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<th>Synthesis and the Intestinal Glucosidase Inhibitory Activity of 2-Aminoresorcinol Derivatives toward an Investigation of Its Binding Site</th>
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<td>Author(s)</td>
<td>KATO, Eisuke; OIKAWA, Kenichi; TAKAHASHI, Keisuke; KAWABATA, Jun</td>
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**General methods.**

Intestinal acetone powder from rat was purchased from Sigma-Aldrich Co. All other commercially available chemicals were purchased from Wako Pure Chem. Ind. Ltd. and used without further purification. Structures of the synthetic compounds were determined by NMR and Mass spectrometry. Bruker AMX500 or Jeol JNM-EX 270 was used to obtain NMR spectrum and either tetramethylsilane (TMS) or residual solvent peak was used as an internal standard (\(^1\text{H NMR: TMS 0.00 ppm for CDCl}_3, \text{acetone-}d_6 2.04 \text{ ppm, CD}_3\text{OD 3.30 ppm, DMSO-}d_6 2.50 \text{ ppm; } ^{13}\text{C NMR: CDCl}_3 77.0 \text{ ppm, acetone-}d_6 29.8 \text{ ppm, CD}_3\text{OD 49.0 ppm, DMSO-}d_6 39.5 \text{ ppm}). Jeol JMS SX-102A (FAB-MS) or Jeol JMS-T100GCV (FD-MS) or Thermo Scientific Exactive (ESI-MS) was used to obtain mass spectrum. Absorbance was measured by Synergy\textsuperscript{TM} MX (Bio-tech Instruments Inc.,) microplate reader.

**Intestinal \(\alpha\)-glucosidase inhibitory activity determination.**

Sucrase inhibition (SI) and maltase inhibition (MI) designates an inhibition of sucrose and maltose hydrolyzing activity in rat intestinal glucosidase complexes. Rat intestinal acetone powder (10 g) was homogenized in 70 mL of 0.1 M phosphate buffer (pH 7.0, 5 mM EDTA), centrifuged (15,000 g \(\times\) 30 min) and the supernatant was used as the crude intestinal \(\alpha\)-glucosidase. The reaction mixture consisting from crude enzyme, substrate (56 mM sucrose or 3.5 mM maltose in phosphate buffer) and the test sample (in 50\% DMSO aq.) was mixed and incubated at 37 °C as written in bellow table. The reaction was stopped by adding 0.75 mL of 2 M Tris-HCl buffer (pH 7.0) and then passed through a short column of Cosmosil 75C\textsubscript{18}-OPN (Nacalai Tesque, Inc.). The amount of liberated glucose was measured by glucose oxidase method using Glucose CII-test Wako (Wako Pure Chem. Co.).

<table>
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<th>Crude enzyme</th>
<th>Substrate</th>
<th>Sample</th>
<th>Incubation time</th>
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<td>0.20 mL</td>
<td>0.1 mL</td>
<td>30 min</td>
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<td>MI assay</td>
<td>0.05 mL</td>
<td>0.35 mL</td>
<td>0.1 mL</td>
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Synthesis of 2-aminoresorcinol derivatives.

Scheme S1. Reagent and conditions: (a) H₂, Pd/C (10%), MeOH, rt (b) AcCl, MeOH, -40°C to rt (c) BnBr, K₂CO₃, MeCN, rt (d) Zn, AcOH, rt (e) MeI, K₂CO₃, acetone, reflux (f) MeOH, DIAD, PPh₃, THF, rt (g) Me₂SO₄, K₂CO₃, acetone, reflux.
Scheme S2. Reagent and conditions: (a) propanol, DIAD, PPh₃, THF, rt (b) H₂, 10% Pd/C, MeOH, rt (c) heptanol, DIAD, PPh₃, THF, rt.

