Full Paper

Design, Synthesis, and Biological Evaluation of Bromophenol Derivatives as Protein Tyrosine Phosphatase 1B Inhibitors

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3-Bromo-4,5-*bis*(2,3-dibromo-4,5-dihydroxybenzyl)-1,2-benzenediol (BDB) is a bromophenol purified from the marine red alga *Rhodomela confervoides* and exhibits potent protein tyrosine phosphatase 1B (PTP1B) inhibition (IC_{50} = 1.7 μmol/L). In an effort to improve the PTP1B inhibitory activity, a series of derivatives were designed, synthesized, and evaluated *in vitro*. The preliminary structure–activity relationship indicated that the tricyclic scaffold and multi-bromine atoms (four to five) attached to the aryl rings are important for PTP1B inhibition. Among these, compound **26** exhibited remarkable inhibitory activity against PTP1B with an IC_{50} of 0.89 μmol/L, which was approximately two-fold more potent than the initial lead compound BDB.

Keywords: Bromophenol / Protein tyrosine phosphatase 1B inhibitor / Structure–activity relationship / Type 2 diabetes mellitus

Received: October 21, 2011; Revised: December 1, 2011; Accepted: December 6, 2011

DOI 10.1002/ardp.201100373

Introduction

Protein tyrosine phosphatases (PTPs) are crucial for the regulation of cellular processes and therefore have been linked to various diseases [1]. Among various members of the PTP superfamily, protein tyrosine phosphatase 1B (PTP1B) was the first characterized enzyme and has attracted considerable attention owing to its implication in the insulin and leptin signal transduction process as a major negative regulator [2, 3]. Accumulating evidence demonstrates that PTP1B could dephosphorylate the insulin receptor (IR) or insulin receptor substrate (IRS) in skeletal muscle and liver, which is involved in the control of the IR signaling pathway, and these signaling events result in the homeostatic regulation of the blood glucose level [4, 5]. Additionally, the PTP1B knockout mice experiment also confirmed the insulin antagonizing activity of PTP1B [6, 7]. Based on these data, PTP1B is currently considered one of the best-validated biological targets for non-insulin dependent diabetes and obesity [8]. Moreover, several groups have established a role for PTP1B in cancer, and selective PTP1B inhibitors can be used for effective treatment of cancer [9–11].

Over the past decades, a large number of PTP1B inhibitors have been developed aiming at developing potent and selective compounds as drug candidates [12–16]. Most of the reported compounds containing negatively charged non-hydrolyzable pTyr mimetics have exhibited excellent potency in *in vitro* studies. Unfortunately, the poor cell permeability and low bioavailability of these compounds have limited their application for the development of effective drugs [17, 18]. To the best of our knowledge, no small molecule PTP1B inhibitors are currently reported in human clinical trials, hence it is urgent for medicinal chemists to develop small molecule, cell permeable, and orally available PTP1B inhibitors.

Bromophenols are widely distributed throughout the marine red algae [19–21] and have been reported to exhibit a wide spectrum of biological and pharmacological activities including antibacterial, antifeedant [22], α-glucosidase inhibition [23], and cytotoxic activities [24]. We recently reported the isolation and total synthesis of 3-bromo-4,5-*bis*(2,3-dibromo-4,5-dihydroxybenzyl)-1,2-benzenediol (BDB), which exhibited

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Abbreviations: insulin receptor (IR); insulin receptor substrate (IRS); polyphosphoric acid (PPA); potent protein tyrosine phosphatase 1B (PTP1B); trifluoroacetic acid (TFA); thin-layer chromatography (TLC).

significant inhibition against PTP1B (IC_{50} = 1.7 μmol/L) [25, 26]. In an effort to improve the PTP1B inhibitory activity, optimization of the lead compound BDB included varying the number of aryl rings, substituted positions and number of bromine atoms, and the presence of free hydroxyl groups. Herein, we wish to report the synthesis of a series of derivatives and their PTP1B inhibition assay results.

Results and discussion

Chemistry

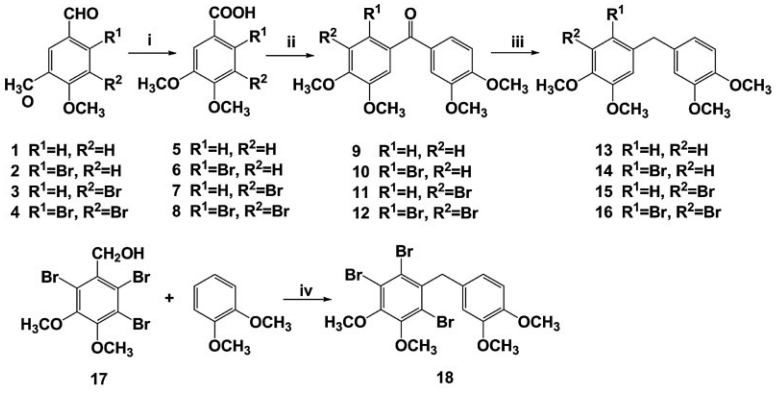
The synthetic routes of target compounds **13**–**16** and **18** are shown in Scheme 1. Compounds **1**–**4** were prepared according to our previous work [26]. Oxidation of the arylaldehydes using $KMnO_4$ as oxidant affords the aryl acids **5**–**8**. Subsequent treatment with commercially available veratrole in the presence of polyphosphoric acid (PPA) provided the corresponding diaryl-methanones **9**–**12** in good yields. Reduction of compounds **9**–**12** to diaryl-methanes **13**–**16** was carried out by treatment with excess $NaBH_4$ in trifluoroacetic acid (TFA) [27]. Friedel–Crafts reaction between substituted benzyl alcohol **17** and veratrole in the presence of $AlCl_3$ gave the target compound **18**.

Synthesis of tricyclic scaffold compounds was carried out following the synthetic steps in Scheme 2. Inspired by the synthesis of compound **18**, we used two equivalents of substituted benzyl alcohols **19**–**21** and veratrole in the presence of $AlCl_3$ to provide corresponding compounds **22**, **24**, and **26**. Replacing veratrole by compound **14**, the target compound **28** was prepared in a similar manner. As a crucial intermediate, compound **26** provided a versatile scaffold for varying both position and number of the bromine substituent on the phenyl ring. Firstly, treatment of compound **26** with two equivalents of bromine in the apolar solvent CH_2Cl_2 afforded the compound **30**. Then further bromination of **30** took place smoothly under the control of a quantity of NBS (1 equiv., 2 equiv., or 3 equiv.) in polar solvent H_2SO_4 affording multi-brominated compounds in 40–50% yield. Target compounds **38** and **43** were prepared using Friedel–Crafts reaction between benzylbromide **37** and substituted veratrole as described aforementioned (Fig. 1). Finally, all of the compounds bearing free hydroxyl were obtained by demethylation of corresponding compounds with boron bromide in dry CH_2Cl_2 in 80–90% yield [28].

The tetracyclic scaffold compounds were prepared by the procedure shown in Scheme 3. As an example, reaction of diaryl-methanes **13** and two equivalents of *bis*-brominated benzyl alcohol **21** in the presence of $AlCl_3$ afforded a mixture of tricyclic compound **44** and tetracyclic **47**. Purification by silica gel chromatography provided compounds **44** and **47**, respectively. Compounds **46** and **49** were prepared in a similar manner.

