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Bromophenols as inhibitors of protein tyrosine phosphatase 1B with antidiabetic properties

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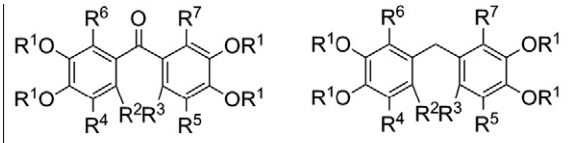
ABSTRACT

A series of bromophenol derivatives were synthesized and evaluated as protein tyrosine phosphatase 1B (PTP1B) inhibitors in vitro and in vivo based on bromophenol **4e** (IC_{50} = 2.42 μmol/L), which was isolated from red algae *Rhodomela confervoides*. The results showed that all of the synthesized compounds displayed weak to good PTP1B inhibition at tested concentration. Among them, highly brominated compound **4g** exhibited promising inhibitory activity against PTP1B with IC_{50} 0.68 μmol/L, which was approximately fourfold more potent than lead compound **4e**. Further, compound **4g** demonstrated high selectivity against other PTPs (TCPTP, LAR, SHP-1 and SHP-2). More importantly, in vivo antidiabetic activities investigations of compound **4g** also demonstrated inspiring results.

In recent years, protein tyrosine phosphatase 1B (PTP1B), the first characterized protein tyrosine phosphatase (PTPases), has attracted intensive research because of its involvement in the insulin signaling cascade as a major negative regulator.[1] Accumulating evidence indicate that PTP1B could dephosphorylate the insulin receptor (IR) or insulin receptor substrate (IRS) in skeletal muscle and liver, which involved in the control of insulin signaling pathway, and these signaling events result in the homeostatic regulation of the blood glucose level.[2–4] In addition, molecular biology investigations have been already proved that PTP1B knock-out mice exhibit the phenotypes of increased insulin sensitivity, improved glucose tolerance, and resistance to diet-induced obesity.[5,6] Based on above research results, the inhibition of PTP1B has emerged as a novel therapeutic strategy for the treatments of type 2 diabetes mellitus.

In the past decades, there were a number of reports on the design and development of synthetic PTP1B inhibitors.[7,8] At the same while, more and more studies were focused on PTP1B inhibitors isolated from plants.[9–13] In our screening program to search for PTP1B inhibitors from marine algae, the ethanol-soluble extract of *Rhodomela confervoides* exhibited significant inhibitory activity against PTP1B in vitro. The results were also confirmed by following in vivo anti-hyperglycemic effects on streptozotocin-diabetes in male Wistar rats fed with high fat diet.[14] Then bioassay-guided separation of ethanol extract using a variety of chromatographic techniques lead to a series of bromophenol derivatives.[15] One of them, bromophenol **4e** showed good inhibitory activity against PTP1B in vitro (IC_{50} = 2.42 μmol/L),[14] which makes it an attractive starting point to be developed into more potent small molecular PTP1B inhibitor. Based on the naturally potent PTP1B inhibitor, a series of bromophenol derivatives have been synthesized and evaluated as a novel class of small molecular PTP1B inhibitors. Their structures are shown in Figure 1.



	R^1	R^2	R^3	R^4	R^5	R^6	R^7
1a	CH_3	H	H	H	H	H	H
1b	CH_3	Br	H	H	H	H	H
1c	CH_3	Br	Br	H	H	H	H
1d	CH_3	Br	Br	Br	H	H	H
1e	CH_3	Br	Br	Br	Br	H	H
1f	CH_3	Br	Br	Br	Br	Br	H
1g	CH_3	Br	Br	Br	Br	Br	Br
2a	H	H	H	H	H	H	H
2b	H	Br	H	H	H	H	H
2c	H	Br	Br	H	H	H	H
2d	H	Br	Br	Br	H	H	H
2e	H	Br	Br	Br	Br	H	H
2f	H	Br	Br	Br	Br	Br	H
2g	H	Br	Br	Br	Br	Br	Br

	R^1	R^2	R^3	R^4	R^5	R^6	R^7
3a	CH_3	H	H	H	H	H	H
3b	CH_3	Br	H	H	H	H	H
3c	CH_3	Br	Br	H	H	H	H
3d	CH_3	Br	Br	Br	H	H	H
3e	CH_3	Br	Br	Br	Br	H	H
3f	CH_3	Br	Br	Br	Br	Br	H
3g	CH_3	Br	Br	Br	Br	Br	Br
4a	H	H	H	H	H	H	H
4b	H	Br	H	H	H	H	H
4c	H	Br	Br	H	H	H	H
4d	H	Br	Br	Br	H	H	H
4e	H	Br	Br	Br	Br	H	H
4f	H	Br	Br	Br	Br	Br	H
4g	H	Br	Br	Br	Br	Br	Br

Figure 1. Structures of synthetic bromophenol derivatives.

