Supplementary Materials

Design and Synthesis of $\pi$-extended resveratrol analogues and in vitro antioxidant and anti-inflammatory activity evaluation

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General remarks

All starting materials, chemical and biological reagents, and solvents were purchased from commercial sources and used without any additional purification. Solvents used for reactions were purchased as either anhydrous grade products or freshly distilled using proper dehydrating agents. $^1$H NMR and $^{13}$C NMR spectra were recorded at room temperature on a Varian Mercury TM 300 MHz FT-NMR and JNM-ECZ400S (400 MHz) FT-NMR (JEOL Ltd., Tokyo, Japan). Chloroform-$d$/acetone-$d_6$/methanol-$d_4$/dimethyl sulfoxide-$d_6$ was used as a solvent. Chemical shifts (δ) were reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS). The following pattern was used for $^1$H NMR data: δ value (multiplicity (singlet = s), (doublet = d), (triplet = t), (quartet = q), (doublet of doublet = dd), and (multiplet = m), number of protons, coupling constants (J) quoted in Hz). Mass spectra analyses were taken on a JMS-700 (JEOL Ltd) spectrometer at the central laboratory of Kangwon National University. Melting points were uncorrected and observed on a MEL-TEMP II (Triad Scientific, Manasquan, NJ, USA) open capillary melting points apparatus. All reactions were monitored through thin-layer chromatography utilizing Merck silica gel plates 60 F$_{254}$ and spots visualization was accomplished by UV light absorption and/or p-anisaldehyde/phosphomolybdic acid stain. Silica gel 60 [230–400 mesh (40–63 μm), Merck, Darmstadt, Germany] was employed for chromatographic purification. Antioxidant activity was tested in the dark room by ABTS assay. UV-1800 (Shimadzu Corporation, Japan) was used to measure UV absorption. Hellma's 104.600-QC Quartz cell was used as a UV cell. IC$_{50}$ values were obtained using OriginPro 8.0 software.

Experimental procedure & Product Characterization

3,5-Dibenzylxybenzaldehyde (9)

\[
\begin{align*}
\text{R}_f &= 0.50 \text{ (EtOAc/hexane = 1/4)}; \\
^1\text{H NMR} \ (300 \text{ MHz, CDCl}_3): \delta &\ 9.85 \ (1\text{H, s), 7.39–7.31} \ (10\text{H, m), 7.08 (2H, s), 6.84 (1H, s), 5.06 (4H, s);} \\
^{13}\text{C NMR} \ (75 \text{ MHz, CDCl}_3): \delta &\ 191.3, 160.4,
\end{align*}
\]
Diethyl 3,5-bis(benzyloxy)benzylphosphonate (10)

\[
\begin{array}{c}
\text{PO(OEt)}_2 \\
\text{BnO} \\
\text{Bn}
\end{array}
\]

R\(_f\) = 0.3 (EtOAc/hexane = 1/1); \(^1^H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.39–7.27 (10H, m), 6.54 (2H, d, \(J = 2.4\) Hz), 6.49 (1H, t, \(J = 2.4\) Hz) 4.99 (4H, s), 4.01–3.93 (4H, m), 3.06 (2H, d, \(J = 21.5\) Hz), 1.23 (6H, t, \(J = 7.1\) Hz).

Benzyl 6-(benzyloxy)-2-naphthoate (12)

\[
\begin{array}{c}
\text{BnO} \\
\text{O} \\
\text{Bn}
\end{array}
\]

R\(_f\) = 0.64 (EtOAc/hexane = 1/2); \(^1^H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 8.52 (1H, s), 8.02 (1H, d, \(J = 8.4\) Hz), 7.80 (1H, d, \(J = 9.0\) Hz), 7.69 (1H, d, \(J = 8.4\) Hz), 7.44–7.19 (12H, m), 5.38 (2H, s), 5.14 (2H, s); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 166.5, 158.6, 137.1, 136.5, 136.3, 130.9, 128.5, 128.1, 127.4, 126.8, 125.9, 125.4, 119.8, 107.3, 70.2, 66.7

6-Benzylxxy-2-naphthaldehyde (13)

\[
\begin{array}{c}
\text{BnO} \\
\text{O} \\
\text{Bn}
\end{array}
\]

R\(_f\) = 0.32 (EtOAc/hexane = 1/7); \(^1^H\) NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 7.79–7.71 (3H, m), 7.50 (1H, s), 7.47 (1H, s), 7.41–7.31 (5H, s), 7.19 (1H, dd, \(J = 8.8, 2.9\) Hz), 5.20 (2H, s), 5.14 (1H, br s), 4.61 (2H, d, \(J = 5.4\) Hz); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 155.6, 137.5, 136.7, 132.9, 128.8, 128.1, 128.0, 127.4, 127.3, 126.1, 125.5, 124.1, 118.3, 107.2, 69.2, 62.8.
The reaction mixture of (6-(benzyloxy)naphthalen-2-yl)methanol (0.36 g, 1.36 mmol) and IBX (2-iodoxybenzoic acid, 0.57 g, 2.04 mmol) in DMSO (dimethyl sulfoxide, 5 mL) was stirred for 30 minutes at room temperature under argon. Then ethyl acetate (15 mL) was added to the reaction mixture and the organic layer was washed with sat. NaHCO₃ (20 mL x 3) and brine (20 mL x 3). The organic layer was dried over Na₂SO₄ and solvent was removed under reduced pressure. The desired product 6-benzyloxy-2-naphthaldehyde (1.2 g, 94.1%) was obtained as a light brown solid. Rᵣ = 0.31 (EtOAc/hexane = 1/7); ¹H NMR (300 MHz, CDCl₃): δ 10.07 (1H, s), 8.25 (1H, s), 7.90 (2H, d, J = 8.7 Hz), 7.79 (1H, d, J = 8.7 Hz), 7.24–7.49 (7H, m), 5.21 (2H, s); ¹³C NMR (75 MHz, CDCl₃): δ 191.3, 159.2, 138.0, 136.3, 133.6, 132.5, 131.0, 128.5, 128.1, 128.0, 127.6, 127.3, 123.6, 120.0, 107.7, 70.3; MS (EI⁺) m/z (%): 262 ([M]+, 100).