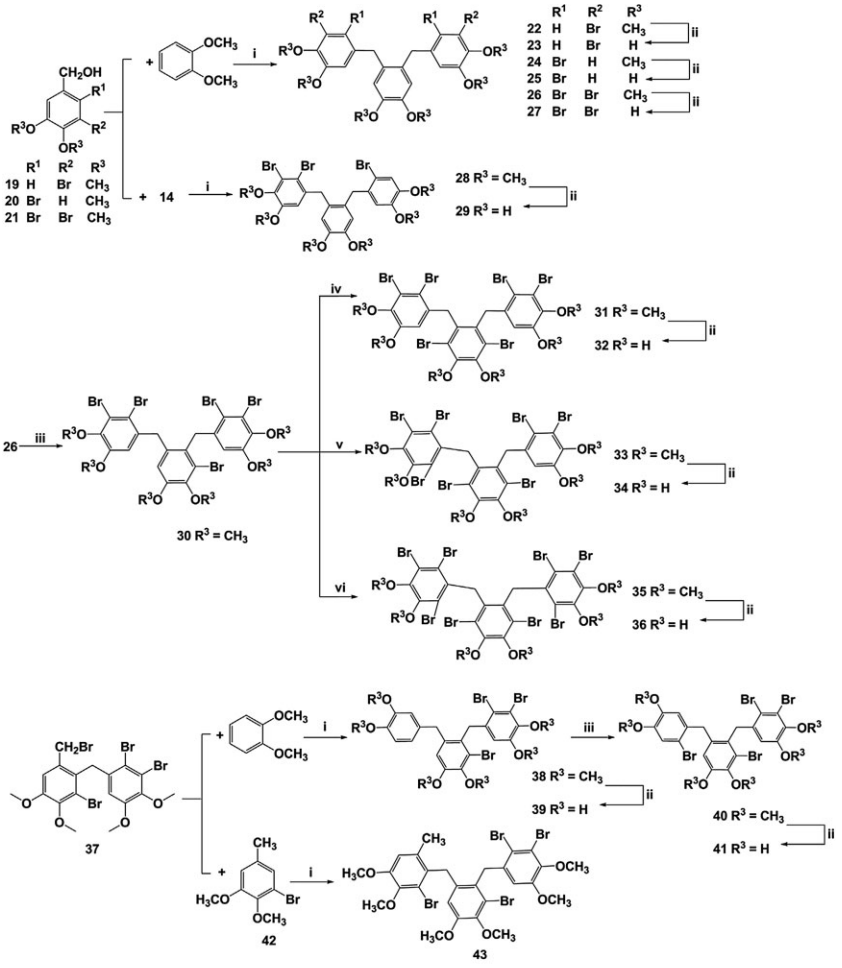
In vitro PTP1B inhibitory assay

All the derivatives were evaluated in the enzyme inhibition assay against human recombinant PTP1B. Firstly, we measured the percentage inhibitory rates of all the derivatives at concentration of 20 μg/mL, and the compounds with good inhibition rates (>90% at 20 μg/mL) were selected for IC_{50} assay. As summarized in Table 1, all of the compounds exhibited a broad range (potent to inactive) of PTP1B inhibitory activities at 20 μg/mL. Compounds **17**, **23**, **25**–**34**, **38**–**41**, **45**, and **48**–**50** exhibited good PTP1B inhibitory activity with the inhibition range from 60.31% (**17**) to 100.21% (**30**). In general, the tricyclic scaffold compounds (**22**–**46**) exhibited more potent PTP1B inhibition than the bicyclic and tetracyclic ones. Among them, **26**, **30**, **39**–**41**, and **45** had inhibitory activities (93.44–100.21%) much higher than that of the initial lead BDB (80.18% inhibition at 20 μg/mL), indicating



Reagents and conditions: (i) $KMnO_4$, $NaHCO_3$, H_2O, 90°C; (ii) veratrole, PPA, 80°C; (iii) $NaBH_4$, TFA, 0°C; (iv) $AlCl_3$, CH_2Cl_2, r.t.

Scheme 1. Synthesis of bicyclic scaffold compounds.



Reagents and conditions: (i) $AlCl_3$, CH_2Cl_2, 0°C; (ii) BBr_3, CH_2Cl_2, 0°C -r.t.; (iii) Br_2, CH_2Cl_2, r.t.; (iv) NBS (1 eqv), conc. H_2SO_4, AcOH, 0°C; (v) NBS (2 eqv), conc. H_2SO_4, AcOH, 0°C; (vi) NBS (4 eqv), conc. H_2SO_4, AcOH, 0°C.

Scheme 2. Synthesis of tricyclic scaffold compounds.

that the tricyclic scaffold is favorable to PTP1B inhibitory activity. It is of interest that compounds with four or five bromine atoms attached to the tricyclic scaffold (**26**, **30**, and **39**–**41**) displayed significant PTP1B inhibitory activity, but a further increase in the number of bromine substitution (**35** and **36**) resulted in a loss of PTP1B inhibition (25.61 and 35.43%). In addition, there is no obvious potency difference between compounds with free hydroxyl and their corresponding methylating ones. To determine the exact potency of the compounds that possessed potent inhibitory activities against PTP1B, compounds **26**, **30**, and **40** were selected for further determination of IC_{50} values and the results are shown in Table 2. It is notable that compound **26** exhibited remarkable inhibitory activity against PTP1B with an IC_{50} of 0.89 μmol/L, which was approximately two-fold more potent than the initial lead compound BDB (IC_{50} = 1.7 μmol/L).

Conclusion

In summary, a series of bromophenol derivatives were designed and synthesized for the discovery of more potent PTP1B inhibitors based on the initial hit BDB. The results showed that the derivatives exhibited a broad range of PTP1B inhibitory activity *in vivo*. The preliminary SAR acquired indicate that (i) the tricyclic scaffold is favorable to PTP1B inhibitory activity and (ii) multi-bromine atoms (four to five) attached to the tricyclic scaffold are important for PTP1B inhibition. Among these, compound **26** exhibited remarkable inhibitory activity against PTP1B with 0.89 μmol/L, which was approximately two-fold more potent than the initial lead compound BDB (IC_{50} = 1.7 μmol/L). As an interesting entity, compound **26** is currently used for further investigation including anti-hyperglycemic activity *in vivo*

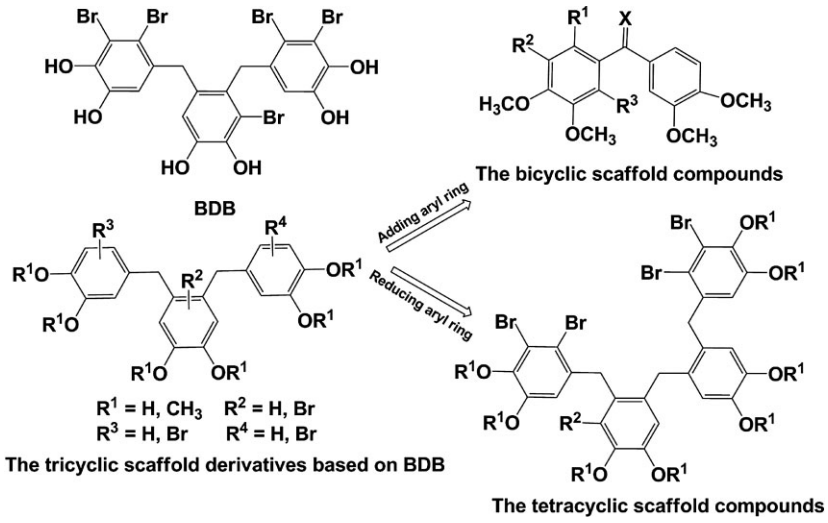
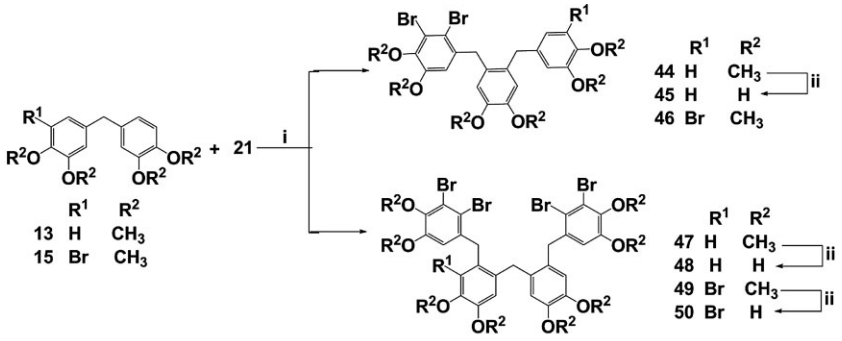


Figure 1. Structures of lead compound BDB and the derivatives.