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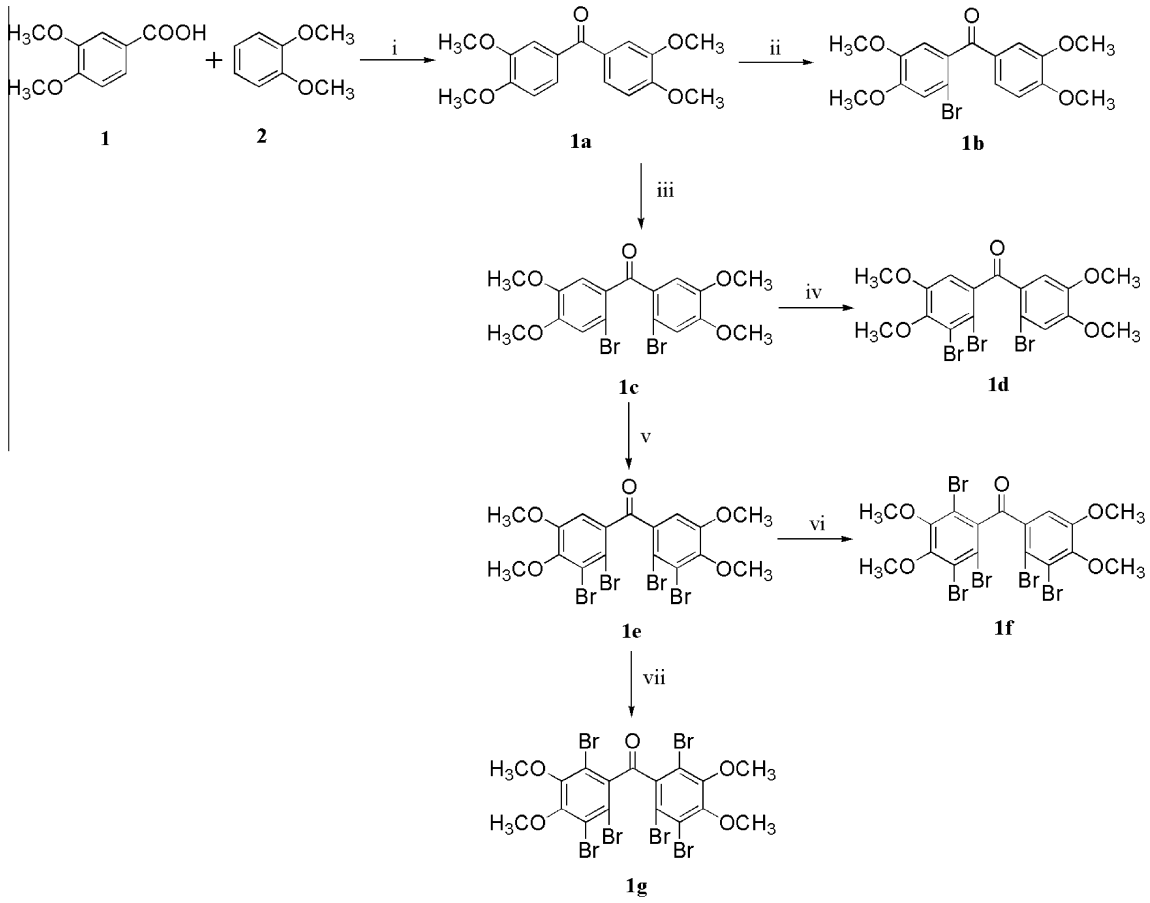
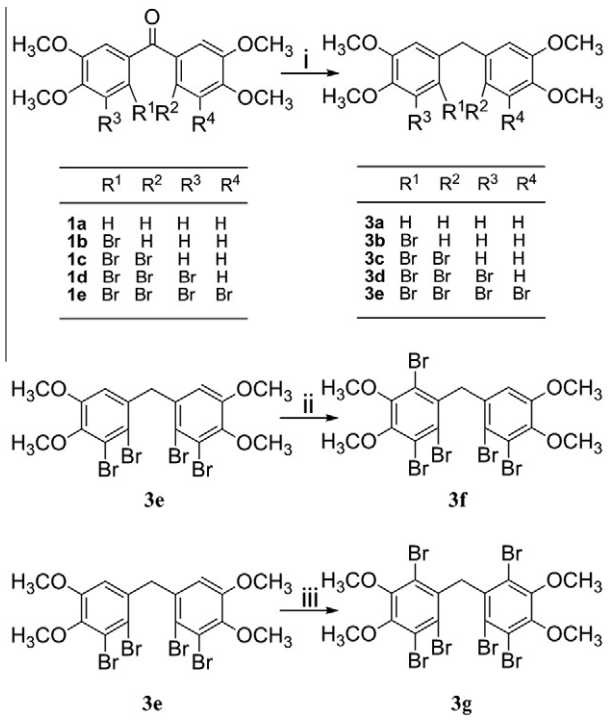


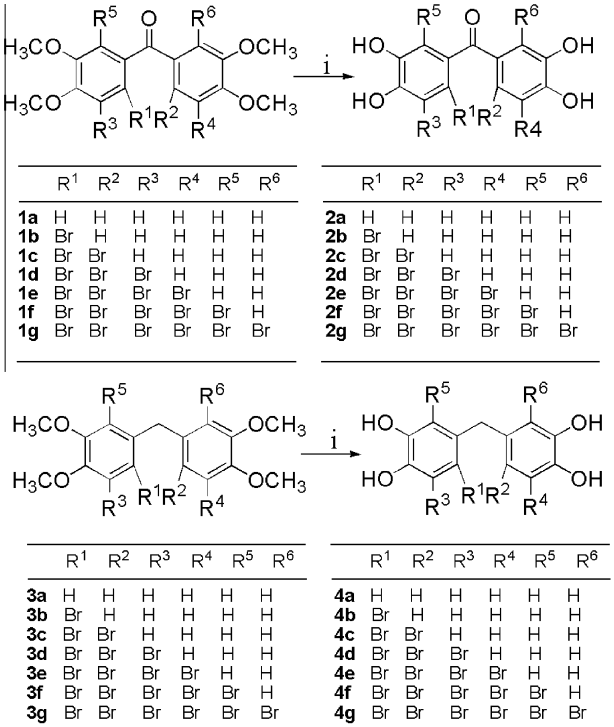
Scheme 1. Reagents and conditions: (i) PPA, 80 °C, 1 h; (ii) Br_2 (1.1 equiv), CH_2Cl_2, rt; (iii) Br_2 (2 equiv), AcOH, rt; (iv) Br_2 (1.1 equiv), $AlCl_3$, AcOH, 40 °C; (v) Br_2 (3 equiv), $AlCl_3$, AcOH, 80 °C; (vi) NBS (1 equiv), AcOH, concd H_2SO_4, 0 °C to rt; (vii) NBS (2 equiv), concd H_2SO_4, 0 °C to rt.



	R^1	R^2	R^3	R^4
1a	H	H	H	H
1b	Br	H	H	H
1c	Br	Br	H	H
1d	Br	Br	Br	H
1e	Br	Br	Br	Br

	R^1	R^2	R^3	R^4
3a	H	H	H	H
3b	Br	H	H	H
3c	Br	Br	H	H
3d	Br	Br	Br	H
3e	Br	Br	Br	Br

Scheme 2. Reagents and conditions: (i) Et_3SiH, CF_3COOH, rt; (ii) Br_2 (1 equiv), $AlCl_3$, AcOH, 70–90 °C; (iii) NBS (2 equiv), concd H_2SO_4, 0 °C to rt.



	R^1	R^2	R^3	R^4	R^5	R^6
1a	H	H	H	H	H	H
1b	Br	H	H	H	H	H
1c	Br	Br	H	H	H	H
1d	Br	Br	Br	H	H	H
1e	Br	Br	Br	Br	H	H
1f	Br	Br	Br	Br	Br	H
1g	Br	Br	Br	Br	Br	Br

	R^1	R^2	R^3	R^4	R^5	R^6
2a	H	H	H	H	H	H
2b	Br	H	H	H	H	H
2c	Br	Br	H	H	H	H
2d	Br	Br	Br	H	H	H
2e	Br	Br	Br	Br	H	H
2f	Br	Br	Br	Br	Br	H
2g	Br	Br	Br	Br	Br	Br

	R^1	R^2	R^3	R^4	R^5	R^6
3a	H	H	H	H	H	H
3b	Br	H	H	H	H	H
3c	Br	Br	H	H	H	H
3d	Br	Br	Br	H	H	H
3e	Br	Br	Br	Br	H	H
3f	Br	Br	Br	Br	Br	H
3g	Br	Br	Br	Br	Br	Br

	R^1	R^2	R^3	R^4	R^5	R^6
4a	H	H	H	H	H	H
4b	Br	H	H	H	H	H
4c	Br	Br	H	H	H	H
4d	Br	Br	Br	H	H	H
4e	Br	Br	Br	Br	H	H
4f	Br	Br	Br	Br	Br	H
4g	Br	Br	Br	Br	Br	Br

Scheme 3. Reagents and conditions: (i) BBr_3, dry CH_2Cl_2, rt, 4 h.