Synthesis of N-(3-(benzyloxy)phenyl)acetamide (14)

To a stirred solution of N-(3-hydroxyphenyl)acetamide (5.0 g, 33.08 mmol) in acetone (130 mL) was added K₂CO₃ (18.23 g, 132.31 mmol) under argon atmosphere and stirred for 30 min at room temperature. Benzyl bromide (3.93 mL, 33.08 mmol) was added dropwise and stirred for 2 h. After completion of the reaction, the solid was filtered off and the filtrate was concentrated under reduced pressure. The crude was purified by column chromatography (MeOH/CH₂Cl₂ = 1:19) afford the desired product (7.82 g, 98.0%) as white solid. Rᵣ = 0.3 (MeOH/CH₂Cl₂ = 1/19); ¹H NMR (300 MHz, CDCl₃) δ 7.61 (1H, s), 7.39–7.23 (6H, m), 7.15 (1H, t, J = 7.3 Hz), 6.97 (1H, d, J = 7.8 Hz), 6.69 (1H, dd, J = 8.1, 2.2 Hz), 5.00 (2H, s), 2.12 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 168.4, 159.1, 139.0, 136.7, 129.5, 128.4, 127.8, 127.4, 112.2, 110.8, 106.4, 69.9, 24.7; EI-MS m/z 241 ([M]+, 100%).
Synthesis of 7-(benzyloxy)-2-chloroquinoline-3-carbaldehyde (15)

To a stirred solution of compound 14 (2.0 g, 8.20 mmol) in anhydrous \( N, N \)-dimethylformamide (1.93 mL, 24.87 mmol) was added POCl\(_3\) (9.38 mL, 100.3 mmol) dropwise under argon atmosphere at 0 \(^\circ\)C. The reaction mixture was warmed to 90 \(^\circ\)C and stirred for 2 h. After completion of the reaction, cooled to room temperature and ice cold water was added slowly and stirred until a brown solid is formed. The solid was filtered, washed with \( \text{H}_2\text{O} \) and dried to afford the title compound 15 (1.91 g, 77.5 %). \( R_f = 0.74 \) (EtOAc/hexane = 1/1); \(^1\text{H}\text{NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 10.45 (1H, s), 8.60 (1H, s) 7.81 (1H, d, \( J = 9.0 \) Hz), 7.46–7.29 (7H, m), 5.20 (2H, s); \(^{13}\text{C}\text{NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) 188.6, 163.1, 151.7, 150.9, 139.3, 135.5, 130.7, 128.6, 128.3, 127.5, 124.5, 121.8, 121.6, 108.1, 70.7; EI-MS \( m/z \) 297 ([M]\(^+\), 100%).

Synthesis of 7-(benzyloxy)quinoline-3-carbaldehyde (16)

To a stirred solution of compound 15 (1.0 g, 3.36 mmol) in degassed \( N, N \)-dimethylformamide (6 mL) was added Pd(PPh\(_3\))\(_4\) (0.19 g, 0.17 mmol, 0.05 equiv.) and triethylamine (7.50 mL, 53.74 mmol) under argon atmosphere at room temperature. To this mixture, formic acid (0.8 mL, 18.14 mmol) was added dropwise at 0 \(^\circ\)C and degassed for 4 min. The reaction mixture was warmed to 110 \(^\circ\)C and stirred for 2 h. After completion of the reaction, cooled to room temperature and extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with \( \text{H}_2\text{O} \) (3 x 15 mL) and brine (15 mL), dried over
anhyd. Na$_2$SO$_4$ and concentrated in vacuo. The crude was purified by column chromatography (EtOAc/hexane = 1/2) to afford the desired product 16 (0.66 g, 74.2 %) as pale yellow solid. R$_f$ = 0.26 (EtOAc/hexane = 1/2); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 10.16 (1H, s), 9.24 (1H, d, $J$ = 2.1 Hz), 8.51 (1H, d, $J$ = 2.1 Hz), 7.85 (1H, d, $J$ = 9.0 Hz), 7.55 (1H, d, $J$ = 2.4 Hz), 7.48–7.33 (6H, m), 5.24 (2H, s); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 190.2, 162.3, 152.7, 150.0, 138.8, 135.8, 130.5, 128.7, 128.3, 127.6, 127.2, 122.3, 121.5, 109.1, 70.6; EI-MS m/z 263 ([M]$^+$, 100%).

6-(Benzyloxy)-2-methylquinoline (18)

To a stirred solution of 4-(benzyloxy)aniline 17 (0.83 g, 4.16 mmol) and ethyl vinyl ether (0.88 mL, 9.15 mmol) in anhyd. toluene (6 mL) was added iodine (0.053 g, 0.21 mmol) under argon atmosphere at room temperature. The reaction mixture was warmed to 80 ºC and stirred for 2 h. After completion of the reaction, cooled to room temperature and aqueous saturated Na$_2$S$_2$O$_3$ solution was added to it. Two layers separated and the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with H$_2$O (3 x 20 mL) and brine (20 mL), dried over anhyd. Na$_2$SO$_4$ and concentrated in vacuo. The crude was purified by column chromatography (EtOAc/hexane = 1/4) to afford the desired product 18 (0.51 g, 49.1 %) as beige solid. R$_f$ = 0.5 (EtOAc/hexane = 1/1); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.91 (1H, d, $J$ = 9.0 Hz), 7.88 (1H, d, $J$ = 8.4 Hz), 7.31–7.46 (6H, m), 7.19 (1H, d, $J$ = 8.4 Hz), 7.09 (1H, d, $J$ = 2.7 Hz), 5.14 (2H, s), 2.69 (3H, s); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 156.4, 156.3, 144.1, 136.7, 134.9, 130.2, 128.5, 127.9, 127.4, 127.2, 122.1, 122.0, 107.0, 70.5, 25.1; EI-MS m/z 250 ([M+H]$^+$, 130).

5-(Benzyloxy)-2-bromobenzaldehyde (20)
To a stirred solution of compound 19 (5 g, 24.87 mmol) in anhyd. N, N-dimethylformamide (30 mL) was added K₂CO₃ (5.16 g, 37.30 mmol) under argon atmosphere and stirred for 30 min at room temperature. Benzyl bromide (3.25 mL, 27.36 mmol) was added dropwise and the mixture was stirred for 2 h. After completion of the reaction, neutralized with 3N HCl and extract with EtOAc (3 x 40 mL). The combined organic layer was washed with H₂O (3 x 25 mL) and brine (25 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude was purified by column chromatography (EtOAc/hexane = 1/16) to afford the desired product 20 (6.52 g, 90.1 %) as white solid. Rf = 0.85 (EtOAc/hexane = 1/4); ¹H NMR (300 MHz, CDCl₃) δ 10.26 (1H, s), 7.50–7.28 (7H, m), 7.06 (1H, dd, J = 8.7, 3.0 Hz), 5.06 (2H, s); ¹³C NMR (75 MHz, CDCl₃) δ 191.2, 158.4, 135.9, 134.5, 134.1, 128.6, 128.2, 127.4, 123.5, 117.9, 114.2, 70.6; EI-MS m/z 292 ([M]+2, base), 290 ([M]+), 212, 199.