Reagents and conditions: (i) $AlCl_3$, CH_2Cl_2, r.t.; (ii) BBr_3, CH_2Cl_2, 0°C -r.t

Scheme 3. Synthesis of tetracyclic scaffold compounds.

and selectivity against other PTPase, and the results will be reported in due course.

Experimental

Chemistry

Melting points were determined using a Boetius electrothermal capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C-NMR spectra were recorded on an Inova spectrometer operating at 500 and 125 MHz, respectively. High-resolution mass spectra (HRMS) were obtained on an Autospec Ultima-Tof mass spectrometer. Column chromatography was carried out using silica gel (200–300 mesh). Thin-layer chromatography (TLC) was performed on silica gel GF_{254}. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification.

*General procedure for synthesis of compounds **5–8***

Corresponding benzaldehydes **1–4** (30 mmol) and $NaHCO_3$ (30 mmol) were suspended in 100 mL H_2O. The mixture was heated to 90°C, then $KMnO_4$ (30 mmol) was added over 1 h, and TLC was used to monitor the reaction. After the reaction, MnO_2 was filtered and the filtrate was acidified to pH = 2 by adding 10% HCl. The precipitate was collected to afford white solids **5–8** in 70–90% yield.

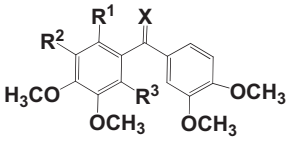
*General procedure for synthesis of compounds **9–12***

Benzoic acids **5–8** (20 mmol) and veratrol (20 mmol) were stirred in 50 g of PPA at 80°C for 2 h, the mixture was poured into ice-water. The precipitate was filtered and dissolved in 100 mL CH_2Cl_2, washed with 10% Na_2CO_3, and brine successively. The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give compounds **9–12**.

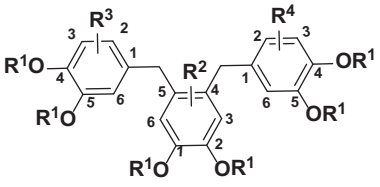
*Bis-(3,4-dimethoxyphenyl)methanone **9***

Yield 86%, white solid. m.p. 145–146°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.42 (d, J = 1.7 Hz, 2H, ArH × 2), 7.36 (dd, J = 8.4 and 1.7 Hz, 2H, ArH × 2), 6.88 (d, J = 8.4 Hz, 2H, ArH × 2), 3.94 (s, 6H, OCH_3 × 2), 3.92 (s, 6H, OCH_3 × 2): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 194.4, 152.6, 148.9, 130.8, 124.7, 112.4, 109.8, 56.0.

Table 1. Structures and *in vitro* inhibitory activity of compounds against PTP1B



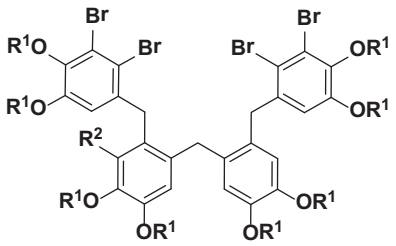
Compds	R^1	R^2	R^3	X	% Inhibition at 20 μg/mL
9	H	H	H	O	2.72
10	Br	H	H	O	12.98
11	H	Br	H	O	12.54
12	Br	Br	H	O	35.56
13	H	H	H	H	3.43
14	Br	H	H	H	12.42
15	H	Br	H	H	15.81
16	Br	Br	H	H	46.85
17	Br	Br	Br	H	60.31



Compds	R^1	R^2	R^3	R^4	% Inhibition at 20 μg/mL
22	CH_3	H	3-Br	3-Br	45.78
23	H	H	3-Br	3-Br	80.79
24	CH_3	H	2-Br	2-Br	25.08
25	H	H	2-Br	2-Br	79.48
26	CH_3	H	2,3-Br	2,3-Br	97.48
27	H	H	2,3-Br	2,3-Br	63.27
28	CH_3	H	2-Br	2,3-Br	70.19
29	H	H	2-Br	2,3-Br	79.04
30	CH_3	3-Br	2,3-Br	2,3-Br	100.21
31	CH_3	3,6-Br	2,3-Br	2,3-Br	66.43
32	H	3,6-Br	2,3-Br	2,3-Br	60.21
33	CH_3	3,6-Br	2,3,6-Br	2,3-Br	77.22
34	H	3,6-Br	2,3,6-Br	2,3-Br	56.99
35	CH_3	3,6-Br	2,3,6-Br	2,3,6-Br	25.61
36	H	3,6-Br	2,3,6-Br	2,3,6-Br	35.43
38	CH_3	3-Br	H	2,3-Br	68.48
39	H	3-Br	H	2,3-Br	93.44
40	CH_3	3-Br	2-Br	2,3-Br	96.50
41	H	3-Br	2-Br	2,3-Br	96.06
44	CH_3	H	H	2,3-Br	7.39
45	H	H	H	2,3-Br	94.64
46	CH_3	H	3-Br	2,3-Br	49.74
BDB	H	3-Br	2,3-Br	2,3-Br	80.18

continued

Table 1. (*continued*)



Compds	R^1	R^2	% Inhibition at 20 μg/mL
47	CH_3	H	24.84
48	H	H	68.67
49	CH_3	Br	68.24
50	H	Br	60.46

Table 2. Determination of IC_{50} values of selected compounds

Compds	IC_{50} (μmol/L)
26	0.89
30	3.10
40	1.34
BDB	1.70

*(2-Bromo-4,5-dimethoxyphenyl)-(3,4-dimethoxyphenyl)methanone **10***

Yield 87%, white solid. m.p. 129–130°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.54 (d, J = 1.9 Hz, 1H, Ar*H*), 7.25 (dd, J = 8.4 and 1.9 Hz, 1H, Ar*H*), 7.07 (s, 1H, Ar*H*), 6.87 (s, 1H, Ar*H*), 6.85 (d, J = 8.4 Hz, 1H, Ar*H*), 3.94 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 194.2, 153.9, 150.7, 149.3, 148.3, 132.9, 129.6, 126.2, 115.8, 112.1, 111.4, 110.7, 110.0, 56.3, 56.2, 56.1, 56.0.