Table 1
In vitro PTP1B inhibitory activities of synthetic bromophenol derivatives

Compds	Inhibition (%)		IC_{50} (μmol/L)
	20 μg/mL	5 μg/mL	
1a	2.72	ND	ND
1b	12.98	ND	ND
1c	33.64	ND	ND
1d	37.55	ND	ND
1e	21.35	ND	ND
1f	69.81	50.63[a]	3.26[b]
1g	105.06	47.83[a]	2.02
2a	13.48	ND	ND
2b	11.25	ND	ND
2c	8.74	ND	ND
2d	42.71	ND	ND
2e	20.28	ND	ND
2f	95.07	72.13[a]	2.45[b]
2g	78.64	29.18[a]	ND
3a	38.43	ND	ND
3b	14.42	ND	ND
3c	33.64	ND	ND
3d	52.49	40.16[a]	ND
3e	60.44	28.95[a]	ND
3f	98.71	49.32[a]	ND
3g	96.91	37.89[a]	ND
4a	9.27	ND	ND
4b	12.25	ND	ND
4c	20.92	ND	ND
4d	40.45	ND	ND
4e	91.32	38.94[a]	2.42
4f	92.26	45.27[a]	ND
4g	101.05	86.72[a]	0.68[b]

ND = not determined.
[a] Values were tested only if its inhibitory ratio greater than 50% at the dose of 20 μg/mL.
[b] Values were tested only if its inhibitory ratio greater than 50% at the dose of 5 μg/mL.

Table 2
Inhibitory activity of compound **4g** against various PTPs

Compd	IC_{50} (μmol/L)				
	PTP1B	TCPTP	SHP-1	SHP-2	LAR
4g	0.68	>50	>50	>50	>50

The synthetic routes of compounds **1a–g** are shown in Scheme 1. Bis-(3,4-dimethoxy-phenyl)-methanone **1a**, which was synthesized by 3,4-dimethoxybenzoic acid **1** on reaction with 1,2-dimethoxybenzene **2** in the presence of polyphosphoric acid at 80 °C for one hour,[16] was regarded as the crucial intermediate to provide a versatile platform for varying both position and number of bromine substitution on the phenyl ring. Firstly, treatment of compound **1a** with two equivalents of bromine in apolar solvent CH_2Cl_2 to afford the mixture of mono-brominated compound **1b** and di-brominated compound **1c**. By modification of the reacting conditions that using 1 equiv of bromine reacted with **1a** in CH_2Cl_2 at 0 °C, mono-brominated compound **1b** was obtained in 64% yield, while in polar solvent acetic acid, di-brominated compound **1c** was yielded in 82% yield.[17,18] Inspired by the outcome aforementioned, further bromination of compound **1c** took place smoothly under the control of quantity of bromine, type of brominating reagent (Br_2 and NBS), solvent polarity (acetic acid and concd H_2SO_4) and addition of catalyst ($AlCl_3$) to afforded multi-brominated compounds **1d–g** in 40–50% yield.[19] As outlined in Scheme 2, reduction of diarylketone compounds **1a–e** were carried out with triethylsilane in trifluoroacetic acid to obtain the corresponding diarylmethane compounds **3a–e** in 73–80% yield.[20] Further bromination of compound **3e** took place using process as shown in Scheme 2 to give compounds **3f** and **3g**. Finally, demethylation of compounds **1a–g** and **3a–g** with boron bromide in CH_2Cl_2 cleanly gave corresponding bromophenols **2a–g** and **4a–g** in 90–94% yield[21,22] and the synthetic routes are shown in Scheme 3. Analytical data for the target compounds and intermediates were provided in Ref. 23.

All the derivatives (**1a–g, 2a–g, 3a–g** and **4a–g**) were evaluated in the enzyme inhibition assay against human recombinant PTP1B prepared as described.[24] As summarized in Table 1, all of the synthetic compounds demonstrated weak to good PTP1B inhibitory activity at 20 μg/mL. Especially, compounds **1g** and **4g** exhibited significant PTP1B inhibition (105.06% and 101.05%, respectively), which showed stronger inhibitory activity than compound **4e** (91.32%). Compound **3a**, the reductive compound of **1a**, displayed 38.42% inhibition that was much higher than **1a** (2.72%) at 20 μg/mL. Accordingly, compounds **3d,e** demonstrated higher inhibition than their carbonyl compounds **1d,e**. And this trend also partly applies to compounds **4a–e** and **1a–e**. In general, the diarylmethane compounds exhibited more potent PTP1B inhibition than the diarylmethanones, which indicating that the flexibility of diarylmethane scaffold is favorable to PTP1B inhibitory activity. It is also found that there is no obvious potency difference between compounds with free hydroxyl and their corresponding methylating ones. Furthermore, it is notable that the multi-brominated compounds especially the pentabromo- or hexabromo-compounds (**1g, 2f,g, 3f,g** and **4e–g**) displayed more significant PTP1B inhibitory activity than mono-brominated compounds, indicating that increasing of the number of bromine substitutions on phenyl ring promote PTP1B inhibitory activity. In addition to potency improvements, we investigated the selectivity of compound **4g** against other PTPs (TCPTP, LAR, SHP-1 and SHP-2). As shown in Table 2, compound **4g** demonstrated excellent selectivity against TCPTP, LAR, SHP-1 and SHP-2 (>70-fold).