Methyl 7-(benzyloxy)isoquinoline-3-carboxylate (21)

To a stirred solution of compound 20 (1.0 g, 3.36 mmol) in anhyd. DMSO (5 mL) was added methyl 2-acetamidoacrylate (0.58 g, 4.02 mmol), triethylamine (1.51 mL, 10.82 mmol), tri(o-tolyl) phosphine (0.19 g, 0.62 mmol) and Pd(OAc)₂ (0.06 g, 0.30 mmol) and degassed for 5-10 min. The reaction mixture was warmed to 110 ºC and stirred for 18 h. After completion of the reaction, cooled to room temperature, aqueous saturated NH₄Cl solution (5 mL) was added and extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with H₂O (3 x 20 mL) and brine (20 mL), dried over anhyd. Na₂SO₄ and concentrated in vacuo. The crude was purified by column chromatography (EtOAc/hexane = 1/2) to afford the desired product 21 (0.66 g, 74.2 %) as pale brown solid. Rf = 0.3 (EtOAc/hexane = 1/1); ¹H NMR (300 MHz, CDCl₃) δ 9.14 (1H, s), 8.44 (1H, s), 7.79 (1H, d, J = 9.0 Hz), 7.44–7.30 (7H, m), 5.17 (2H, s), 4.00 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 165.9, 159.1, 150.7, 139.7,
135.7, 131.2, 130.6, 129.3, 128.4, 128.0, 127.2, 124.1, 123.4, 106.3, 70.2, 52.4; EI-MS m/z 293 ([M]+, base), 262, 234.

(7-(Benzyloxy)isoquinolin-3-yl)methanol (22)

![Structure of 22]

To a stirred solution of compound 21 (0.89 g, 3.05 mmol) in anhydrous THF (8 mL) was added LiAlH4 solution (1.0 M in THF, 3.96 mL, 3.96 mmol) dropwise at 0 ºC under argon atmosphere. The reaction was warmed to room temperature and stirred for 1 h. After completion of the reaction, the reaction mixture was cooled to 0 ºC and the excess LiAlH4 was quenched by the slow addition of aqueous saturated Na2CO3 solution (4 mL) and stirred for 20 min. The resulting suspension was filtered, washed with EtOAc (50 mL). The filtrate was washed with H2O (3 x 15 mL) and brine (15 mL), dried over anhydrous Na2SO4 and concentrated under reduced pressure. The crude was purified by column chromatography (MeOH/CH2Cl2 = 1/19) to afford the pure product 22 (0.49 g, 60.5%) as pale brown liquid. Rf = 0.1 (EtOAc/hexane = 1/1); 1H NMR (300 MHz, CDCl3) δ 8.99 (1H, s), 7.63 (1H, d, J = 9.0 Hz), 7.58 (1H, s), 7.47–7.32 (6H, m), 7.18 (1H, s), 5.12 (2H, s), 5.08 (1H, br s), 4.91 (2H, s); 13C NMR (75 MHz, CDCl3) δ 157.2, 151.5, 150.2, 136.2, 132.0, 128.7, 128.5, 128.0, 127.9, 127.3, 123.9, 116.6, 106.2, 70.2, 64.9; EI-MS m/z 265 ([M]+, base), 263.

7-(Benzyloxy)isoquinoline-3-carbaldehyde (23)
To a stirred solution of IBX (0.08 g, 0.28 mmol) in anhydrous DMSO (2.5 mL) was added compound 22 (0.05 g, 0.19 mmol) in anhydrous DMSO (2.5 mL) under argon atmosphere at room temperature and the reaction mixture was stirred for 1 h. After completion of the reaction, diluted with EtOAc (25 mL) and washed with aqueous saturated NaHCO₃ solution (3 x 10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by column chromatography (EtOAc/hexane = 1/2) to afford the pure product 23 (0.03 g, 66.0 %) as pale brown solid. R_f = 0.6 (EtOAc/hexane = 1/1); ¹H NMR (300 MHz, CDCl₃) δ 10.19 (1H, s), 9.21 (1H, s), 8.29 (1H, s), 7.90 (1H, d, J = 8.7 Hz), 7.51–7.35 (7H, m), 5.23 (2H, s); ¹³C NMR (75 MHz, CDCl₃) δ 192.8, 159.8, 151.4, 145.9, 135.8, 132.2, 130.7, 130.2, 128.7, 128.3, 127.4, 124.6, 121.2, 106.7, 70.6; EI-MS m/z 263 ([M]+, base).

**Ethyl 2-((4-fluoro-2-nitrophenyl)amino)propanoate (25)**

To a stirred solution of compound 24 (0.34 mL, 3.14 mmol) in pyridine (6 mL) were added L-alanine ethyl ester hydrochloride (0.72 g, 4.71 mmol) and triethylamine (0.88 mL, 6.29 mmol) under argon atmosphere and the reaction mixture was stirred at 80 °C for 17 h. After completion of the reaction, cooled to room temperature, diluted with EtOAc (40 mL) and sequentially washed with 10% aqueous CuSO₄ (10 mL) solution, H₂O (3 x 10 mL) and brine.
(10 mL). The organic layer was dried over anhyd. Na$_2$SO$_4$ and concentrated in vacuo. The crude was purified by column chromatography (EtOAc/hexane = 1/10) to afford the desired product 25 (0.75 g, 92.6%) as orange solid. R$_f$ = 0.4 (EtOAc/hexane = 1/8); $^1$H NMR (300 MHz, CDCl$_3$) δ 8.16 (1H, d, $J$ = 6.8 Hz), 7.87 (1H, dd, $J$ = 9.0, 3.1 Hz), 7.26–7.19 (1H, m), 6.70 (1H, dd, $J$ = 9.0, 4.4 Hz), 4.30–4.19 (3H, m), 1.60 (3H, d, $J$ = 6.8 Hz), 1.29 (3H, t, $J$ = 7.2 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 172.1, 152.8 ($J$ = 237.4 Hz), 140.8, 131.9, 124.3 ($J$ = 23.3 Hz), 115.1 ($J$ = 7.1 Hz), 112.3 ($J$ = 26.2 Hz), 61.6, 51.8, 18.6, 14.1.