Scheme S3. Reagent and conditions: (a) N-iodosuccinimide, trifluoroacetic acid, rt (b) MOMCl, i-Pr₂NEt, DMF, rt (c) methyl acrylate, Et₃N, Pd(OAc)₂, tri-O-tolylphosphine, MeCN, 70°C (d) Mel, K₂CO₃, acetone, reflux (e) AcCl, MeOH, rt (f) H₂, Pd/C, Boc₂O, THF, rt (g) LiAlH₄, THF, rt (h) H₂O, reflux.
Scheme S4. Reagent and conditions: (a) BnBr, K₂CO₃, MeCN, reflux (b) AcCl, MeOH, rt (c) MeI, K₂CO₃, acetone, reflux (d) H₂, Pd/C, Boc₂O, THF, rt (e) LiAlH₄, THF, rt (f) H₂O, reflux.

Scheme S5. Reagent and conditions: (a) BF₃·Et₂O, RCO₂H, 80ºC (b) 70% HNO₃ aq., AcOH, rt (c) H₂, Pd/C, MeOH, rt.

Scheme S6. Reagent and conditions: (a) ROH, H₂SO₄, reflux (b) H₂, Pd/C, MeOH, rt.
Scheme S7. Reagent and conditions: (a) MOMCl, i-Pr₂NEt, THF, rt (b) LiAlH₄, THF, Et₂O, 0°C (c) conc. HCl, MeOH, 60°C (d) 10% Pd/C, H₂, MeOH, rt (e) HCl, 1,4-dioxane, rt.

Scheme S8. Reagent and conditions: (a) H₂, Pd/C, Boc₂O, THF, rt (b) MOMCl, i-Pr₂NEt, DMF, 0°C (c) 36, 50% NaOH aq., 1,4-dioxane, rt (d) H₂, Pd/C, MeOH, rt (e) 3-(chlorosulfonyl)benzoyl chloride, pyridine, CH₂Cl₂, 0 °C (f) 9-azidononanol, DMAP, CH₂Cl₂, 0°C (g) HCl, 1,4-dioxane, 0°C.
\[
\text{OH} \quad \text{N} \quad \text{OH} \\
\text{O} \quad \text{N-(2,6-Dihydroxyphenyl)acetamide (2).}^{19} \text{2-Nitroresorcinol (15, 1.0 g, 6.4 mmol) was dissolved in MeOH (20 mL) and 10\% Pd/C (100 mg) was added to the solution. After stirring overnight under hydrogen atmosphere, the reaction mixture was passed through Celite}^\circledR \text{ pad. The filtrate was cooled to -40\ºC and AcCl (2 mL) was added dropwise. The mixture was warmed to rt and stirred for 5 hours. The reaction mixture was evaporated and suspended in acetone. The resulting suspension was filtered and the filtrate was dried to give 2 (0.57 g, 53\%).}
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FD-MS (positive): \( m/z \) (\%) 167 (100, [M]+). \(^1\)H-NMR (270 MHz, acetone-\( d_6 \), rt): 2.25 (s, 3H, CH\(_3\)), 6.38 (d, 2H, \( J = 8.0 \) Hz, H-3,5), 6.84 (t, 1H, \( J = 8.0 \) Hz, H-4) ppm.

\[
\text{OBn} \quad \text{O} \quad \text{2-Nitroresorcinol (15, 1.0 g, 6.4 mmol) was dissolved in MeOH (20 mL) and 10\% Pd/C (100 mg) was added to the solution. After stirring overnight under hydrogen atmosphere, the reaction mixture was passed through Celite}^\circledR \text{ pad. The filtrate was cooled to -40\ºC and AcCl (2 mL) was added dropwise. The mixture was warmed to rt and stirred for 5 hours. The reaction mixture was evaporated and suspended in acetone. The resulting suspension was filtered and the filtrate was dried to give 2 (0.57 g, 53\%).}
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\text{OBn} \quad \text{O} \quad \text{OBn} \\
\text{1,3-Bis(benzyloxy)-2-nitrobenzene (16). 2-Nitroresorcinol (15, 1.66 g, 10.7 mmol) was dissolved in MeCN (40 mL) and K\(_2\)CO\(_3\) (5.0 g, 36.2 mmol), benzyl bromide (3.0 mL, 25.2 mmol) was added. After stirring for 10 days, the reaction mixture was filtered and the filtrate was evaporated. The residue was purified by silica-gel column chromatography (Hexane/EtOAc) to give 16 (2.67 g, 74\%).}
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HR-FD-MS (positive): Found \( m/z \) 335.1151 ([M]+, calcd. for C\(_{20}\)H\(_{17}\)NO\(_4\) 335.1158); \(^1\)H-NMR (270 MHz, CDCl\(_3\), rt): 5.16 (s, 4H, OCH\(_2\)), 6.64 (d, 2H, \( J = 8.5 \) Hz, H-3,5), 7.23 (t, 1H, \( J = 8.5 \) Hz, H-4), 7.31-7.38 (m, 10H, Ph) ppm.