*(3-Bromo-4,5-dimethoxyphenyl)-(3,4-dimethoxyphenyl)methanone **11***

Yield 85%, white solid. m.p. 131–132°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.53 (s, 1H, Ar*H*), 7.46 (s, 1H, Ar*H*), 7.38 (d, J = 8.0 Hz, 1H, Ar*H*), 7.35 (s, 1H, Ar*H*), 6.93 (d, J = 8.0 Hz, 1H, Ar*H*), 3.99 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 193.4, 153.5, 153.1, 149.6, 149.0, 134.7, 129.7, 127.1, 125.2, 117.0, 112.7, 112.0, 109.8, 60.8, 56.2, 56.1.

*(2,3-Dibromo-4,5-dimethoxyphenyl)-(3,4-dimethoxyphenyl)methanone **12***

Yield 85%, white solid. m.p. 146–147°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.60 (s, 1H, Ar*H*), 7.21(d, J = 8.0 Hz, 1H, Ar*H*), 6.85–6.86 (m, 2H, Ar*H* × 2), 3.94 (s, 3H, OCH_3), 3.96 (s, 6H, OCH_3 × 2), 3.92 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3): ^{13}C-NMR

(125 MHz, $CDCl_3$) δ: 193.6, 154.2, 152.6, 149.4, 148.4, 138.1, 128.5, 126.7, 122.6, 112.7, 111.0, 110.7, 110.0, 60.7, 56.3, 56.2, 56.1.

*General procedure for synthesis of compounds **13–16***

To a solution of compounds **9–10** (10 mmol) in 20 mL TFA was added sodium borohydride (100 mmol) over 30 min. After the reaction, the mixture was poured into water and extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was combined and dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give compounds **13–16**.

*Bis-(3,4-dimethoxyphenyl)methane **13***

Yield 89%, pale solid. m.p. 70–71°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.79 (d, J = 7.6 Hz, 2H, Ar*H* × 2), 6.72 (d, J = 1.9 Hz, 2H, Ar*H* × 2), 6.69 (dd, J = 7.6 and 1.9 Hz, 2H, Ar*H* × 2), 3.88 (s, 2H, ArC*H*$_2$Ar), 3.85 (s, 6H, OC*H*$_3$ × 2), 3.83 (s, 6H, OC*H*$_3$ × 2): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 149.0, 147.5, 133.9, 120.8, 112.4, 111.4, 55.9, 55.8, 41.0.

*1-Bromo-2-(3,4-dimethoxybenzyl)-4,5-dimethoxybenzene **14***

Yield 88%, white solid. m.p. 74–75°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.04 (s, 1H, Ar*H*), 6.79 (d, J = 8.0 Hz, 1H, Ar*H*), 6.73 (d, J = 1.9 Hz, 1H, Ar*H*), 6.69 (dd, J = 8.0 and 1.9 Hz, 1H, Ar*H*), 6.64 (s, 1H, Ar*H*), 3.99 (s, 2H, ArC*H*$_2$Ar), 3.86 (s, 3H, OC*H*$_3$), 3.85 (s, 3H, OC*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 3.76 (s, 3H, OC*H*$_3$): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 149.1, 148.6, 148.2, 147.6, 132.6, 132.5, 120.8, 115.7, 114.5, 113.7, 112.3, 111.4, 56.2, 56.1, 55.9, 55.8, 40.9.

*1-Bromo-5-(3,4-dimethoxybenzyl)-2,3-dimethoxybenzene **15***

Yield 91%, white solid. m.p. 64–65°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.94 (s, 1H, Ar*H*), 6.82 (d, J = 8.12 Hz, 1H, Ar*H*), 6.72 (d, J = 8.12 Hz, 1H, Ar*H*), 6.68 (s, 1H, Ar*H*), 6.65 (s, 1H, Ar*H*), 3.87 (s, 3H, OC*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 3.85 (s, 2H, ArC*H*$_2$Ar), 3.83 (s, 3H, OC*H*$_3$), 3.80 (s, 3H, OC*H*$_3$): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 153.6, 149.1, 147.8, 144.8, 138.5, 132.8, 124.8, 120.9, 117.5, 112.4, 111.5, 60.5, 56.1, 55.9 × 2, 40.9. HRMS for $C_{17}H_{19}O_4{}^{79}Br$ $[M+H]^+$: Calcd., 366.0467; found, 366.0464.

*2,3-Dibromo-1-(3,4-dimethoxybenzyl)-4,5-dimethoxybenzene **16***

Yield 88%, white solid. m.p. 91–92°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.82 (d, J = 8.17 Hz, 1H, Ar*H*), 6.74 (s, 1H, Ar*H*), 6.70 (d, J = 8.17 Hz, 1H, Ar*H*), 6.65 (s, 1H, Ar*H*), 4.08 (s, 2H, ArC*H*$_2$Ar), 3.87 (s, 3H, OC*H*$_3$), 3.85 (s, 3H, OC*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 3.75 (s, 3H, OC*H*$_3$): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 152.4, 149.1, 147.8, 146.2, 138.1, 131.6, 121.9, 121.0, 117.8, 113.7, 112.5, 111.4, 60.5, 56.2, 55.9 × 2, 43.0. HRMS for $C_{17}H_{18}O_4{}^{79}Br{}^{81}Br$ $[M+H]^+$: Calcd., 445.9551; found, 445.9550.

*Procedure for synthesis of compound **18***

To a solution of compound **17** [26] (5 mmol) and veratrole (5 mmol) in 10 mL dry CH_2Cl_2 was added $AlCl_3$ (7 mmol). The mixture was stirred at 35°C for 5 h and poured into ice-water. The organic phase was washed with 1 M HCl and brine successively, then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was recrystallized in methanol to give compound **18**.

*1,2,4-Tribromo-3-(3,4-dimethoxybenzyl)-5,6-dimethoxybenzene **18***

Yield 56%, white solid. m.p. 88–89°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.79 (s, 1H, Ar*H*), 6.76 (d, J = 8.23 Hz, 1H, Ar*H*), 6.63 (d, J = 8.23 Hz, 1H, Ar*H*), 4.47 (s, 2H, ArC*H*$_2$Ar), 3.91 (s, 3H, OC*H*$_3$), 3.90 (s, 3H, OC*H*$_3$), 3.84 (s, 3H, OC*H*$_3$), 3.83 (s, 3H, OC*H*$_3$): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 150.8, 150.7, 149.0, 147.7, 137.7, 130.0, 123.2, 121.7, 121.2, 120.2, 112.2, 111.3, 60.8, 60.7, 56.0, 55.9. HRMS for $C_{17}H_{17}O_4{}^{79}Br_2{}^{81}Br$ $[M+H]^+$: Calcd., 523.8656; found, 523.8679.

*General procedure for synthesis of compounds **22**, **24**, and **26***

$AlCl_3$ (10 mmol) was added slowly to the solution of the corresponding benzylalcohols **19–21** [26] (6 mmol) and veratrole (3 mmol) in 10 mL dry CH_2Cl_2 at 0°C with stirring. After the reaction, the mixture was poured into ice-water. The organic phase was washed with 1 M HCl and brine successively, then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was recrystallized in methanol to give compounds **22**, **24**, and **26**.

*5-(2-(3-Bromo-4,5-dimethoxybenzyl)-4,5-dimethoxybenzyl)-1-bromo-2,3-dimethoxybenzene **22***

Yield 80%, white solid. m.p. 120–122°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.74 (s, 2H, Ar*H* × 2), 6.68 (s, 2H, Ar*H* × 2), 6.46 (s, 2H, Ar*H* × 2), 3.84 (s, 4H, ArC*H*$_2$Ar × 2), 3.81 (s, 12H, OC*H*$_3$ × 4), 3.74 (s, 6H, OC*H*$_3$ × 2): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 153.5, 147.9, 144.7, 137.9, 130.2, 124.3, 117.5, 114.4, 112.1, 60.5, 56.1, 56.0, 38.2. HRMS for $C_{26}H_{28}O_6{}^{79}Br{}^{81}Br$ $[M+H]^+$: Calcd., 596.0232; found, 596.0206.