7-Fluoro-3-methylquinoxalin-2(1H)-one (26)

To a stirred solution of compound 25 (0.75 g, 2.93 mmol) in EtOH/H$_2$O (10/1; 8.8 mL) was added tin (II) chloride dihydrate (2.64 g, 11.71 mmol) at room temperature and the reaction was refluxed for 1 h. After completion of the reaction, cooled to room temperature, basified using 2N NaOH, filtered through Celite® pad and washed with diethyl ether (10 mL) and tetrahydrofuran (5 mL). The filtrate was concentrated under reduced pressure. The crude was dissolved in CH$_3$CN (8 mL), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.0 g, 4.39 mmol) was added to it and stirred for 30 min. After completion of the reaction, filtered through Celite® pad and washed with EtOAc/THF (4/1; 20 mL). The filtrate was diluted with EtOAc (25 mL), sequentially washed with aqueous saturated NaHCO$_3$ (2 x 15 mL), H$_2$O (2 x 15 mL) and brine (15 mL), dried over anhyd. Na$_2$SO$_4$ and concentrated under reduced pressure. The crude was triturated with hexane and diethyl ether to give the desired product 26 (0.52 g, quantitative) as brown solid. R$_f$ = 0.4 (EtOAc/hexane = 1/1); $^1$H NMR (300 MHz, DMSO-d$_6$)
δ 12.32 (1H, br s), 7.72 (1H, dd, $J = 8.7, 6.0$ Hz), 7.10 (1H, td, $J = 8.7, 2.6$ Hz), 6.99 (1H, dd, $J = 9.8, 2.6$ Hz), 2.38 (3H, s); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 161.3 ($J = 237.4$ Hz), 157.8, 154.3, 133.0 ($J = 12.5$ Hz), 129.7 ($J = 10.6$ Hz), 128.4, 110.4 ($J = 23.7$ Hz), 100.8 ($J = 26.5$ Hz), 20.0.

3-Chloro-6-fluoro-2-methylquinoxaline (27)

![3-Chloro-6-fluoro-2-methylquinoxaline](image)

To a stirred solution of compound 26 (2.37 g, 13.30 mmol) in N, N-dimethylaniline (20 mL) was added phosphoryl chloride (37.31 mL, 399.1 mmol) dropwise at room temperature under argon atmosphere. The reaction was warmed to 110 ºC and stirred for 1 h. After completion of the reaction, cooled to room temperature and H$_2$O (5 mL) was added dropwise. The reaction mixture was extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with H$_2$O (3 x 20 mL) and brine (20 mL), dried over anhyd. Na$_2$SO$_4$ and concentrated under reduced pressure. The crude was purified by column chromatography (EtOAc/hexane = 1/16) to afford the desired product 27 (2.26 g, 86.1%) as pale yellow solid. $R_f = 0.5$ (EtOAc/hexane = 1/8); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.98 (1H, dd, $J = 9.1, 5.8$ Hz), 7.58–7.45 (2H, m), 2.81 (3H, s); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 162.6 ($J = 244.6$ Hz), 151.9 ($J = 3.1$ Hz), 148.8, 141.6 ($J = 13.1$ Hz), 138.1, 130.4 ($J = 10.0$ Hz), 120.0 ($J = 25.6$ Hz), 111.9 ($J = 22.2$ Hz), 23.1.

6-Fluoro-2-methylquinoxaline (28)
To a stirred solution of compound 27 (1.18 g, 6.02 mmol) in degassed N, N-dimethylformamide (15 mL) was added Pd(PPh₃)₄ (0.35 g, 0.30 mmol) and triethylamine (13.43 mL, 96.27 mmol) under argon atmosphere at room temperature. To this mixture, formic acid (1.23 mL, 32.49 mmol) was added dropwise at 0 °C and degassed for 4 min. The reaction mixture was warmed to 110 ºC and stirred for 2 h. After completion of the reaction, cooled to room temperature and extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with H₂O (3 x 25 mL) and brine (25 mL), dried over anhyd. Na₂SO₄ and concentrated in vacuo. The crude was purified by column chromatography (EtOAc/hexane = 1/8) to afford the desired product 28 (0.81 g, 5.00 mmol, 83.1 %) as beige solid. Rf = 0.4 (EtOAc/hexane = 1/4); ¹H NMR (300 MHz, CDCl₃) δ 8.71 (1H, s), 7.98 (1H, dd, J = 9.0, 5.8 Hz), 7.66 (1H, dd, J = 9.0, 3.0 Hz) 7.53–7.46 (1H, m), 2.75 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 161.9 (J = 248.8 Hz), 152.9, 146.5, 141.6 (J = 12.8 Hz), 139.2, 130.6 (J = 9.7 Hz), 120.0 (J = 25.6 Hz), 112.7 (J = 21.3 Hz), 22.4.

6-(Benzyloxy)-2-methylquinoxaline (29)

To a stirred suspension of NaH (60% in mineral oil, 0.40 g, 9.95 mmol) in N, N-dimethylformamide (4 mL) was added benzyl alcohol (0.67 mL, 6.47 mmol) in N, N-dimethylformamide (3 mL) dropwise under argon atmosphere at room temperature and stirred for 30 min. Compound 28 (0.80 g, 4.98 mmol) in N, N-dimethylformamide (8 mL)
was added dropwise to the above mixture. The resulting mixture was warmed 100 ºC and stirred for 2h. After completion of the reaction, cooled to 0 ºC, quenched with H₂O (5 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with H₂O (3 x 20 mL) and brine (20 mL), dried over anhyd. Na₂SO₄ and concentrated in vacuo. The crude was purified by column chromatography (EtOAc/hexane = 1/4) to afford the desired product 29 (1.04 g, 83.4 %) as pale yellow solid. (R₉ = 0.4 (EtOAc/hexane = 1/1); ¹H NMR (300 MHz, CDCl₃) δ 8.63 (1H, s), 7.89 (1H, d, J = 9.0 Hz), 7.48–7.30 (7H, m), 5.19 (2H, s), 2.72 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 159.0, 151.1, 145.7, 142.3, 138.3, 136.2, 129.7, 128.6, 128.1, 127.5, 123.2, 108.3, 70.6, 22.2; EI-MS m/z 250 ([M]+, base).