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\text{OBn} \quad \text{Me}_2\text{N} \quad \text{OBn} \\
\text{2,6-Bis(benzyloxy)-N,N-dimethylaniline (17). Compound 16 (934.5 mg, 2.8 mmol) was dissolved in}
\]

acetic acid (50 mL) and zinc powder (10.8 g, 165.1 mmol) was added. After stirring for 30 min, the reaction mixture was passed through Celite® pad and evaporated. The residue was dissolved in acetone (5 mL) and K₂CO₃ (336 mg, 2.4 mmol), iodomethane (0.39 mL, 5.93 mmol) was added. The mixture was refluxed overnight, then cooled to rt, filtered and evaporated. The residue was purified by silica-gel column chromatography (Hexane/EtOAc) to give 17 (730.4 mg, 79%).

HR-FD-MS (positive): Found m/z 333.1727 ([M]+, calcd. for C₂₂H₂₃NO₂ 333.1729); ¹H-NMR (270 MHz, CDCl₃, rt): 2.89 (s, 6H, NMe₂), 5.14 (s, 4H, OCH₂), 6.56 (d, 2H, J = 8.3 Hz, H-3,5), 6.91 (t, 1H, J = 8.3 Hz, H-4), 7.30-7.46 (m, 10H, Ph) ppm; ¹³C-NMR (67.5 MHz, CDCl₃, rt): 43.6, 70.7, 107.11, 107.13, 124.6, 127.1, 127.6, 128.4, 137.6, 156.8 ppm.

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\text{2,6-Dihydroxy-N,N-dimethylaniline (3). Compound 17 (730 mg, 2.2 mmol) was dissolved in MeOH (15 mL) and 10\% Pd/C (39.3 mg) was added. After stirring overnight under hydrogen atmosphere, the resulting mixture was passed through Celite® pad and evaporated. The residue was purified by silica-gel column chromatography (CHCl₃/MeOH) to give 3 (49.8 mg, 15\%).}
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HR-FD-MS (positive): Found m/z 153.0771 ([M]+, calcd. for C₈H₁₁NO₂ 153.0790); ¹H-NMR (270 MHz, CD₃OD, rt): 2.71 (s, 6H, NMe₂), 6.22 (d, 2H, J = 8.1 Hz, H-3,5), 6.74 (t, 1H, J = 8.1 Hz, H-4) ppm; ¹³C-NMR (67.5 MHz, CD₃OD, rt): 43.6, 107.1, 126.9, 127.8, 156.7 ppm.

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\text{2,6-Dimethoxyaniline (4).}^{20} \text{2-Nitroresorcinol (15, 833 mg, 5.37 mmol) was dissolved in acetone (15 mL) and K₂CO₃ (1.5 g, 10.87 mmol), dimethyl sulfate (1.05 mL, 12 mmol) was added and refluxed overnight. The reaction mixture was filtered and evaporated. The residue was partially purified by}
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silica-gel column chromatography (Hexane/EtOAc) and the crude product (1.11 g) was dissolved in acetone (40 mL). Zinc powder (9.6 g) was added to the solution and the mixture was stirred for 30 min. The reaction mixture was passed through Celite® pad and evaporated. The residue was purified by silica-gel column chromatography (Hexane/EtOAc) to give 4 (240 mg, 29%).