As an interesting new entity, compound **4g** was selected for further antidiabetic activities evaluation in vivo.[25] During 6-week intervention, body weight and food consumption of db/db mice in treatment group exhibited a downward trend compared with the model group, and no obvious toxicity observed. The antihyperglycemic activity profile was illustrated in Table 3, compound **4g** was active in vivo at a dose of 25 and 50 mg/kg, decreasing plasma

Table 3
In vivo antihyperglycemic activity profile of compound **4g** in db/db mice model

Group	Dose (mg/kg)	Plasma glucose (mmol/L)[a]			% Decrease in plasma glucose	HbA1c (%)[a]
		Baseline	2 weeks	6 weeks		
Control		5.1 ± 0.4	5.2 ± 0.4	6.7 ± 0.8		2.65 ± 0.40
Model		15.5 ± 2.8**	16.2 ± 4.0**	15.8 ± 1.8**		4.90 ± 0.31**
4g	50	15.6 ± 2.6	18.1 ± 1.6	9.3 ± 1.0##	40.4	3.05 ± 0.92##
	25	15.8 ± 2.4	15.2 ± 2.8	10.5 ± 2.4##	33.5	3.05 ± 0.60##
Rosiglitazone	50	15.3 ± 2.4	9.7 ± 1.2##	7.9 ± 1.5##	48.4	2.56 ± 0.44##

[a] Data are means ± SD.
P <0.01 when compared to the model group.
** P <0.01 when compared to the control group.

Table 4
In vivo antidyslipidemic activities of compound **4g**

Group	Dose (mg/kg)	Triacylglycerols (mmol/L)[a]			Total cholesterol (mmol/L)[a]		
		Baseline	2 weeks	6 weeks	Baseline	2 weeks	6 weeks
Control		1.16 ± 0.09	1.08 ± 0.07	1.0 5 ± 0.11	3.6 ± 0.2	3.5 ± 0.2	3.3 ± 0.5
Model		1.30 ± 0.25	1.24 ± 0.12**	1.56 ± 0.17**	6.2 ± 1.7**	9.8 ± 0.7**	9.2 ± 1.2**
4g	50	1.31 ± 0.28	1.28 ± 0.11	1.51 ± 0.23	6.3 ± 1.8	7.1 ± 1.0##	8.4 ± 0.1
	25	1.29 ± 0.18	1.20 ± 0.13	1.45 ± 0.15	6.3 ± 1.3	8.3 ± 0.5##	9.1 ± 1.0
Rosiglitazone	50	1.31 ± 0.38	1.06 ± 0.19#	1.29 ± 0.14##	6.1 ± 1.7	6.5 ± 0.4##	7.7 ± 1.0#

[a] Data are means ± SD.
# P <0.05.
P <0.01 when compared to the model group.
** P <0.01 when compared to the control group.

glucose levels in the db/db mice by 33% and 40%, respectively. The positive drug rosiglitazone showed 48.4% plasma glucose lowering activity after six weeks treatment in similar conditions at a dose of 50 mg/kg. Furthermore, compound **4g** also remarkably decreased HbA1c levels at 25 and 50 mg/kg (P <0.01). The total cholesterol concentration of both high and low dose of compound **4g** was significantly reduced after the intervention of two weeks compared with baseline. Unfortunately, no significant changes of triacylglycerol concentration were observed during the intervention period (Table 4).

In summary, a series of bromophenol derivatives were designed and synthesized for the discovery of potent PTP1B inhibitors. The preliminary structure-activity relationship acquired show that (i) the diarylmethane scaffold is favorable to PTP1B inhibitory activity, (ii) multi-bromine atoms (four to six) attached to the phenyl ring is important for PTP1B inhibition. Among these, compound **4g** exhibited remarkable inhibitory activity against PTP1B with IC_{50} 0.68 μmol/L, which was approximately four-fold potent than the lead compound **4e** (IC_{50} = 2.42 μmol/L). As an interesting entity, compound **4g** exhibited high selectivity against other PTPs in vitro and promising antidiabetic activities in vivo. The chemical entities reported in this study could provide a possible opportunity for developing novel PTP1B inhibitors with promising selectivity and pharmacological properties.

Acknowledgments

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23. *Experimental:* Melting points were determined using Boetius electrothermal capillary melting point apparatus and are uncorrected. IR (in cm^{-1}) spectra in KBr pellets on a IMPACT-400 spectrophotometer. ^1H and ^{13}C spectra were recorded on an Inova (500 MHz) NMR spectrometer for proton and at 125 MHz for carbon. Mass spectra were recorded on Autospec Ultima-Tof mass spectrometer and Thermo LTQ-Orbitrap. Column chromatography was carried out using silica gel (200–300 mesh). Thin-layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates. Solvents were purchased from Shanghai Chemical Reagent Company and used without further purification.
*Procedures for the synthesis of compound **1a**:* 22.08 g (120 mmol) of 3,4-dimethoxybenzoic acid **1** and 16.92 g (120 mmol) of 1,2-dimethoxybenzene **2** were stirred in 100 g of polyphosphoric acid at 80 °C for 1 h. The mixture was then cooled to 60 °C, and 250 mL of water was added over 30 min. The precipitate was filtered and dissolved in 100 mL CH_2Cl_2, washed with 3% NaOH and water successively. The organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give 30.7 g **1a**, yield 85%.
*Analytic data for compound **1a**:* white powder, mp 145.3–246.1 °C (lit[16] mp 147 °C). ^1H NMR (500 MHz, $CDCl_3$): δ 3.92 (s, 6H), 3.94 (s, 6H), 6.88 (d, 2H, J = 8.4 Hz), 7.36 (dd, 2H, J = 8.4, 1.7 Hz), 7.42 (d, 2H, J = 1.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.03, 109.79, 112.39, 124.69, 130.82, 148.90, 152.61, 194.35.
*Procedures for the synthesis of compound **1b**:* To solution of compound **1a** (3 g, 10 mmol) in CH_2Cl_2 (20 mL) was added bromine (0.56 mL in 10 mL CH_2Cl_2, 11 mmol) dropwise while stirring. The mixture was stirred at room temperature. Thin Layer Chromatography (TLC) was used to monitor the reaction end point. After the reaction, the mixture was concentrated in vacuo. The residue was chromatographed on a silica gel column (petroleum ether:acetone, 8:1) to afford 2.43 g **1b**, yield 64%.
*Analytic data for compound **1b**:* white powder, mp 129.9–230.5 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 3.84 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 6.85 (d, 1H, J = 8.4 Hz), 6.87 (s, 1H), 7.07 (s, 1H), 7.25 (dd, 1H, J = 8.4, 1.9 Hz), 7.54 (d, 1H, J = 1.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.05, 56.09, 56.19, 56.32, 110.01, 110.65, 111.37, 112.10, 115.81, 126.22, 129.58, 132.85, 148.25, 149.29, 150.66, 153.89, 194.25.
*Procedures for the synthesis of compound **1c**:* To solution of **1a** (15.1 g, 50 mmol) in 120 mL acetic acid was added bromine (5.4 mL in 10 mL AcOH, 105 mmol) dropwise while stirring. The mixture was stirred at room temperature. TLC was used to monitor the reaction end point. Then the mixture was concentrated in vacuo. The residue was dissolved in $CHCl_3$ and washed with 5% $NaHSO_3$, 3%

NaOH and brine successively. The organic phase was dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 18.87 g **1c**, yield 82%.