*1-(2-(2-Bromo-4,5-dimethoxybenzyl)-4,5-dimethoxybenzyl)-2-bromo-4,5-dimethoxybenzene **24***

Yield 85%, white solid. m.p. 125–127°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.02 (s, 2H, Ar*H* × 2), 6.58 (s, 2H, Ar*H* × 2), 6.41 (s, 2H, Ar*H* × 2), 3.90 (s, 4H, ArC*H*$_2$Ar × 2), 3.85 (s, 6H, OC*H*$_3$ × 2), 3.78 (s, 6H, OC*H*$_3$ × 2), 3.72 (s, 6H, OC*H*$_3$ × 2): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 148.5, 148.1, 147.6, 131.8, 130.1, 115.6, 114.7, 113.6, 113.4, 56.2, 55.9 × 2, 38.4. HRMS for $C_{26}H_{28}O_6{}^{79}Br{}^{81}Br$ $[M+H]^+$: Calcd., 596.0232; found, 596.0243.

*1-(2-(2,3-Dibromo-4,5-dimethoxybenzyl)-4,5-dimethoxybenzyl)-2,3-dibromo-4,5-dimethoxybenzene **26***

Yield 90%, white solid. m.p. 152–154°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.63 (s, 2H, Ar*H* × 2), 6.38 (s, 2H, Ar*H* × 2), 3.96 (s, 4H, ArC*H*$_2$Ar × 2), 3.82 (s, 6H, OC*H*$_3$ × 2), 3.79 (s, 6H, OC*H*$_3$ × 2), 3.65 (s, 6H, OC*H*$_3$ × 2); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 152.3, 148.0, 146.2, 137.1, 129.7, 121.8, 117.8, 114.2, 113.4, 60.5, 56.1, 40.9. HRMS for $C_{26}H_{26}O_6{}^{79}Br_2{}^{81}Br_2$ $[M+H]^+$: Calcd., 753.8422; found, 753.8428.

*Procedure for synthesis of compound **28***

$AlCl_3$ (12 mmol) was added slowly to the solution of compound **21** (10 mmol) and **14** (10 mmol) in 10 mL dry CH_2Cl_2 at 0°C with stirring. The mixture was warmed to room temperature and stirred for a further 30 min. Then the mixture was poured into ice-water. The organic phase was washed with 1 M HCl and brine successively, then dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on a silica gel column (petroleum ether/ethyl acetate, 5:1) to afford compound **28**.

1-(2-(2-Bromo-4,5-dimethoxybenzyl)-4,5-dimethoxybenzyl)-2,3-dibromo-4,5-dimethoxybenzene ***28***

Yield 77%, white solid. m.p. 110–112°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.00 (s, 1H, Ar*H*), 6.61 (s, 2H, Ar*H* × 2), 6.41 (s, 1H, Ar*H*), 6.38 (s, 1H, Ar*H*), 3.99 (s, 2H, ArCH_2Ar), 3.87 (s, 2H, ArCH_2Ar), 3.84 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 152.4, 148.5, 148.2, 147.9, 147.8, 146.2, 137.4, 131.6, 130.4, 129.4, 121.8, 117.9, 115.6, 114.7, 114.0, 113.8, 113.4, 113.3, 60.5, 56.2, 56.1 × 2, 56.0 × 2, 40.7, 38.5. HRMS for $C_{26}H_{27}O_6{}^{79}Br_2{}^{81}Br$ $[M+H]^+$: Calcd., 673.9337; found, 673.9360.

Procedure for synthesis of compound ***30***

To solution of **26** (10 mmol) in 50 mL CH_2Cl_2 was added dropwise bromine (15 mmol) while stirring. The mixture was stirred at room temperature for further 24 h, then was washed with 5% Na_2SO_3, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was recrystallized in methanol to give compound **30**.

1,2-Bis(2,3-dibromo-4,5-dimethoxybenzyl)-3-bromo-4,5-dimethoxybenzene ***30***

Yield 81%, white solid. m.p. 178–180°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.60 (s, 1H, Ar*H*), 6.45 (s, 1H, Ar*H*), 6.14 (s, 1H, Ar*H*), 4.20 (s, 2H, ArCH_2Ar), 3.96 (s, 2H, ArCH_2Ar), 3.88 (s, 3H, OCH_3), 3.80 (s, 6H, OCH_3 × 2), 3.79 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 152.4, 152.3, 152.2, 146.5, 146.0, 145.6, 136.0, 135.4, 135.2, 129.9, 122.8, 122.1, 121.7, 118.1, 117.5, 114.0, 113.8, 111.9, 60.5, 60.4, 56.2, 56.1, 42.1, 40.5. HRMS for $C_{26}H_{25}O_6{}^{79}Br_3{}^{81}Br_2$ $[M+H]^+$: Calcd., 831.7527; found, 831.7531.

General procedure for synthesis of compounds ***31***, ***33***, *and* ***35***

To solution of **30** (0.6 mmol) in 20 mL conc. H_2SO_4 was added 10 mL glacial acetic acid at 0°C with stirring. After 5 min, NBS (0.6, 1.2, or 2.4 mmol) was added in portions and the mixture was stirred for a further 20 min. The mixture was poured into 50 mL ice-water and extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was combined and concentrated *in vacuo*, the residue was chromatographed on a silica gel column (petroleum ether/ethyl acetate, 8:1 or 30:1) to afford compounds **31**, **33**, and **35**.

1,2-Bis(2,3-dibromo-4,5-dimethoxybenzyl)-3,6-dibromo-4,5-dimethoxybenzene ***31***

Yield 40%, yellowish solid. m.p. 175–177°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.11 (s, 2H, Ar*H* × 2), 4.19 (s, 4H, ArCH_2Ar × 2), 3.97 (s, 6H, OCH_3 × 2), 3.78 (s, 6H, OCH_3 × 2), 3.61 (s, 6H, OCH_3 × 2): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 152.1, 150.5, 146.2, 135.7, 134.4, 122.4, 121.9, 117.8, 112.0, 60.9, 60.5, 56.2, 41.9. HRMS for $C_{26}H_{24}O_6{}^{79}Br_3{}^{81}Br_3$ $[M+H]^+$: Calcd., 911.6612; found, 911.6631.

1-(2-(2,3-Dibromo-4,5-dimethoxybenzyl)-3,6-dibromo-4,5-dimethoxybenzyl)-2,3,6-tribromo-4,5-dimethoxybenzene ***33***

Yield 40%, white solid. m.p. 195–196°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.95 (s, 1H, Ar*H*), 4.91 (s, 2H, ArCH_2Ar), 4.00 (s, 2H, ArCH_2Ar), 3.97 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.65 (s, 6H, OCH_3 × 2): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 151.6, 150.4 150.3, 150.2, 150.1, 145.2, 136.1, 136.0, 133.9, 133.6, 124.2, 122.9, 122.1, 121.6, 120.8, 116.2, 111.2, 60.9, 60.8, 60.7, 60.6, 60.4, 55.7, 44.1, 43.0.