HR-FD-MS (positive): Found m/z 153.0771 ([M]+, calcd. for C₈H₁₁NO₂ 153.0790); ¹H-NMR (270 MHz, CDCl₃, rt): 3.85 (6H, s), 6.53 (2H, d, J = 8.1 Hz), 6.69 (1H, t, J = 8.1 Hz) ppm

2-Amino-3-methoxyphenol (5). 2-Nitroresorcinol (15, 250 mg, 1.60 mmol) was dissolved in THF (15 mL) and MeOH (60 µL, 1.90 mmol), Ph₃P (420 mg, 1.60 mmol) was added. After stirring for 10 min under nitrogen atmosphere, diisopropyl azodicarboxylate (DIAD, 0.32 mL, 1.60 mmol) was added and stirred overnight under nitrogen atmosphere. The reaction mixture was evaporated and the residue was partially purified by silica-gel column chromatography (Hexane/EtOAc). The crude product (119.3 mg) was dissolved in MeOH (5 mL), 10% Pd/C (12.7 mg) was added and stirred overnight under hydrogen atmosphere. The reaction mixture was passed through Celite® pad and the filtrate was evaporated. The residue was purified by silica-gel column chromatography (Hexane/EtOAc) to give 5 (43.4 mg, 20%).

HR-FD-MS (positive): Found m/z 139.0630 ([M]+, calcd. for C₇H₉NO₂ 139.0633); ¹H-NMR (270 MHz, CDCl₃, rt): 3.84 (3H, s), 4.28 (2H, s), 6.46 (2H, d, J = 8.0 Hz), 6.65 (1H, t, J = 8.0 Hz) ppm

2-Nitro-3-propoxyphenol (18). To the solution of 2-nitroresorcinol (15, 0.25 g, 1.6 mmol) dissolved in THF (15 mL), propanol (0.12 mL, 1.6 mmol) and Ph₃P (0.42 g, 1.6 mmol) were added and stirred
for 10 min under argon atmosphere. To this mixture, DIAD (0.32 mL, 1.6 mmol) was added and further stirred overnight under argon atmosphere. The reaction mixture was evaporated and purified by silica-gel column chromatography (Hexane/EtOAc) to give 18 (136.9 mg, 43%).

HR-FD-MS (positive): Found m/z 197.0698 ([M]+, calcd. for C9H11NO4 197.0688); 1H-NMR (270 MHz, CDCl3, rt): 1.09 (3H, t, J = 7.4 Hz), 1.94-1.81 (2H, m), 4.03 (2H, t, J = 6.3 Hz), 6.52 (1H, d, J = 8.4 Hz), 6.68 (1H, d, J = 8.4 Hz), 7.37 (1H, t, J = 8.4 Hz), 10.19 (1H, s), ppm; 13C-NMR (67.5 MHz, CDCl3, rt): 10.3, 22.2, 71.2, 104.4, 110.1, 135.4, 155.2, 155.3 ppm

2-Amino-3-propoxyphenol (7). Compound 18 (128 mg, 0.65 mmol) was dissolved in MeOH (5 mL), 10% Pd/C (11.7 mg) was added and stirred overnight under hydrogen atmosphere. The reaction mixture was passed through Celite® pad and evaporated. The residue was purified by silica-gel column chromatography (Hexane/EtOAc) to give 7 (60.7 mg, 56%).

HR-FD-MS (positive): Found m/z 167.0943 ([M]+, calcd. for C9H13NO2 167.0946); 1H-NMR (270 MHz, CD3OD, rt): 1.01 (3H, t, J = 7.4 Hz), 1.88-1.75 (2H, m), 4.00 (2H, t, J = 6.6 Hz), 6.55 (1H, d, J = 8.4 Hz), 6.56 (1H, d, J = 8.4 Hz), 7.09 (1H, t, J = 8.4 Hz) ppm; 13C-NMR (67.5 MHz, CD3OD, rt): 10.7, 23.3, 71.7, 104.4, 109.2, 109.3, 129.8, 152.5, 154.0 ppm

3-Heptyloxy-2-nitrophenol (19). To the solution of 2-nitroresorcinol (15, 0.25 g, 1.6 mmol) dissolved in THF (15 mL), heptanol (0.23 mL, 1.6 mmol) and Ph3P (0.42 g, 1.6 mmol) were added and stirred for 10 min under argon atmosphere. To this mixture, DIAD (0.32 mL, 1.6 mmol) was added and further stirred overnight under argon atmosphere. The reaction mixture was evaporated and purified
by silica-gel column chromatography (Hexane/EtOAc) to give 19 (203.6 mg, 50%).

