethenesulfonic acid ester derivatives against PTP1B and TCPTP were determined with our published procedure, and the IC_{50} values of the compounds are shown in the Table.

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