1-(2-(2,3,6-Tribromo-4,5-dimethoxybenzyl)-3,6-dibromo-4,5-dimethoxybenzyl)-2,3,6-tribromo-4,5-dimethoxybenzene ***35***

Yield 51%, white solid. m.p. 164–165°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.52 (s, 4H, ArCH_2Ar × 2), 3.88 (s, 6H, OCH_3 × 2), 3.87 (s, 6H, OCH_3 × 2), 3.85 (s, 6H, OCH_3 × 2): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 150.7, 150.6, 149.9, 136.4, 135.6, 123.1, 122.9, 122.2, 122.1, 121.7, 121.5, 121.3, 61.0, 60.9, 60.8, 44.1.

Procedure for synthesis of compounds ***38*** *and* ***43***

The preparations of compounds **38** and **43** were according to the general procedure for synthesis of compounds **22**, **24**, and **26**.

2-(2,3-Dibromo-4,5-dimethoxybenzyl)-1-(3,4-dimethoxybenzyl)-3-bromo-4,5-dimethoxybenzene ***38***

Yield 84%, yellowish solid. m.p. 137–138°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.79 (s, 1H, Ar*H*), 6.66 (d, J = 8.05 Hz, 1H, Ar*H*), 6.51 (d, J = 8.05 Hz, 1H, Ar*H*), 6.49 (s, 1H, Ar*H*), 5.98 (s, 1H, Ar*H*), 4.18 (s, 2H, ArCH_2Ar), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.78 (s, 2H, ArCH_2Ar), 3.76 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 152.2, 152.1, 148.8, 147.5, 145.9, 145.3, 137.3, 135.7, 131.9, 129.7, 122.8, 121.4, 120.5.6, 117.3, 114.1, 112.2, 112.0, 111.3, 60.5, 60.4, 56.1, 55.9, 55.8, 55.7, 40.3, 39.9. HRMS for $C_{26}H_{27}O_6{}^{79}Br_2{}^{81}Br$ $[M+H]^+$: Calcd., 673.9337; found, 673.9361.

2-(2,3-Dibromo-4,5-dimethoxybenzyl)-1-(2-bromo-3,4-dimethoxy-6-methylbenzyl)-3-bromo-4,5-dimethoxybenzene ***43***

Yield 65%, yellow solid. m.p. 106–107°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.71 (s, 1H, Ar*H*), 6.29 (s, 1H, Ar*H*), 6.13 (s, 1H, Ar*H*), 4.36 (s, 2H, ArCH_2Ar), 3.89 (s, 2H, ArCH_2Ar), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 2.03 (s, 3H, ArCH_3): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 152.5, 152.3, 151.9, 146.3, 145.0, 144.9, 135.6, 135.1, 134.0, 129.5, 129.3, 122.5, 122.2, 121.8, 117.7, 113.8, 112.0, 111.2, 60.5, 60.4 × 2, 56.1, 56.1, 55.9, 40.3, 36.4, 20.6. HRMS for $C_{27}H_{28}O_6{}^{79}Br_2{}^{81}Br_2$ $[M+H]^+$: Calcd., 767.8578; found, 767.8611.

Procedure for synthesis of compound ***40***

The preparation of compound **40** was according to the procedure for synthesis of compound **28**.

2-(2,3-Dibromo-4,5-dimethoxybenzyl)-1-(2-bromo-4,5-dimethoxybenzyl)-3-bromo-4,5-dimethoxybenzene ***40***

Yield 82%, yellowish solid. m.p. 151–152°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.97 (s, 1H, Ar*H*), 6.56 (s, 1H, Ar*H*), 6.41 (s, 1H, Ar*H*), 6.16 (s, 1H, Ar*H*), 4.23 (s, 2H, ArCH_2Ar), 3.87 (s, 3H, OCH_3), 3.86 (s, 2H, ArCH_2Ar), 3.84 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 152.3, 152.2, 148.5, 148.4, 146.1, 145.3, 135.9, 135.6, 130.5, 129.7, 122.7, 121.6, 117.6, 115.7, 114.9, 113.8, 113.5, 112.1, 60.5, 60.4,

56.2, 56.1, 56.0 × 2, 40.4, 39.7. HRMS for $C_{26}H_{26}O_6{}^{79}Br_2{}^{81}Br_2$ $[M+H]^+$: Calcd., 753.8422; found, 753.8416.

*General procedure for synthesis of compounds **44**, **46**, **47**, and **49***

The preparations of compounds **44**, **46**, **47**, and **49** were according to the general procedure for synthesis of compounds **22**, **24**, and **26**.

*2,3-Dibromo-1-(2-(3,4-dimethoxybenzyl)-4,5-dimethoxybenzyl)-4,5-dimethoxybenzene **44***

Yield 32%, white solid. m.p. 151–152°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.76 (s, 1H, Ar*H*), 6.71 (d, J = 7.94 Hz, 1H, Ar*H*), 6.60 (s, 1H, Ar*H*), 6.57 (d, J = 7.94 Hz, 1H, Ar*H*), 6.56 (s, 1H, Ar*H*), 6.22 (s, 1H, Ar*H*), 3.97 (s, 2H, ArCH_2Ar), 3.87 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.79 (s, 2H, ArCH_2Ar), 3.77 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 152.2, 148.4, 147.8, 147.7, 147.3, 146.0, 137.7, 133.0, 131.9, 129.3, 121.6, 120.4, 117.5, 114.1, 114.0, 113.1, 112.0, 111.2, 60.5, 56.1, 56.0, 55.9, 55.8, 55.7, 40.5, 38.5. HRMS for $C_{20}H_{16}O_6{}^{79}Br^{81}Br$ $[M+H]^+$: Calcd., 596.0232; found, 596.0205.

*2,3-Dibromo-1-(2-(3-bromo-4,5-dimethoxybenzyl)-4,5-dimethoxybenzyl)-4,5-dimethoxybenzene **46***

Yield 31%, white solid. m.p. 126–127°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.77 (s, 1H, Ar*H*), 6.69 (s, 1H, Ar*H*), 6.62 (s, 1H, Ar*H*), 6.50 (s, 1H, Ar*H*), 6.14 (s, 1H, Ar*H*), 3.95 (s, 2H, ArCH_2Ar), 3.90 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.79 (s, 2H, ArCH_2Ar), 3.78 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 153.2, 152.2, 147.9, 147.8, 145.9, 144.5, 137.5, 137.3, 130.8, 129.4, 124.1, 121.5, 117.4, 117.3, 114.3 × 2, 112.8, 112.1, 60.5, 60.4, 56.1 × 2, 56.0, 55.9, 40.7, 38.6. HRMS for $C_{26}H_{27}O_6{}^{79}Br_2{}^{81}Br$ $[M+H]^+$: Calcd., 673.9337; found, 673.9359.

*Bis(2-(2,3-dibromo-4,5-dimethoxybenzyl)-4,5-dimethoxyphenyl)methane **47***

Yield 30%, white solid. m.p. 161–162°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.55 (s, 2H, Ar*H* × 2), 6.52 (d, 2H, Ar*H* × 2), 6.34 (s, 2H, Ar*H* × 2), 3.87 (s, 4H, ArCH_2Ar × 2), 3.79 (s, 12H, OCH_3 × 4), 3.75 (s, 6H, OCH_3 × 2), 3.63 (s, 2H, ArCH_2Ar), 3.61 (s, 6H, OCH_3 × 2): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 152.4, 147.8, 147.6, 146.2, 137.3, 130.9, 129.3, 121.8, 117.7, 113.8, 113.5, 113.1, 60.5, 56.1, 56.0, 40.6, 35.6, 30.8. HRMS for $C_{35}H_{36}O_8{}^{79}Br_2{}^{81}Br_2$ $[M+H]^+$: Calcd., 903.9103; found, 903.9070.