HR-FD-MS (positive): Found m/z 253.1306 ([M]+, calcd. for C_{13}H_{19}NO_{4} 253.1314); \(^1\)H-NMR (270 MHz, CDCl\(_3\), rt): 0.90 (3H, t, J = 6.5 Hz), 1.56-1.26 (8H, m), 1.85 (2H, m), 4.06 (2H, t, J = 6.4 Hz), 6.52 (1H, d, J = 8.5 Hz), 6.67 (1H, d, J = 8.5 Hz), 7.37 (1H, t, J = 8.5 Hz), 10.19 (1H, s) ppm; \(^{13}\)C-NMR (67.5 MHz, CDCl\(_3\), rt): 14.0, 22.5, 25.8, 28.9, 29.0, 31.7, 69.9, 104.4, 105.7, 110.2, 135.5, 155.4, 155.5 ppm

2-Amino-3-heptyloxyphenol (8). Compound 19 (198.2 mg, 0.78 mmol) was dissolved in MeOH (5 mL), 10% Pd/C (14 mg) was added and stirred overnight under hydrogen atmosphere. The reaction mixture was passed through Celite\(^\circledR\) pad and evaporated to give 8 (193.8 mg, quant.)

HR-FD-MS (positive): Found m/z 223.1544 ([M]+, calcd. for C_{13}H_{21}NO_{2} 223.1572); \(^1\)H-NMR (270 MHz, CDCl\(_3\), rt): 0.89 (3H, t, J = 6.7 Hz), 1.55-1.22 (8H, m), 1.80 (2H, m), 3.97 (2H, t, J = 6.5 Hz), 4.06 (2H, br s), 6.45 (2H, d, J = 8.0 Hz), 6.65 (1H, t, J = 8.0 Hz) ppm; \(^{13}\)C-NMR (67.5 MHz, CDCl\(_3\), rt): 14.0, 22.5, 25.9, 29.0, 29.3, 31.7, 68.5, 104.0, 108.9, 119.8, 121.5, 145.9, 148.8 ppm.

1-Iodo-2,4-bis(methoxymethoxy)-3-nitrobenzene (20).\(^{22}\) 2-Nitroresorcinol (15, 1.61g, 10.4 mmol) was dissolved in TFA (45 mL) and NIS (2.28 g, 10.1 mmol) was added in portion at 0°C. After stirring for 30 min at rt, cold water was added to the reaction mixture and extracted with toluene. The organic layer was washed with sat. NaHSO\(_3\) aq., dried over sodium sulfate and evaporated to dryness. The residue was dissolved in DMF (45 mL), i-Pr\(_2\)NEt (4.5 mL, 27.6 mmol) and MOMCl (2.55 mL, 31.6 mmol) was added and stirred for 5 hours at rt. Water was added to the reaction mixture and the
resulting solution was extracted with EtOAc. Organic layer was washed with water, dried over sodium sulfate and evaporated to dryness. The residue was purified by silica-gel column chromatography (Hexane/EtOAc = 5/1) to obtain 20 (3.56 g, 93%).

FD-MS (positive): m/z 369 ([M]+); ¹H-NMR (270 MHz, CDCl₃, rt): 3.48 (3H, s), 3.54 (3H, s), 5.14 (2H, s), 5.22 (2H, s), 6.89 (1H, d, J = 9.0 Hz), 7.79 (1H, d, J = 9.0 Hz) ppm.