6-(Benzyloxy)-2-methylquinazoline (30)

To a stirred solution of compound 20 (5 g, 17.17 mmol) in anhyd. N, N-dimethylformamide (50 mL) were added acetamidine hydrochloride (1.79 g, 18.89 mmol), L-proline (0.40 g, 3.43 mmol), Cs₂CO₃ (16.79 g, 51.52 mmol) and CuI (0.33 g, 1.72 mmol) under argon atmosphere at room temperature. The mixture was warmed to 110 ºC and stirred for 18 h. After completion of the reaction, cooled to room temperature, filtered through Celite® pad and washed with EtOAc (20 mL). The filtrate was neutralized with 1N HCl and extract with EtOAc (3 x 50 mL). The combined organic layer was washed with H₂O (3 x 30 mL) and brine (30 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude was purified by column chromatography (EtOAc/hexane = 1/2) to afford the desired product 30 (1.16 g, 27.0 %) as brown solid. R₉ = 0.3 (EtOAc/hexane = 1/2); ¹H NMR (300 MHz, CDCl₃) δ 9.16 (1H, s), 7.84 (1H, d, J = 9.3 Hz) 7.57 (1H, dd, J = 9.3, 2.7 Hz), 7.46–7.33 (5H, m), 7.16 (1H, d, J = 2.4 Hz), 5.15 (2H, s), 2.85 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 162.4, 158.5, 156.8, 146.5, 136.0, 129.2, 128.6, 128.1, 127.3, 127.1, 123.5, 105.3, 70.5, 26.1; EI-MS m/z 250 ([M]+, base).
(E)-2-Benzylxyloxy-6-(3,5-bis(benzylxyloxy)styryl)naphthalene (31)

To a solution of the compound 10 (0.4 g, 0.9 mmol) in anhydrous DMF (5 mL) was added sodium hydride (60% NaH in mineral oil, 0.11 g, 2.72 mmol) at 0 °C under argon. After 30 minutes, compound 13 (0.24 g, 0.9 mmol) was added and the reaction mixture was stirred for 2 hours at room temperature. The reaction was quenched by 1N HCl at 0 °C (pH ≈ 5). After filtration with Celite® 545, the organic layer was extracted with DCM (15 mL) and washed with brine (20 mL x 3). The solvent was evaporated in vacuo to give the crude product, which was purified on a silica gel (DCM:hexanes = 1:1) to afford the desired product 31 (0.43 g, 86.0 %) as a white solid. Rf = 0.46 (EtOAc/hexane = 1/6); 1H NMR (300 MHz, CDCl3): δ 7.68–7.77 (4H, m), 7.32–7.50 (15H, m), 7.17–7.28 (2H, m), 7.11 (1H, s), 7.06 (1H, s), 6.81 (2H, d, J = 2.1 Hz), 6.55 (1H, t, J = 2.2 Hz), 5.17 (2H, s), 5.08 (4H, s); 13C NMR (75 MHz, CDCl3): δ 160.1, 156.9, 139.6, 136.9, 136.8, 134.2, 132.6, 129.5, 129.4, 129.2, 128.5, 127.9, 127.4, 127.2, 126.5, 124.1, 119.3, 107.4, 105.9, 101.6, 70.2; MS (EI+) m/z(%): 548 ([M]+, 100).

Synthesis of (E)-7-(benzylxyloxy)-3-(3,5-bis(benzylxyloxy)styryl)quinoline (32)

To a stirred suspension of NaH (60% in mineral oil, 0.27 g, 6.73 mmol) in N, N-dimethylformamide (3 mL) was added compound 10 (1.09 g, 2.47 mmol) in N, N-dimethylformamide (3 mL) dropwise under argon atmosphere at room temperature and stirred for 30 min. Compound 4 (0.60 g, 2.24 mmol) in N, N-dimethylformamide (3 mL) was added dropwise to the above mixture and the reaction mixture stirred for 2h. After completion of the reaction, cooled to 0 °C, quenched with H2O (3 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with H2O (3 x 20 mL) and brine (20 mL),
dried over anhyd. Na$_2$SO$_4$ and concentrated in vacuo. The crude was purified by column chromatography (MeOH/CH$_2$Cl$_2$ = 1/19) to afford the desired product 5 (1.10 g, 89.4 %) as pale yellow solid. R$_f$ = 0.41 (EtOAc/hexane = 1/2); $^1$H NMR (300 MHz, CDCl$_3$) δ 8.97 (1H, s), 8.05 (1H, s) 7.68 (1H, d, $J$ = 9.0 Hz), 7.48–7.22 (17H, m), 7.13 (2H, s), 6.79 (2H, s), 6.56 (1H, s), 5.19 (2H, s), 5.06 (4H, s); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 160.3, 159.8, 149.7, 149.2, 139.1, 137.0, 136.5, 131.9, 129.8, 128.8, 128.6, 128.5, 128.4, 128.0, 127.9, 127.5, 127.4, 126.1, 123.4, 120.4, 109.1, 106.3, 102.4, 70.4; EI-MS m/z 549 ([M]$^+$, base), 458, 368.

**(E)-7-(Benzyloxy)-3-(3,5-bis(benzyloxy)styryl)isoquinoline (33)**

![33](image)

To a stirred suspension of NaH (60% in mineral oil, 0.07 g, 1.82 mmol) in N, N-dimethylformamide (2 mL) was added compound 10 (0.32 g, 0.73 mmol) in N, N-dimethylformamide (3 mL) dropwise under argon atmosphere at room temperature and stirred for 30 min. Compound 23 (0.16 g, 0.61 mmol) in N, N-dimethylformamide (3 mL) was added dropwise to the above mixture. The resulting mixture was warmed to room temperature and stirred for 2h. After completion of the reaction, cooled to 0 ºC, quenched with H$_2$O (3 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with H$_2$O (3 x 15 mL) and brine (15 mL), dried over anhyd. Na$_2$SO$_4$ and concentrated in vacuo. The crude was purified by column chromatography (EtOAc/hexane = 1/4) to afford the desired product 33 (0.33 g, 81.8 %) as pale yellow solid. R$_f$ = 0.6 (EtOAc/hexane = 1/2); $^1$H NMR (300 MHz, CDCl$_3$) δ 9.05 (1H, s), 7.62 (1H, d, $J$ = 15.3 Hz), 7.57–7.17 (20H, m), 6.81 (2H, s), 6.53 (1H, s) 5.06 (2H, s), 4.99 (4H, s); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 160.0, 157.3, 151.0, 147.7, 139.2, 136.9, 136.3, 131.9, 130.7, 128.9, 128.6, 128.4, 128.3, 128.1,
To a stirred solution of compound 18 (0.35 g, 1.40 mmol) and 3,5-dibenzylxybenzaldehyde (0.54 g, 1.68 mmol) in anhyd. toluene (6 mL) were added Fe(OAc)$_2$ (0.01 g, 0.07 mmol) and trifluoroacetic acid (0.01 mL, 0.14 mmol) under argon atmosphere at room temperature. The reaction mixture was refluxed for 24 h. After completion of the reaction, cooled to room temperature and diluted with aqueous saturated NaHCO$_3$ solution. Two layers separated and the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with H$_2$O (2 x 20 mL) and brine (20 mL), dried over anhyd. Na$_2$SO$_4$ and concentrated in vacuo. The crude was purified by column chromatography (EtOAc/hexane = 1/10) to afford the desired product 34 (0.43 g, 55.8 %) as orange solid. R$_f$ = 0.4 (EtOAc/hexane = 1/4); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.95 (1H, d, $J = 9.0$ Hz), 7.87 (1H, d, $J = 8.4$ Hz), 7.50–7.25 (19H, m), 7.03 (1H, d, $J = 2.7$ Hz), 6.56 (2H, t, $J = 2.1$ Hz), 6.84 (1H, t, $J = 2.1$ Hz) 5.08 (2H, s), 5.01 (4H, s); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 160.0, 156.6, 153.4, 144.2, 138.7, 136.8, 136.4, 134.8, 133.0, 130.6, 129.5, 129.0, 128.44, 128.39, 128.1, 127.9, 127.8, 127.3, 122.4, 119.4, 106.7, 106.3, 102.8, 70.2, 70.1; EI-MS m/z 549 ([M]$^+$, base), 458, 367.