Analytic data for compound ***1c***: pale yellow powder, mp 172.5–273.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.87 (s, 6H), 3.94 (s, 6H), 7.05 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.26, 56.33, 113.22, 114.00, 116.37, 131.76, 148.40, 152.01, 194.26.

Procedures for the synthesis of compound ***1d***: To the suspension of compound **1c** (4.6 g, 10 mmol) and 1.0 g $AlCl_3$ in 100 mL acetic acid was added bromine (1 mL in 10 mL AcOH, 20 mmol) dropwise while stirring. The reaction mixture was heated at 40 °C. After the reaction, the mixture was poured into 3% HCl and extracted with CH_2Cl_2. The combined extracts were concentrated in vacuo and the residue was chromatographed on a silica gel column (petroleum ether:EtOAc, 6:1) to afford 2.21 g **1d**, yield 41%.

Analytic data for compound ***1d***: white powder, mp 160.8–261.3 °C. HRMS-EI *m/z*: measured 537.8453 ($[M]^+$, calcd 537.8449 for $C_{17}H_{15}O_5{}^{79}Br_2{}^{81}Br$). MS-EI *m/z* (% relative intensity): 542/540/538/536 ($[M]^+$, 17/43/45/17), 461/459/457 (3/5/3), 380/378 (99/100), 325/323/321 (9/20/11), 245/243 (50/51). IR (KBr): 2926, 2842, 1653, 1585, 1506, 1463, 1420, 1374, 1302, 1259, 1204, 1159, 1074, 934, 882, 841, 654 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.87 (s, 6H), 3.92 (s, 3H), 3.94 (s, 3H), 6.97 (s, 1H), 7.07 (s, 1H), 7.16 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.35, 56.39, 56.44, 60.76, 113.08, 114.32, 114.47, 114.67, 116.85, 123.05, 130.04, 137.84, 148.44, 149.69, 152.69, 152.74, 193.61.

Procedures for the synthesis of compound ***1e***: To a suspension of compound **1c** (4.6 g, 10 mmol) and 1.0 g $AlCl_3$ in 100 mL acetic acid was added excess bromine (4 equiv) dropwise while stirring at room temperature. The mixture was heated at 80 °C and TLC was used to monitor the reaction end point. After the reaction, the mixture was poured into 3% HCl and extracted with CH_2Cl_2. The combined extracts were concentrated in vacuo and the residue was chromatographed on a silica gel column (petroleum ether:EtOAc, 8:1) to afford 3.17 g **1e**, yield 51%.

Analytic data for compound ***1e***: pale yellow powders, mp 120.7–221.4 °C. HRMS-EI *m/z*: measured 617.7537 ($[M]^+$, calcd 617.7534 for $C_{17}H_{14}O_5{}^{79}Br_2{}^{81}Br_2$). MS-EI *m/z* (% relative intensity): 622/620/618/616/614 ($[M]^+$, 4/26/34/26/3), 541/539/537/535 (2/4/4/2), 460/458/456 (52/100/52), 379/377 (5/4), 325/323/321 (32/63/36). IR (KBr): 3197, 2940, 2872, 1684, 1576, 1465, 1419, 1368, 1304, 1261, 1205, 1162, 1096, 1049, 1001, 850, 825, 632 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.86 (s, 6H), 3.91 (s, 6H), 7.03 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.55, 60.81, 114.01, 115.24, 123.56, 136.34, 150.33, 152.48, 193.55.

Procedures for the synthesis of compound ***1f***: To the suspension of compound **1e** (6.2 g, 10 mmol) in 50 mL acetic acid and 150 mL con.H_2SO_4 was added NBS (1.8 g, 10 mmol) under ice-bath, and the mixture was stirred for further 2 h at room temperature. The mixture was poured into 200 mL ice-cold water and extracted with CH_2Cl_2 (3 × 300 mL). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4, and evaporated in vacuo to provide the brownish residue. The residue was purified by silica gel column chromatography (petroleum ether:EtOAc, 50:1) to afford 3.01 g **1f**, yield 43%.

Analytic data for compound ***1f***: white powder, mp 113.3–214.7 °C. HRMS-EI *m/z*: measured 696.6701 ($[M+H]^+$, calcd 696.6712 for $C_{17}H_{14}O_5{}^{79}Br_3{}^{81}Br_2$). MS-EI *m/z* (% relative intensity): 700/698/696/694 ($[M]^+$, 18/37/37/20), 540/538/536/534 (22/67/68/22), 460/458/456 (52/100/52), 405/403/401/399 (10/16/30/32), 325/323/321 (50/100/51). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.84 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 7.36 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.48 (q), 60.77 (q), 61.11 (q), 61.16 (q), 115.32 (d), 115.82 (d), 117.51 (s), 117.63 (d), 122.27(s), 124.79(s), 132.22 (s), 139.09 (s), 151.75 (s), 152.11 (s), 152.92 (s), 190.17 (s).

Procedures for the synthesis of compound ***1g***: To the suspension of compound **1e** (6.2 g, 10 mmol) in 50 mL concd H_2SO_4 was added NBS (3.6 g, 20 mmol) under ice-bath, and the mixture was stirred for further 2 h at room temperature. TLC was used to monitor the reaction end point. The mixture was poured into 100 mL ice-cold water and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4, and evaporated in vacuo to provide the brownish residue. The residue was purified by silica gel column chromatography (petroleum ether:EtOAc, 50:1) to afford 7.37 g **1g**, yield 95%.

Analytic data for compound ***1g***: white powder, mp 140–242 °C. HRMS-EI *m/z*: measured 772.5835 ($[M+H]^+$, calcd 772.5837 for $C_{17}H_{13}O_5{}^{79}Br_5{}^{81}Br$). MS-EI *m/z* (% relative intensity): 780/778/776/774/772 ($[M]^+$, 25/32/48/32/25), 618/616/614 (67/100/67), 405/403/401/399 (25/81/81/25). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.87 (s, 6H), 3.95 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 60.93 (q), 61.10 (q), 119.32(s), 120.66(s), 123.23(s), 136.61 (s), 150.89 (s), 153.78 (s), 189.25(s).