Methyl 2-hydroxy-4-methoxymethoxy-3-nitrocinnamate (21). Compound 20 (1.97 g, 5.3 mmol) was dissolved in MeCN (70 mL) and Methyl acrylate (2.86 mL, 30 mmol), tri-O-tolyolphosine (1.2 g, 5.2 mmol), TEA (7.0 mL, 52 mmol), Pd(OAc)₂ (590 mg, 2.6 mmol) was added. The mixture was stirred for 6 hours at 70°C under nitrogen atmosphere. Sat. NH₄Cl aq. was added and the reaction mixture was extracted with EtOAc. Organic layer was washed with brine, dried over sodium sulfate and evaporated to dryness. The residue was partly purified by silica-gel column chromatography (Hexane/EtOAc = 4/1) to obtain 21 (1.54 g, quant).

HR-FD-MS (positive): Found m/z 283.0684 ([M]+, calcd. for C₁₂H₁₃NO₇ 283.0692); ¹H-NMR (270 MHz, CDCl₃, rt): 3.54 (3H, s), 3.81 (3H, s), 5.33 (2H, s), 6.52 (1H, d, J = 16.2 Hz), 6.84 (1H, d, J = 9.0 Hz), 7.63 (1H, d, J = 9.0 Hz), 7.91 (1H, d, J = 16.2 Hz) ppm

Methyl 2-methoxy-4-methoxymethoxy-3-nitrocinnamate (22). Compound 21 (1.45 g, 5.12 mmol) was dissolved in acetone (5 mL) and K₂CO₃ (307 mg, 2.2 mmol), MeI (0.36 mL, 5.8 mmol) was added. The mixture was refluxed for 5 hours, cooled to rt, filtered and the filtrate was evaporated to dryness. Water was added to the residue and the resulting suspension was extracted by EtOAc. The organic
layer was washed with brine, dried over sodium sulfate and evaporated to dryness. The residue was purified by silica-gel column chromatography (Hexane/EtOAc = 5/1) to obtain 22 (0.87 g, 58%). HR-FD-MS (positive): Found m/z 297.0837 ([M]⁺, calcd. for C₁₃H₁₅NO₇ 297.0849); ¹H-NMR (270 MHz, CDCl₃, rt): 3.49 (3H, s), 3.82 (3H, s), 3.90 (3H, s), 5.26 (2H, s), 6.46 (1H, d, J = 16.2 Hz), 7.07 (1H, d, J = 9.1 Hz), 7.58 (1H, d, J = 9.1 Hz), 7.79 (1H, d, J = 16.2 Hz) ppm.

Methyl 4-hydroxy-2-methoxy-3-nitrocinnamate (23). Compound 22 (1.61 g, 5.43 mmol) was dissolved in MeOH (45 mL) and AcCl (3.5 mL) was added to the solution. The mixture was stirred for 8.5 hours at rt and then evaporated to dryness. The residue was purified by silica-gel column chromatography (Hexane/EtOAc = 3/1) to obtain 23 (1.31 g, 95%). HR-FD-MS (positive): Found m/z 253.0592 ([M]⁺, calcd. for C₁₁H₁₁NO₆ 253.0586); ¹H-NMR (270 MHz, acetone-d₆, rt): 3.71 (3H, s), 3.85 (3H, s), 6.48 (1H, d, J = 16.1 Hz), 6.94 (1H, d, J = 8.9 Hz), 7.71 (1H, d, J = 16.1 Hz), 7.77 (1H, d, J = 8.9 Hz) ppm.