(E)-6-(Benzylxy)-2-(3,5-bis(benzylxy)styryl)quinoline (34)
To a stirred solution of compound 29 (0.88 g, 3.52 mmol) and compound 9 (1.34 g, 4.22 mmol) in anhyd. toluene (10 mL) were added Fe(OAc)$_2$ (0.03 g, 0.18 mmol) and trifluoroacetic acid (0.03 mL, 0.35 mmol) under argon atmosphere at room temperature. The reaction mixture was refluxed for 24 h. After completion of the reaction, cooled to room temperature and diluted with aqueous saturated NaHCO$_3$ solution. Two layers were separated and the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with H$_2$O (2 x 20 mL) and brine (20 mL), dried over anhyd. Na$_2$SO$_4$ and concentrated in vacuo. The crude was purified by column chromatography (EtOAc/hexane = 1/8) to afford the desired product 35 (1.25 g, 64.4 %) as pale yellow solid. R$_f$ = 0.4 (EtOAc/hexane = 1/1); $^1$H NMR (300 MHz, CDCl$_3$) δ 8.89 (1H, s), 7.92 (1H, d, J = 9.0 Hz), 7.66 (1H, d, J = 16.2 Hz), 7.48–7.29 (17H, m), 7.26 (1H, d, J = 16.2 Hz), 6.86 (2H, d, J = 2.1 Hz), 6.60 (1H, t, J = 2.1 Hz), 5.19 (2H, s), 5.06 (4H, s); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 160.3, 159.4, 148.3, 144.3, 143.1, 138.6, 138.3, 136.8, 136.2, 134.8, 130.2, 128.6, 128.5, 128.2, 127.9, 127.5, 127.4, 126.0, 123.6, 108.3, 106.7, 103.4, 70.7, 70.4; EI-MS m/z 550 ([M]+, base), 459, 368.

(*E*)-6-(Benzyloxy)-2-(3,5-bis(benzyloxy)styryl)quinazoline (36)

To a stirred solution of compound 30 (0.38 g, 1.522 mmol) and compound 9 (0.58 g, 1.823 mmol) in anhyd. DMF (12 mL) was added tBuOK (0.26 g, 2.283 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 17 h at room temperature. After completion of the reaction, H$_2$O (4 mL) was added dropwise to quench the excess tBuOK. The reaction mixture was extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with H$_2$O (4 x 20 mL) and brine (2 x 20 mL), dried over anhyd. Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The crude was purified by column chromatography (EtOAc/hexane = 1/5–1/3) to afford the desired product 36 (0.5 g, 59.8%) as pale yellow color solid. R$_f$ = 0.56 (EtOAc/hexane = 1/3); $^1$H NMR (300 MHz, CDCl$_3$): δ 9.15 (1H, s), 7.94 (1H, d, J = 15.9 Hz) 7.86 (1H, d, J = 9.0 Hz), 7.55–7.26 (17H, m), 7.10 (1H, s), 6.88 (2H, s), 6.85 (2H, s), 6.62 (2H, s), 5.21 (2H, s), 5.12 (4H, s), 4.32 (2H, s), 4.06 (2H, d, J = 18 Hz), 3.94 (2H, s).
6.58 (1H, d, $J = 1.5$ Hz), 5.11 (2H, s), 5.02 (4H, s); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 160.0, 159.3, 158.3, 157.0, 146.5, 138.3, 136.9, 136.7, 135.9, 129.5, 128.5, 128.3, 128.0, 127.7, 127.2, 127.0, 124.0, 106.6, 105.7, 103.3, 70.4, 70.1; EI-MS $m/z$ 550 ([M]$^+$, base), 460, 368.

(E)-5-(2-(6-hydroxynaphthalen-2-yl)vinyl)benzene-1,3-diol (2)

1H NMR (300 MHz, CD$_3$OD) $\delta$ 7.71–7.56 (4H, m), 7.14 (1H, d, $J = 16.2$ Hz), 7.02 (1H, d, $J = 16.2$ Hz), 7.07–7.02 (2H, m), 6.53 (2H, d, $J = 2.1$ Hz), 6.21 (1H, t, $J = 2.2$ Hz); $^{13}$C NMR (75 MHz, CD$_3$OD) $\delta$ 159.5, 156.4, 141.0, 135.9, 133.4, 130.4, 129.9, 129.8, 128.8, 127.5, 127.3, 124.8, 119.4, 110.1, 106.1, 103.1; HRMS $m/z$ (M$^+$) calcd for C$_{18}$H$_{14}$O$_3$: 278.0943, Found: 278.0941.

Synthesis of (E)-5-(2-(7-hydroxyquinolin-3-yl)vinyl)benzene-1,3-diol (3)

To a stirred solution of compound 32 (1.07 g, 1.95 mmol) in anhyd. CH$_2$Cl$_2$ (10 mL) was added BBr$_3$ (1.0 M in CH$_2$Cl$_2$, 7.79 mL) dropwise at -20 °C under argon atmosphere and stirred for 2 h. After completion of the reaction, MeOH (3.5 mL) was added dropwise to quench the excess BBr$_3$, warmed to room temperature in 20 min and the solvent was removed under reduced pressure. H$_2$O (15 mL) was added to the crude residue and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with H$_2$O (3 x 20 mL) and brine (20 mL), dried over anhyd. Na$_2$SO$_4$ and concentrated in vacuo. The crude was purified by column chromatography (MeOH/CH$_2$Cl$_2$ = 1/19) to afford the desired product 3 (0.47 g, 87.0 %) as pale orange solid. mp 262 °C; $R_f = 0.37$ (MeOH/CH$_2$Cl$_2$ = 1/9); 1H NMR (300 MHz, CD$_3$OD) $\delta$ 9.08 (1H, s), 9.01 (1H, s) 8.11 (1H, d, $J = 9.3$ Hz), 7.40 (1H, dd, $J = 9.3, 2.1$ Hz).
Hz), 7.32 (1H, d, J = 2.1 Hz), 7.26 (1H, d, J = 16.5 Hz), 7.12 (1H, d, J = 16.5 Hz), 6.44 (2H, d, J = 1.8 Hz), 6.07 (1H, d, J = 1.8 Hz); \(^{13}\)C NMR (75 MHz, CD\(_3\)OD) \(\delta\) 159.2, 158.6, 148.9, 148.3, 139.2, 132.9, 130.2, 129.4, 128.4, 124.7, 123.1, 119.9, 109.0, 105.2, 102.5; HRMS \(m/z\) (M\(^+\)) calcd for C\(_{17}\)H\(_{13}\)NO\(_3\): 279.0895, Found: 279.0892; UV-Vis (MeOH): \(\lambda_{\text{abs}}\) 240, 287, 337, 391.