General procedures for the synthesis of compounds ***3a–e***: To stirred solutions of the compounds **1a–e** (10 mmol) in 20 mL trifluoroactic acid was added triethylsilane (22 mmol, 2.2 equiv). The mixture was stirred at room temperature and TLC was used to monitor the reaction end point. After the reaction, the mixture was poured into ice-cold water and extracted 3 times with 60 mL of CH_2Cl_2. The combined organic extracts were concentrated in vacuo to afford corresponding compounds **3a–e**.

Analytic data for compound ***3a***: Yield 73%, white powder, mp 70.4–21.3 °C (lit[16] 68–29 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.83 (s, 6H), 3.85 (s, 6H), 3.88 (s, 2H), 6.69 (dd, 2H, *J* = 7.6, 1.9 Hz), 6.72 (d, 2H, *J* = 1.9 Hz), 6.79 (d, 2H, *J* = 7.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 40.96, 55.82, 55.91, 111.43, 112.35, 120.77, 133.94, 147.49, 149.02.

Analytic data for compound ***3b***: Yield 75%, white powder, mp 74.5–24.9 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.76 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 3.99 (s, 2H), 6.64 (s, 1H) 6.69 (dd, 1H, *J* = 8.0, 1.9 Hz), 6.73 (d, 1H, *J* = 1.9 Hz), 6.79 (d, 1H, *J* = 8.0 Hz), 7.04 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 40.86 55.89, 55.93, 56.06, 56.21, 111.41, 112.32, 113.74, 114.51, 115.72, 120.76, 132.52, 132.60, 147.62, 148.21, 148.58, 149.07.

Analytic data for compound ***3c***: Yield 80%, white powder, mp 98.6–28.7 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.74 (s, 6H), 3.86 (s, 6H), 4.06 (s, 2H), 6.59 (s, 2H), 7.05 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 40.94, 56.06, 56.20, 113.43, 114.55, 115.65, 131.31, 148.30, 148.61.

Analytic data for compound ***3d***: Yield 70%, white powder, mp 113.3–214.7 °C. HRMS-EI *m/z*: measured 523.8660 ($[M]^+$, calcd 523.8656 for $C_{17}H_{17}O_4{}^{79}Br_2{}^{81}Br$). MS-EI *m/z* (% relative intensity): 528/526/524/522 ($[M]^+$, 51/100/100/52), 448/446/444 (5/10/7), 366/364 (91/90), 285 (23). IR (KBr): 3078, 2935, 2845, 1601, 1581, 1548, 1504, 1461, 1423, 1371, 1335, 1317, 1259, 1219, 1191, 1163, 1053, 1032, 1008, 860, 841, 649, cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.71 (s, 3H), 3.77 (s, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 4.15 (s, 2H), 6.54 (s, 1H), 6.62 (s, 1H), 7.07 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 43.13 56.16, 56.20, 56.20, 60.50, 113.32, 113.68, 114.86, 115.76, 117.71, 121.91, 130.61, 136.71, 146.35, 148.58, 148.73, 152.53.

Analytic data for compound ***3e***: Yield 73%, white powder, mp 149.9–250.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.75 (s, 6H), 3.85 (s, 6H), 4.24 (s, 2H), 6.58 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 45.29, 56.30, 60.54, 113.56, 118.02, 122.12, 136.00, 146.66, 152.65.

Procedures for the synthesis of compound ***3f***: To solution of compound **3e** (6.0 g, 10 mmol) in 100 mL acetic acid was added 1.0 g $AlCl_3$ at 45 °C. After 30 min, 0.6 mL bromine in 10 mL acetic acid was added dropwise while stirring at room temperature. The reaction mixture was then heated at 70–20 °C (TLC monitored). At the end, the mixture was poured into 3% HCl and extracted with CH_2Cl_2. The organic extract was dried over anhydrous Na_2SO_4, and evaporated in vacuo to provide the brownish residue. The residue was chromatographed on a silica gel column (petroleum ether:EtOAc, 50:1) to afford 4.43 g **1e**, yield 65%.

Analytic data for compound ***3f***: white powder, mp 160.8–261 °C. HRMS-EI *m/z*: measured 680.6754 ($[M+H]^+$, calcd 680.6763 for $C_{17}H_{14}O_4{}^{79}Br_3{}^{81}Br_2$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.62(s, 3H), 3.83 (s, 3H), 3.92 (s, 3H), 3.95 (s, 3H), 4.55 (s, 2H), 6.13 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 46.54 (t), 56.40 (q), 60.52 (q), 60.89 (q), 60.98 (q), 111.82 (d), 117.95 (s), 121.49 (s), 121.86 (s), 122.04 (s), 123.63 (s), 134.03 (s), 136.40 (s), 146.54 (s), 150.93 (s), 151.24 (s), 152.53 (s).

Procedures for the synthesis of compound ***3g***: To the suspension of compound **3e** (6.0 g, 10 mmol) in 50 mL con.H_2SO_4 was added NBS (3.6 g, 20 mmol) under ice-bath, and the mixture was stirred at room temperature. TLC was used to monitor the reaction end point. The mixture was poured into 100 mL ice-cold water and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4, and evaporated in vacuo to provide the brownish residue. The residue was purified by silica gel column chromatography (petroleum ether:EtOAc, 50:1) to afford 7.09 g **3g**, yield 93%.

Analytic data for compound ***3g***: white powder, mp 123–224 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.87 (s, 6H), 3.90 (s, 6H), 4.91 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 47.68 (t), 60.78 (q), 60.93 (q), 121.76 (s), 121.99 (s), 123.27 (s), 136.04 (s), 150.58 (s), 150.64 (s).

General procedures for the synthesis of compounds **2a–g** and **4a–g**: Compounds **1a–g** and **3a–g** (10 mmol) was dissolved in 30 mL dry dichloromethane, then 40 mL BBr_3 (1 mol/L in CH_2Cl_2) was added dropwise while stirring in ice bath. The reaction mixture stirred for further 4 h at room temperature. Then the solution was poured into ice-cold water and extracted with EtOAc (3 × 60 mL). The organic extracts was dried over anhydrous Na_2SO_4, and evaporated in vacuo to provide the brownish residue. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 15:1) to afford corresponding compounds **2a–g** and **4a–g**.

Analytic data for compound ***2a***: Yield 91%, yellow powder, mp 224.3–225.2 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.81 (d, 2H, *J* = 8.2 Hz) 7.04 (dd, 2H, *J* = 8.2, 2.1 Hz), 7.15 (d, 2H, *J* = 2.1 Hz), 9.31 (s, 2H), 9.70 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 114.78, 116.80, 122.47, 129.26, 144.76, 149.53, 193.08.