Methyl 3-((tert-butoxycarbonyl)amino)-4-hydroxy-2-methoxyphenylpropanoate (24). Compound 23 (1.25 g, 4.9 mmol) was dissolved in THF (35 mL) and 10% Pd on activated carbon (0.18 g), Boc₂O (2.7 g, 12.4 mmol) were added. The mixture was stirred overnight under hydrogen atmosphere. MeOH was added to the reaction mixture and the resulting suspension was passed through Celite® pad. The residue was partially purified by silica-gel column chromatography (Hexane/EtOAc = 2/1) to obtain 24 (1.21 g, 75%). HR-FD-MS (positive): Found m/z 325.1504 ([M]⁺, calcd. for C₁₆H₂₃NO₆ 325.1525); ¹H-NMR (270 MHz, acetone-d₆, rt): 3.71 (3H, s), 3.85 (3H, s), 6.48 (1H, d, J = 16.1 Hz), 6.94 (1H, d, J = 8.9 Hz), 7.71 (1H, d, J = 16.1 Hz), 7.77 (1H, d, J = 8.9 Hz) ppm.
MHz, CDCl₃, rt): 1.54 (9H, s), 2.58 (2H, t, \( J = 7.8 \) Hz), 2.88 (2H, t, \( J = 7.8 \) Hz), 3.67 (3H, s), 3.75 (3H, s), 6.72 (1H, d, \( J = 8.5 \) Hz), 6.86 (1H, d, \( J = 8.5 \) Hz), 6.97 (1H, br s), 9.13 (1H, br s) ppm.

3-(N-(tert-Butoxycarbonyl)-3-amino-4-hydroxy-2-methoxyphenyl)propanol (25). Compound 24 (1.17 g, 3.6 mmol) was dissolved in THF (30 mL) and LiAlH₄ (0.15 g, 4.0 mmol) was added at 0ºC. The mixture was stirred overnight and EtOAc was added to the reaction mixture. The resulting solution was washed with 1 M HCl aq. and brine, then dried over sodium sulfate, and evaporated to dryness. The residue was purified by silica-gel column chromatography (CHCl₃/MeOH = 100/1) to obtain 25 (0.86 g, 80%).

HR-FD-MS (positive): Found \( m/z \) 297.1548 ([M]+, calcd. for C₁₅H₂₃NO₅ 297.1576); \(^1\)H-NMR (270 MHz, CDCl₃, rt): 1.54 (9H, s), 1.87-1.77 (2H, m), 2.66 (2H, t, \( J = 7.4 \) Hz), 3.58 (2H, t, \( J = 6.2 \) Hz), 3.75 (3H, s), 6.75 (1H, d, \( J = 8.5 \) Hz), 6.88 (1H, d, \( J = 8.5 \) Hz), 6.96 (1H, br s), 9.12 (1H, br s) ppm.

3-(3-Amino-4-hydroxy-2-methoxyphenyl)propanol (9). Compound 25 (48 mg, 0.16 mmol) was suspended in water (3.2 mL) and refluxed for two hours. The reaction mixture was cooled and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and evaporated to obtain pure 9 (17.4 mg, 55%).

HR-FD-MS (positive): Found \( m/z \) 197.1042 ([M]+, calcd. for C₁₀H₁₅NO₃ 197.1052); \(^1\)H-NMR (270 MHz, CD₃OD, rt): 1.78-1.67 (2H, m), 2.53 (2H, t, \( J = 7.7 \) Hz), 3.51 (2H, t, \( J = 6.6 \) Hz), 3.69 (3H, s), 6.36 (1H, d, \( J = 8.2 \) Hz), 6.41 (1H, d, \( J = 8.2 \) Hz) ppm.
**Methyl 2-benzyloxy-4-methoxymethoxy-3-nitrocinnamate (26).** Compound 21 was dissolved in MeCN (30 mL) and K$_2$CO$_3$ (1.12 g, 8.11 mmol), BnBr (0.90 mL, 7.57 mmol) was added. The mixture was refluxed for 90 min, cooled to rt and filtered. The filtrate was evaporated to dryness and the residue was purified by silica-gel column chromatography (Hexane/EtOAc = 4/1) to obtain 26 (2.10 g, 87%).

HR-FD-MS (positive): Found $m/z$ 373.1156 ([M]$^+$, calcd. for C$_{19}$H$_{19}$NO$_7$ 373.1162); $^1$H-NMR (270 MHz, CDCl$_3$, rt): 3.50 (3H, s), 3.80 (3H, s), 4.99 (2H, s), 5.27 (2H, s), 6.42 (1H, d, $J$ = 16.2 Hz), 7.10 (1H, d, $J$ = 8.9 Hz), 7.43-7.36 (5H, m), 7.59 (1H, d, $J$ = 8.9 Hz), 7.82 (1H, d, $J$ = 16.2 Hz) ppm.