**(E)-5-(2-(6-Hydroxyquinolin-2-yl)vinyl)benzene-1,3-diol (4)**

To a stirred solution of compound 34 (0.25 g, 0.45 mmol) in anhyd. CH\(_2\)Cl\(_2\) (10 mL) was added BBr\(_3\) (1.0 M in CH\(_2\)Cl\(_2\), 1.82 mL) dropwise at -20 ºC under argon atmosphere. The reaction mixture was warmed to room temperature and stirred for 2 h. After completion of the reaction, cool to 0 ºC, MeOH (2 mL) was added dropwise to quench the excess BBr\(_3\), warmed to room temperature in 20 min and the solvent was removed under reduced pressure. H\(_2\)O (10 mL) was added to the crude residue and extracted with EtOAc (3 x 40 mL). The combined organic layer was washed with H\(_2\)O (3 x 20 mL) and brine (20 mL), dried over anhyd. Na\(_2\)SO\(_4\) and concentrated in vacuo. The crude was purified by column chromatography (MeOH/CH\(_2\)Cl\(_2\) = 1/19) to afford the desired product 4 (0.08 g, 61.3 %) as pale orange solid. mp 182 ºC (decomposed); R\(_f\) = 0.3 (MeOH/CH\(_2\)Cl\(_2\) = 1/9); \(^1\)H NMR (300 MHz, CD\(_3\)OD) \(\delta\) 8.06 (1H, d, J = 8.7 Hz), 7.83 (1H, d, J = 9.3 Hz), 7.76 (1H, d, J = 8.7 Hz), 7.44 (1H, d, J = 16.2 Hz), 7.30 (1H, dd, J = 9.3, 2.7 Hz), 7.22 (1H, d, J = 16.2 Hz), 7.10 (1H, d, J = 2.7 Hz), 6.58 (2H, d, J = 1.8 Hz), 6.26 (1H, t, J = 1.8 Hz); \(^{13}\)C NMR (75 MHz, CD\(_3\)OD) \(\delta\) 159.6, 156.9, 154.4, 143.6, 139.7, 136.7, 135.5, 130.0, 129.9, 128.7, 123.3, 120.0, 109.8, 106.8, 104.4; HRMS \(m/z\) (M\(^+\)) calcd for C\(_{17}\)H\(_{13}\)NO\(_3\): 279.0895, Found: 279.0896; UV-Vis (MeOH): \(\lambda_{\text{abs}}\) 231, 308, 390.

**(E)-5-(2-(7-hydroxyisoquinolin-3-yl)vinyl)benzene-1,3-diol (5)**
To a stirred solution of compound 33 (0.13 g, 0.24 mmol) in anhyd. CH₂Cl₂ (5 mL) was added BBr₃ (1.0 M in CH₂Cl₂, 0.95 mL) dropwise at -20 °C under argon atmosphere. The reaction mixture was warmed to room temperature and stirred for 2 h. After completion of the reaction, cool to 0 °C, MeOH (2 mL) was added dropwise to quench the excess BBr₃, warmed to room temperature in 20 min and the solvent was removed under reduced pressure. H₂O (10 mL) was added to the crude residue and extracted with EtOAc (3 x 35 mL). The combined organic layer was washed with H₂O (3 x 15 mL) and brine (15 mL), dried over anhyd. Na₂SO₄ and concentrated in vacuo. The crude was purified by column chromatography (MeOH/CH₂Cl₂ = 1/19) to afford the desired product 5 (0.04 g, 60.6 %) as pale yellow solid. Rf = 0.4 (MeOH/CH₂Cl₂ = 1/9); ¹H NMR (300 MHz, CD₃OD) δ 8.97 (1H, s), 7.78 (1H, d, J = 8.7 Hz), 7.74 (1H, s), 7.43 (1H, d, J = 15.6 Hz), 7.33 (1H, dd, J = 8.7, 2.4 Hz), 7.26 (1H, d, J = 2.4 Hz), 7.19 (1H, d, J = 15.6 Hz), 6.57 (2H, d, J = 2.4 Hz), 6.23 (1H, t, J = 2.4 Hz); ¹³C NMR (75 MHz, CD₃OD) δ 159.8, 158.1, 151.5, 147.9, 140.4, 132.8, 132.0, 130.8, 129.6, 128.5, 125.0, 119.9, 109.5, 106.3, 103.6; HRMS m/z (M⁺) calcd for C₁₇H₁₃NO₃: 279.0895, Found: 279.0894; UV-Vis (MeOH): λₚₐₛₜ 240, 345.

(E)-5-(2-(6-hydroxyquinoxalin-2-yl)vinyl)benzene-1,3-diol (6)

To a stirred solution of compound 35 (0.12 g, 0.22 mmol) in anhyd. CH₂Cl₂ (4 mL) was added BBr₃ (1.0 M in CH₂Cl₂, 0.87 mL) dropwise at -20 °C under argon atmosphere. The reaction mixture was warmed to room temperature and stirred for 2 h. After completion of the reaction, cool to 0 °C, MeOH (2 mL) was added dropwise to quench the excess BBr₃, warmed
to room temperature in 20 min and the solvent was removed under reduced pressure. H$_2$O (10 mL) was added to the crude residue and extracted with EtOAc (3 x 35 mL). The combined organic layer was washed with H$_2$O (3 x 15 mL) and brine (15 mL), dried over anhyd. Na$_2$SO$_4$ and concentrated in vacuo. The crude was purified by column chromatography (MeOH/CH$_2$Cl$_2$ = 1/19) to afford the desired product 6 (0.04 g, 75.5%) as pale yellow solid. mp 318 °C; R$_f$ = 0.4 (MeOH/CH$_2$Cl$_2$ = 1/9); $^1$H NMR (300 MHz, CD$_3$OD) δ 8.95 (1H, s), 7.80 (1H, d, $J$ = 9.0 Hz), 7.59 (1H, d, $J$ = 15.6 Hz), 7.36 (1H, dd, $J$ = 9.0, 2.7 Hz), 7.23 (1H, d, $J$ = 2.7 Hz), 7.21 (1H, d, $J$ = 15.6 Hz), 6.61 (2H, d, $J$ = 1.8 Hz), 6.28 (1H, t, $J$ = 1.8 Hz); $^{13}$C NMR (75 MHz, CD$_3$OD) δ 159.7, 159.3, 149.1, 145.1, 143.3, 139.1, 138.3, 136.2, 130.5, 125.6, 124.0, 110.2, 106.8, 104.5; HRMS m/z (M$^+$) calcd for C$_{16}$H$_{12}$N$_2$O$_3$: 280.0848, Found: 280.0847; UV-Vis (MeOH): $\lambda_{abs}$ 219, 323, 430.