Analytic data for compound ***2b***: Yield 89%, yellow powder, mp 83.5–24.2 °C. HRMS-EI *m/z*: measured 323.9649 ($[M]^+$, calcd 323.9633 for $C_{13}H_9O_5Br$). MS-EI *m/z* (% relative intensity): 326/324 ($[M]^+$, 70/70), 245 (77), 217/215 (43/45), 137 (100). IR (KBr): 3236, 2981, 2879, 1640, 1587, 1506, 1442, 1418, 1365, 1289, 1186, 1111, 1046, 952, 881, 827, 636 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.71 (s, 1H), 6.80 (d, 1H, *J* = 8.3 Hz), 6.99 (s, 1H), 7.03 (dd, 1H, *J* = 8.3, 2.0 Hz), 7.16 (d, 1H, *J* = 2.0 Hz), 9.40 (s, 1H), 9.52 (s, 1H), 9.79 (s, 1H), 9.94 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 107.28, 115.24, 115.97, 116.56, 119.26, 123.38, 128.07, 131.36, 144.58, 145.14, 147.65, 151.14, 193.21.

Analytic data for compound ***2c***: Yield 89%, white powder, mp 245.6–245.9 °C. HRMS-EI *m/z*: measured 403.8708 ($[M]^+$, calcd 403.8718 for $C_{13}H_8O_5{}^{79}Br{}^{81}Br$). MS-EI *m/z* (% relative intensity): 406/404/402 ($[M]^+$, 18/36/19), 326/324 (13/14), 244 (100), 217/215 (70/73). IR(KBr): 3177, 2978, 2871, 1653, 1585, 1505, 1419, 1286, 1182, 1047, 882, 634 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.82 (s, 2H), 7.00 (s, 2H), 9.56 (s, 2H), 10.09 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 109.57, 118.25, 120.24, 129.79, 144.55, 149.34, 192.88.

Analytic data for compound ***2d***: Yield 90%, light yellow oil. HRMS-EI *m/z*: measured 481.7807 ($[M]^+$, calcd 481.7823 for $C_{13}H_7O_5{}^{79}Br_2{}^{81}Br$). MS-EI *m/z* (% relative intensity): 486/484/482/480 ($[M]^+$, 12/32/34/12), 324/322 (98/100), 297/295/293 (17/38/22), 244 (49), 217/215 (72/79). IR(KBr): 3177, 2957, 2876, 1662, 1588, 1505, 1464, 1393, 1335, 1282, 1210, 1050, 884, 667 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.81 (s, 1H), 6.85 (s, 1H), 7.01 (s, 1H), 9.57 (s, 1H), 10.20 (s, 2H), 10.35 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 110.34, 111.81, 114.41, 115.38, 118.99, 120.72, 128.29, 132.24, 144.50, 144.76, 146.77, 150.01, 192.50.

Analytic data for compound ***2e***: Yield 88%, yellow powder, mp 233.0–233.1 °C.

HRMS-EI *m/z*: measured 561.6892 ($[M]^+$, calcd 561.6908 for $C_{13}H_6O_5{}^{79}Br_2{}^{81}Br_2$). MS-EI *m/z* (% relative intensity): 566/564/562/560/558 ($[M]^+$, 5/23/36/24/5), 485/483/481/479 (7/14/14/5), 404/402/400 (51/100/52), 324/322 (23/24), 297/295/293 (47/98/53). IR(KBr): 3167, 2977, 2878, 1652, 1591, 1569, 1464, 1394, 1280, 1213, 1078, 1047, 865, 646 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 6.88 (s, 2H), 10.38 (s, 4H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 112.65, 114.99, 116.28, 131.02, 144.60, 147.46, 192.48.

Analytic data for compound ***2f***: Yield 90%, white powder, mp 118–220 °C. HRMS-EI *m/z*: measured 639.5931 ($[M-H]^-$, calcd 638.5929 for $C_{13}H_5O_5{}^{79}Br_3{}^{81}Br_2$). MS-EI *m/z* (% relative intensity): 644/642/640/638 ($[M]^+$, 2/4/4/2), 484/482/480/478 (4/10/10/4), 375/373 (5/7), 297/295/293 (5/13/7). ^1H NMR (500 MHz, DMSO): δ = 7.05 (s, 1H)ppm. ^{13}C NMR (125 MHz, DMSO): δ = 108.41 (s), 111.60(d),114.44(s), 115.57(s), 117.34(s), 118.92(s), 126.85(s), 134.13(s), 144.44(s), 144.77(s), 146.62(s), 149.70(s), 190.20(s) ppm.

Analytic data for compound ***2g***: Yield 90%, pale powder, mp 220–222 °C. HRMS-EI *m/z*: measured 718.5014 ($[M-H]^-$, calcd 708.5014 for $C_{13}H_4O_5{}^{79}Br_3{}^{81}Br_3$). MS-EI *m/z* (% relative intensity): 722/720/718 ($[M]^+$, 2/4/2), 562/560/558 (5/10/5), 516/514 (6/4), 377/375/373/371 (3/12/12/3). ^1H NMR (500 MHz, DMSO-d_6): δ 10.12 (s, 2H),10.23 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 111.90 (s), 114.76 (s), 115.26 (s), 131.63 (s), 143.65 (s), 147.57 (s), 189.81 (s).

Analytic data for compound ***4a***: Yield 93%, pink powder, mp 181.3–282.1 °C. ^1H NMR (500 MHz, DMSO-d_6): δ 3.55 (s, 2H), 6.41 (dd, 2H, *J* = 7.9, 1.8 Hz), 6.51 (d, 2H, *J* = 1.8 Hz), 6.61 (d, 2H, *J* = 7.98 Hz) 8.57 (s, 2H), 8.70 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 39.85, 115.31, 115.99, 119.17, 132.74, 143.19, 144.94.

Analytic data for compound ***4b***: Yield 96%, brown powder, mp 128.7–229.1 °C. HRMS-EI *m/z*: measured 309.9834 ($[M]^+$, calcd 309.9841 for $C_{13}H_{11}O_4Br$). MS-EI *m/z* (% relative intensity): 312/310 ($[M]^+$, 53/54), 231 (52), 213 (100), 123 (27). IR(KBr): 3328, 2981, 2878, 1602, 1506, 1431, 1354, 1279, 1191, 1140, 1109, 1045, 879, 820, 639 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 3.68 (s, 2H), 6.42 (d, 1H, *J* = 8.0 Hz), 6.52 (s, 1H), 6.58 (d, 1H, *J* = 1.9 Hz), 6.63 (dd, 1H, *J* = 8.0, 1.9 Hz), 6.90 (s, 1H), 8.63 (s, 1H), 8.75 (s, 1H), 9.08 (s, 1H), 9.18 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 39.19, 111.37, 115.44, 115.96, 117.76, 118.78, 119.34, 130.99, 130.99, 143.44, 144.77, 145.01, 145.04.