*2,3-Dibromo-1-(2-(3-bromo-2-(2,3-dibromo-4,5-dimethoxybenzyl)-4,5-dimethoxybenzyl)-4,5-dimethoxybenzyl)-4,5-dimethoxybenzene **49***

Yield 46%, white solid. m.p. 102–103°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.49 (s, 1H, Ar*H*), 6.48 (s, 1H, Ar*H*), 6.45 (s, 1H, Ar*H*), 6.32 (s, 1H, Ar*H*), 6.15 (s, 1H, Ar*H*), 4.17 (s, 2H, ArCH_2Ar), 3.86 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.78 (s, 2H, ArCH_2Ar), 3.77 (s, 6H, OCH_3 × 2), 3.74 (s, 6H, OCH_3 × 2), 3.65 (s, 3H, OCH_3), 3.64 (s, 2H, ArCH_2Ar), 3.53 (s, 3H, OCH_3): ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 152.5, 152.4, 152.2, 147.8, 146.2, 137.0, 136.5, 135.6, 129.9, 129.8, 129.5, 122.8, 121.9, 121.7, 117.7, 117.5, 113.8, 113.7, 113.4, 113.1, 111.8, 60.5 × 2, 60.4 × 2, 56.2 × 2, 56.0 × 2, 40.7, 40.2, 37.1. HRMS for $C_{35}H_{36}O_8{}^{79}Br_3{}^{81}Br_2$ $[M+H]^+$: Calcd., 978.8327; found, 978.8346.

General procedure for synthesis of demethylate compounds

Compounds **22**, **24**, **26**, **28**, **31**, **33**, **35**, **38**, **40**, **44**, **47**, and **49** (2 mmol) were dissolved in 10 mL dry CH_2Cl_2, then 8 mL BBr_3 (1 mol/L in CH_2Cl_2) was added dropwise while stirring in ice bath. The reaction mixture was stirred for a further 4 h at room temperature. Then the solution was poured into ice-cold water and extracted with EtOAc (3 × 60 mL). The organic extract was dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH, 15:1) to afford the corresponding demethylate compounds.

*5-(2-(3-Bromo-4,5-dihydroxybenzyl)-4,5-dihydroxybenzyl)-3-bromobenzene-1,2-diol **23***

Yield 80%, pale solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 9.61 (s, 2H, O*H* × 2), 8.86 (s, 2H, O*H* × 2), 8.65 s, 2H, O*H* × 2), 6.58 (s, 2H, Ar*H* × 2), 6.55 (s, 2H, Ar*H* × 2), 6.46 (s, 2H, Ar*H* × 2), 3.55 (s, 4H, ArCH_2Ar × 2); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 146.1, 143.4, 140.8, 133.2, 129.2, 122.3, 117.5, 114.5, 109.6, 35.9. HRMS for $C_{20}H_{16}O_6{}^{79}Br^{81}Br$ $[M+H]^+$: Calcd., 511.9293; found, 511.9253.

*4-(2-(2-Bromo-4,5-dihydroxybenzyl)-4,5-dihydroxybenzyl)-5-bromobenzene-1,2-diol **25***

Yield 88%, brownish solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 9.16 (s, 2H, O*H* × 2), 9.07 (s, 2H, O*H* × 2), 8.62 (s, 2H, O*H* × 2), 6.91 (s, 2H, Ar*H* × 2), 6.41 (s, 2H, Ar*H* × 2), 6.35 (s, 2H, Ar*H* × 2), 3.58 (s, 4H, ArCH_2Ar × 2): ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 145.0, 144.7, 143.4, 130.1, 128.4, 118.8, 117.4, 117.0, 111.6, 36.8. HRMS for $C_{20}H_{16}O_6{}^{79}Br^{81}Br$ $[M+H]^+$: Calcd., 511.9293; found, 511.9254.

*5-(2-(2,3-Dibromo-4,5-dihydroxybenzyl)-4,5-dihydroxybenzyl)-3,4-dibromobenzene-1,2-diol **27***

Yield 88%, brownish solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 9.88 (s, 2H, O*H* × 2), 9.38 (s, 2H, O*H* × 2), 8.68 (s, 2H, O*H* × 2), 6.50 (s, 2H, Ar*H* × 2), 6.36 (s, 2H, Ar*H* × 2), 3.68 (s, 4H, ArCH_2Ar × 2): ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 145.2, 143.6, 142.9, 131.7, 128.1, 117.1, 115.9, 114.9, 113.3, 48.6. HRMS for $C_{20}H_{14}O_6{}^{79}Br_2{}^{81}Br_2$ $[M+H]^+$: Calcd., 669.7483; found, 669.7458.

*4-(2,3-Dibromo-4,5-dihydroxybenzyl)-5-(2-bromo-4,5-dihydroxybenzyl)benzene-1,2-diol **29***

Yield 78%, brownish solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 9.87 (s, 1H, O*H*), 9.37 (s, 1H, O*H*), 9.17 (s, 1H, O*H*), 9.07 (s, 1H, O*H*), 8.65 (s, 1H, O*H*), 8.64 (s, 1H, O*H*), 6.91 (s, 1H, Ar*H*), 6.48 (s, 1H, Ar*H*), 6.42 (s, 1H, Ar*H*), 6.36 (s, 1H, Ar*H*), 6.35 (s, 1H, Ar*H*), 3.69 (s, 2H, ArCH_2Ar), 3.57 (s, 2H, ArCH_2Ar): ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 145.1, 145.0, 144.7, 143.5, 143.4, 142.8, 131.8, 129.9, 128.6, 127.9, 118.8, 117.4, 117.1, 117.0, 115.8, 114.9, 113.2, 111.6, 39.4, 36.8. HRMS for $C_{20}H_{15}O_6{}^{79}Br_2{}^{81}Br$ $[M+H]^+$: Calcd., 589.8398; found, 589.8417.

*5-(2-(2,3-Dibromo-4,5-dihydroxybenzyl)-3,6-dibromo-4,5-dihydroxybenzyl)-3,4-dibromobenzene-1,2-diol **32***

Yield 73%, yellowish solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 9.79 (s, 2H, O*H* × 2), 9.71 (s, 2H, O*H* × 2), 9.42 (s, 2H, O*H* × 2), 6.14 (s, 2H, Ar*H* × 2), 3.83 (s, 4H, ArCH_2Ar × 2): ^{13}C-NMR (125 MHz,

DMSO-d_6) δ: 145.1, 143.4, 142.9, 129.5, 129.3, 114.8, 114.5, 113.5, 113.4, 48.5. HRMS for $C_{20}H_{12}O_6{}^{79}Br_3{}^{81}Br_3$ $[M+H]^+$: Calcd., 827.5673; found, 827.5646.

4-(2-(2,3-Dibromo-4,5-dihydroxybenzyl)-3,6-dibromo-4,5-dihydroxybenzyl)-3,5,6-tribromobenzene-1,2-diol ***34***

Yield 73%, pale solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 9.69 (s, 1H, O*H*), 9.65 (s, 1H, O*H*), 9.55 (s, 1H, O*H*), 9.50 (s, 1H, O*H*), 9.47 (s, 1H, O*H*), 9.18 (s, 1H, O*H*), 5.99 (s, 1H, Ar*H*), 4.41 (s, 2H, ArC*H*$_2$Ar), 3.95 (s, 2H, ArC*H*$_2$Ar): ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 144.8, 143.6, 143.4, 142.9, 142.6, 142.5, 130.2, 129.7, 129.3, 129.0, 115.4, 115.3, 114.3, 114.1, 113.7, 112.9, 48.5, 42.7. HRMS for $C_{20}H_{21}O_6{}^{79}Br_4{}^{81}Br_3$ $[M+H]^+$: Calcd., 905.4778; found, 905.4727.