(E)-5-(2-(6-hydroxyquinazolin-2-yl)vinyl)benzene-1,3-diol (7)

![Chemical structure](image)

To a stirred solution of compound 36 (0.05 g, 0.1 mmol) in anhyd. CH$_2$Cl$_2$ (4 mL) was added BBr$_3$ (0.1 mL, 1.0 mmol) dropwise at -20 °C under nitrogen atmosphere and the resulting mixture was stirred for 22 h. After completion of the reaction, solvent was removed in vacuo. To the crude, H$_2$O (3.5 mL) was added and stirred for 10–15 min. The reaction mixture was extracted with THF/EtOAc (1/20) (3 x 25 mL). The combined organic layer was washed with H$_2$O (3 x 15 mL) and brine (2 x 15 mL), dried over anhyd. Na$_2$SO$_4$ and concentrated in vacuo. The crude was purified by column chromatography (MeOH/CH$_2$Cl$_2$ = 1/20–1/10) to afford the desired product 7 (0.01 g, 35.7%) as pale yellow color solid. R$_f$ = 0.32 (MeOH/CH$_2$Cl$_2$ = 1/10). $^1$H NMR (400MHz, DMSO-$d_6$) δ 10.46 (1H, s), 9.43 (2H, s), 9.37 (1H, s), 7.84 (1H, d, $J$ = 7.2 Hz), 7.78 (1H, d, $J$ = 15.6 Hz), 7.53 (1H, dd, $J$ = 7.2, 2.8 Hz), 7.28 (1H, d, $J$ = 2.8 Hz), 7.12 (1H, d, $J$ = 15.6 Hz), 6.55 (2H, d, $J$ = 2.0 Hz), s), 6.25 (1H, t, $J$ = 2.0 Hz); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 158.9, 158.8, 158.0, 156.3, 148.4, 137.6, 136.6, 129.2, 127.6, 127.0, 124.4, 108.0, 105.5, 103.6; EI-MS m/z 281 (M$^+$ + H, base), 280 (M$^+$), 263, 251; HRMS m/z (M$^+$) calcd for C$_{16}$H$_{12}$N$_2$O$_3$: 280.0848, Found: 280.0844; UV-Vis (MeOH): $\lambda_{abs}$ 236, 348.
**Antioxidant assay using ABTS**

The radical cation was prepared by mixing an equal amount of 7mM ABTS (2,2’-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)) stock solution with 2.45 mM potassium persulfate stock solution. This mixture was stored at 0°C for 12 hours under darkness. The above ABTS solution was diluted with methanol appropriately to give UV absorption value of 1.000 at the 734 nm. The compounds 1-7 were dissolved in methanol to prepare 1000 µM stock solutions. Then these solutions were diluted with methanol to 500 µM, 250 µM, 125 µM, 62.5 µM, 31.25 µM, 15.63 µM, 7.81 µM, 3.90 µM, 1.95 µM, and 0.97 µM. In different 3 sets of test tubes, 0.9 mL of the ABTS solution and 0.1 mL of the compound solution were mixed under darkness. After 30 min of incubation, the UV absorption at 734 nm was measured. Control was used the mixture of 0.9 mL ABTS and 0.1 mL methanol. The radical scavenging rates were obtained from these UV absorption data and the resulting IC₅₀ values were calculated using Origin 8.

**NO assay and cell viability test**

Murine macrophage, Raw 264.7 cells were grown in Dulbecco’s modified Eagle’s medium (Gibco, Carlsbad, CA, USA), supplemented with 2 mM glutamine, antibiotics (100 U/mL of penicillin A and 100 mg/mL of streptomycin) and 10% FBS (Gibco). Cells were cultured in 96-well plates (5×10⁴ cells), treated with serial dilutions of compound (3.125-100 µM) and stimulated with LPS (1 µg/mL) for 24 h at 37°C. After incubation, the supernatant was collected and the amount of nitrite was quantified using the Griess Reagent System (Promega, Fitchburg, WI, USA). For the correction of NO production, cell viability was measured using the CellTiter 96® Aqueous one solution cell proliferation assay kit (Promega). Cells were incubated with varying amounts of compound for 24 h, then MTS (tetrazolium salt) reagent was added to the plates. After 1h, the absorbance at 490 nm was read using a microplate reader (Thermo Scientific, Waltham, MA, USA).

**Statistical analysis.** Statistical significance was analyzed using the GraphPad Prism 5 software (GraphPad Software, San Diego, CA, USA). The comparison of two groups was performed by the unpaired t test. Values of *P* less than 0.05, **P** less than 0.01 and ***P*** less than 0.001 were considered statistically significant.
Fig. S1: ABTS assay of compounds 1–7 (Statistical analysis).

Fig. S2: Inhibitory effect of compounds 1–7 on NO production.
Reverse transcriptase-polymerase chain reaction (RT-PCR)

Total RNA was isolated from Raw 264.7 cells using TRIzol reagent (Invitrogen, Waltham, MA, USA). Relative levels of pro-inflammatory cytokine gene expression were tested by 1.5% agarose gel electrophoresis after endpoint RT-PCR using GoScript™ Reverse Transcriptase (Promega). The sequences of the sense and anti-sense primers used for amplification are as follows. IL-1β, 5'-CCTGTGTAATGAAAGACGGCACAC-3', 5'-CTTGTGAGGTGCTGATGTACCAGT-3'; IL-6, 5'-GCCAGAGTCCCTTCAGAGATACA-3', 5'-ATTGGATGTTCTTGTCCCTTAGCC-3'; TNF-α, 5'-TCTCATCAGTTCTATGGCCCAGAC-3', 5'-GGCACCACTAGTGTTGCTTGG-3'. As a control, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene was also amplified using 5'-GACATCAAGAGGTGTTGAGCAG-3', 5'-CCCTGGTTGCTGACGGTATTCC-3'.
UV-Vis absorption spectra in MeOH of compounds 3-7