Analytic data for compound ***4c***: Yield 94%, brown oil. HRMS-EI *m/z:* measured 389.8924 ($[M]^+$, calcd 389.8925 for $C_{13}H_{10}O_4{}^{79}Br^{81}Br$). MS-EI *m/z* (% relative intensity): 392/390/388 ($[M]^+$, 34/66/35), 311/309 (7/7), 230 (100). IR (KBr): 3315, 2981, 2877, 1600, 1505, 1429, 1342, 1275, 1224, 1186, 1142, 1046, 872, 818, 636 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 3.74 (s, 2H), 6.44 (s, 2H), 6.93 (s, 2H) 9.13 (s, 2H), 9.34 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 39.18, 111.55, 117.34, 118.89, 129.15, 144.91, 145.00.

Analytic data for compound ***4d***: Yield 90%, white powder, mp 190.9–291.4 °C. HRMS-EI *m/z*: measured 467.8007 ($[M]^+$, calcd 467.8030 for $C_{13}H_9O_4{}^{79}Br_2{}^{81}Br$). MS-EI *m/z* (% relative intensity): 472/470/468/466 ($[M]^+$, 12/33/34/13), 310/308 (97/100), 229 (65). IR(KBr): 3330, 2955, 2925, 1599, 1506, 1465, 1429, 1405, 1342, 1274, 1222, 1181, 1147, 1047, 856, 824, 637 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 3.84 (s, 2H), 6.45 (s, 1H), 6.48 (s, 1H), 6.95 (s, 1H), 9.16 (s, 1H), 9.24 (s, 1H), 9.42 (s, 1H), 9.91 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 41.61, 111.70, 113.28, 114.80, 115.71, 117.36, 118.98, 128.72, 130.92, 143.03, 145.07, 145.07, 145.15.

Analytic data for compound ***4e***: Yield 91%, yellow powders, mp 199.0–299.8 °C. HRMS-EI *m/z*: measured 547.7101 ($[M]^+$, calcd 547.7115 for $C_{13}H_8O_4{}^{79}Br_2{}^{81}Br_2$). MS-EI *m/z* (% relative intensity): 552/550/548/546/544 ($[M]^+$, 7/24/35/26/8), 390/388/386(50/100/52), 311/309 (50/50). ^1H NMR (500 MHz, DMSO-d_6): δ 3.95 (s, 2H), 6.49 (s, 2H), 9.47 (s, 2H), 9.95 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 43.59, 113.37 114.97, 115.72, 130.50, 143.17, 145.19.

Analytic data for compound ***4f***: Yield 90%, yellow powder, mp 139–240 °C. HRMS-EI *m/z*: measured 624.6140 ($[M-H]^-$, calcd 624.6137 for $C_{13}H_6O_4{}^{79}Br_3{}^{81}Br_2$). ^1H NMR (500 MHz, DMSO): δ 4.27(s, 2H), 6.04 (s, 1H), 9.39 (s, 1H), 9.77 (s, 1H), 9.90 (s, 1H), 10.04 (s, 1H). ^{13}C NMR (125 MHz, DMSO): δ 45.23 (t), 113.24 (s), 113.24 (s), 113.91 (s), 114.13 (d), 114.41 (s), 117.04 (s), 128.56 (s), 129.99 (s), 142.87 (s), 143.95 (s), 144.24 (s), 145.07 (s).

Analytic data for compound ***4g***: Yield 91%, yellow powder; mp 225–226 °C. HRMS-EI *m/z*: measured 704.5218 ($[M]^-$, calcd 704.5221 for $C_{13}H_5O_4{}^{79}Br_3{}^{81}Br_3$). ^1H NMR (DMSO-d_6, 500 MHz): δ 4.69 (s, 2H), 9.68 (s, 2H), 9.85 (s, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 46.61 (t), 114.24 (s), 114.49 (s), 116.93 (s), 130.15 (s), 143.55 (s), 143.60 (s).

24. *Enzyme activity assay in vitro:* The derivatives were assessed against PTP1B with the colorimetric assay. Compounds were solubilized in DMSO, and samples were distributed to 96-well clear polystyrene plate. DMSO was distributed as the full enzyme activity. After adding an assay mixture, GST-PTP1B was added to initiate the reaction. The high-throughput screening was carried out in a mixture containing MOPS, pNPP, PTP1B and DMSO, and the catalysis of pNPP was continuously monitored at 405 nm for 2 min at 30 °C. Inhibitory rate was calculated according to the fomula: % inhibition = $100 \times (V_{DMSO} - V_{sample})/V_{DMSO}$. The IC_{50} value was calculated from the nonlinear curve fitting of the percent inhibition [inhibition (%)] versus the inhibitor concentration [*I*] using the following equation:% inhibition = $100/\{1 + (IC_{50}/[I])^k\}$, where *k* is the Hill coeffcient. In experiments to determine the selectivity over PTPases, the enzymatic systems for other PTPases were the same as it for PTP1B. These enzymes and inhibitors were preincubated for 3 min at 4 °C, and the assays were initiated by adding substrates. Assays performed for SHP1 and SHP2, and LAR were done using OMFP as a substrate.
25. Antidiabetic activity in db/db mice

C57BL/Ks db/db mice 8 weeks, 40–50 g bred in the animal house of China Pharmaceutical University. The mice were housed in groups of four (same sex) in a room controlled for temperature (23 ± 2.0 °C) and 12/12 h light/dark cycle (lights on at 6.00 am). After a 2-week adaptation period, the 10-week-old mice were divided into four groups (n = 8 in each group), the model (0.5% sodium carboxyl methyl cellulose) group, rosiglitazone group (50 mg/kg), compound **4g** high-dose group (50 mg/kg) and compound **4g** low-dose group (25 mg/kg). Rosiglitazone and compound **4g** were dissolved in 0.5% sodium carboxyl methyl cellulose solution and administered orally for six weeks. Body weight was measured weekly from week 1 to week 6. All animals had free access to fresh water and to normal chow. Postprandial blood glucose was checked with an ONE TOUCH® Ultra® glucometer (LifeScan, USA) weekly and triacylglycerols and total cholesterol (Whitman Biotech Co., Ltd, Nanjing, China) were checked by an enzymatic method twice a week. The mice were fasted overnight on week 6 and glycosylated hemoglobin levels were measured by HbA_{1c} reagent (Whitman Biotech Co., Ltd, Nanjing, China).