4-(2-(2,3,6-Tribromo-4,5-dihydroxybenzyl)-3,6-dibromo-4,5-dihydroxybenzyl)-3,5,6-tribromobenzene-1,2-diol ***36***

Yield 73%, yellowish solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 9.86 (s, 2H, O*H* × 2), 9.68 (s, 2H, O*H* × 2), 9.26 (s, 2H, O*H* × 2), 4.36 (s, 4H, ArC*H*$_2$Ar × 2): ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 143.7, 143.5, 142.2, 131.2, 130.5, 116.8, 114.6, 114.3, 42.9.

3,4-Dibromo-5-(2-bromo-6-(3,4-dihydroxybenzyl)-3,4-dihydroxybenzyl)benzene-1,2-diol ***39***

Yield 89%, brownish solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 9.77 (s, 1H, O*H*), 9.65 (s, 1H, O*H*), 9.33 (s, 1H, O*H*), 8.99 (s, 1H, O*H*), 8.74 (s, 1H, O*H*), 8.64 (s, 1H, O*H*), 6.62 (d, J = 6.49 Hz, 1H, Ar*H*), 6.60 (s, 1H, Ar*H*), 6.42 (s, 1H, Ar*H*), 6.30 (d, J = 6.49 Hz, 1H, Ar*H*), 6.13 (s, 1H, Ar*H*), 3.92 (s, 2H, ArC*H*$_2$Ar), 3.47 (s, 2H, ArC*H*$_2$Ar); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 145.1, 144.9, 144.5, 143.4, 142.7, 141.4, 131.8, 130.9, 130.3, 126.9, 119.1, 116.3, 115.8, 115.5, 114.5, 114.4, 113.8, 113.1, 38.6, 37.7. HRMS for $C_{20}H_{15}O_6{}^{79}Br_2{}^{81}Br$ $[M+H]^+$: Calcd., 589.8398; found, 589.8373.

3,4-Dibromo-5-(2-bromo-6-(2-bromo-4,5-dihydroxybenzyl)-3,4-dihydroxybenzyl)benzene-1,2-diol ***41***

Yield 88%, reddish solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 9.76 (s, 1H, O*H*), 9.65 (s, 1H, O*H*), 9.32 (s, 1H, O*H*), 9.23 (s, 1H, O*H*), 9.13 (s, 1H, O*H*), 9.03 (s, 1H, O*H*), 6.91 (s, 1H, Ar*H*), 6.43 (s, 1H, Ar*H*), 6.42 (s, 1H, Ar*H*), 6.17 (s, 1H, Ar*H*), 3.90 (s, 2H, ArC*H*$_2$Ar), 3.54 (s, 2H, ArC*H*$_2$Ar); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 145.1, 145.0, 144.9, 144.6, 142.7, 141.5, 130.4, 130.1, 129.2, 127.0, 118.9.0, 117.4, 115.5, 114.6, 114.5, 113.8, 113.1, 111.7, 38.1, 37.7. HRMS for $C_{20}H_{14}O_6{}^{79}Br_2{}^{81}Br_2$ $[M+H]^+$: Calcd., 669.7483; found, 669.7516.

3,4-Dibromo-5-(2-(3,4-dihydroxybenzyl)-4,5-dihydroxybenzyl)benzene-1,2-diol ***45***

Yield 83%, brownish solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 6.61 (d, J = 7.96 Hz, 1H, Ar*H*), 6.49 (s, 1H, Ar*H*), 6.45 (s, 1H, Ar*H*), 6.43 (s, 1H, Ar*H*), 6.35 (d, J = 7.96 Hz, 1H, Ar*H*), 6.30 (s, 1H, Ar*H*), 3.71 (s, 2H, ArC*H*$_2$Ar), 3.56 (s, 2H, ArC*H*$_2$Ar); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 145.1, 145.0, 143.4, 143.3, 143.1, 142.8, 132.1, 131.7, 130.2, 127.8, 119.2, 117.6, 116.9, 115.9, 115.8, 115.4, 114.8, 113.2, 79.1, 36.8. HRMS for $C_{35}H_{36}O_8{}^{79}Br^{81}Br$ $[M+H]^+$: Calcd., 511.9293; found, 511.9317.

5,5′-(6,6′-Methylenebis(3,4-dihydroxy-6,1-phenylene))-bis(methylene)bis(3,4-dibromobenzene-1,2-diol) ***48***

Yield 78%, brownish solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 9.88 (s, 2H, O*H* × 2), 9.33 (s, 2H, O*H* × 2), 8.60 (s, 4H, O*H* × 4), 6.44 (s, 2H, Ar*H* × 2), 6.37 (s, 2H, Ar*H* × 2), 6.35 (s, 2H, Ar*H* × 2), 3.62 (s, 4H, ArC*H*$_2$Ar × 2), 2.50 (s, 2H, ArC*H*$_2$Ar); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 145.1, 143.5, 143.2, 142.8, 132.0, 129.4, 127.9, 117.1, 117.0, 115.7, 114.8, 113.2, 79.1, 33.9.

3,4-Dibromo-5-(3-bromo-2-(2-(2,3-dibromo-4,5-dihydroxybenzyl)-4,5-dihydroxybenzyl)-4,5-dihydroxybenzyl)benzene-1,2-diol ***50***

Yield 81%, brownish solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 9.82 (s, 1H, O*H*), 9.71 (s, 1H, O*H*), 9.63 (s, 1H, O*H*), 9.33 (s, 1H, O*H*), 9.29 (s, 1H, O*H*), 8.99 (s, 1H, O*H*), 8.65 (s, 1H, O*H*), 8.64 (s, 1H, O*H*), 6.52 (s, 1H, Ar*H*), 6.42 (s, 1H, Ar*H*), 6.33 (s, 1H, Ar*H*), 6.32 (s, 1H, Ar*H*), 6.11 (s, 1H, Ar*H*), 3.83 (s, 2H, ArC*H*$_2$Ar), 3.56 (s, 2H, ArC*H*$_2$Ar), 3.30 (s, 2H, ArC*H*$_2$Ar); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 145.1 × 2, 144.6, 143.6, 143.4, 142.8, 142.7, 141.3, 131.8, 131.2, 130.2, 128.8, 128.0, 127.2, 117.1, 116.9, 116.0, 115.7, 114.8, 114.7, 114.5, 113.7, 113.3, 113.2, 79.1, 34.9.

In vitro PTP1B inhibitory assay

The derivatives were assessed against PTP1B with the colorimetric assay. Compounds were dissolved 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 following fomula:

$$\%\,\text{Inhibition} = 100 \times \frac{V_{\text{DMSO}} - V_{\text{sample}}}{V_{\text{DMSO}}}$$

This study was supported by grants from the National Major Research Program of China "The Creation for Significant Innovative Drugs" (No. 2009ZX09103-148), the National Natural Science Foundation of Shandong (No. BS2009YY011), the National Natural Science Foundation of Qingdao (No. 10-3-4-8-2-JCH), and the Program of Qingdao Shinan District (No. 2009-HY-2-14) for financial assistance.

The authors have declared no conflict of interest.

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