**Methyl 2-benzyloxy-4-hydroxy-3-nitrocinnamate (27).** Compound 26 (2.09 g, 5.6 mmol) was dissolved in MeOH (50 mL) and AcCl (4.4 mL) was added. After stirring overnight, water was added and the reaction mixture was extracted with EtOAc. Organic layer was washed with brine, dried over sodium sulfate and evaporated to dryness. The residue was purified by silica-gel column chromatography (Hexane/EtOAc = 2/1) to obtain 27 (1.51 g, 82%).

HR-FD-MS (positive): Found $m/z$ 329.0879 ([M]$^+$, calcd. for C$_{17}$H$_{15}$NO$_6$ 329.0899); $^1$H-NMR (270 MHz, CDCl$_3$, rt): 3.80 (3H, s), 5.00 (2H, s), 6.36 (1H, d, $J$ = 16.2 Hz), 6.98 (1H, d, $J$ = 9.0 Hz), 7.51-7.38 (5H, m), 7.71 (1H, d, $J$ = 9.0 Hz), 7.90 (1H, d, $J$ = 16.2 Hz), 10.02 (1H, s) ppm.
Methyl 2-benzyloxy-4-methoxy-3-nitrocinnamate (28). Compound 27 (1.51 g, 4.59 mmol) was dissolved in acetone (20 mL) and K₂CO₃ (275 mg, 1.99 mmol), MeI (0.32 mL, 5.1 mmol) was added. The mixture was refluxed for 5 hours and K₂CO₃ (100 mg, 0.72 mmol), MeI (0.20 mL, 3.2 mmol) was added again. After refluxing overnight, the reaction mixture was cooled and filtered. The filtrate was evaporated, water was added to the residue and the suspension was extracted with EtOAc. Organic layer was washed with brine, dried over sodium sulfate and evaporated to dryness. The residue was purified by silica-gel column chromatography (Hexane/EtOAc = 3/1) to obtain 28 (1.80 g, quant).

HR-FD-MS (positive): Found m/z 343.1045 ([M]+, calcd. for C₁₈H₁₇NO₆ 343.1056); ¹H-NMR (270 MHz, CDCl₃, rt): 3.54 (3H, s), 3.81 (3H, s), 5.33 (2H, s), 6.52 (1H, d, \( J = 16.2 \) Hz), 6.84 (1H, d, \( J = 9.0 \) Hz), 7.63 (1H, d, \( J = 9.0 \) Hz), 7.91 (1H, d, \( J = 16.2 \) Hz) ppm.

Methyl 3-((tert-Butoxycarbonyl)amino)-2-hydroxy-4-methoxyphenyl)propanoate (29). To the solution of 28 (1.80 g, 5.24 mmol) dissolved in THF (40 mL), 10% Pd on carbon (185 mg), Boc₂O (1.9 g, 8.71 mmol) was added and stirred overnight under hydrogen atmosphere. The reaction mixture was passed through Celite® pad, evaporated and the residue was purified by silica-gel column chromatography (Hexane/EtOAc = 3/1) to obtain 29 (1.29 g, 76%).

HR-FD-MS (positive): Found m/z 325.1521 ([M]+, calcd. for C₁₆H₂₃NO₆ 325.1525); ¹H-NMR (270 MHz, CDCl₃, rt): 1.53 (9H, s), 2.65 (2H, t, \( J = 7.6 \) Hz), 2.93 (2H, t, \( J = 7.6 \) Hz), 3.66 (3H, s), 3.83 (3H, s), 6.37 (1H, d, \( J = 8.3 \) Hz), 6.89 (1H, d, \( J = 8.3 \) Hz), 6.96 (1H, br s), 9.52 (1H, br s) ppm.
3-(3-(tert-Butoxycarbonyl)amino-2-hydroxy-4-methoxyphenyl)propanol (30). Compound 29 (1.29 g, 3.96 mmol) was dissolved in THF (20 mL) and LiAlH₄ (178 mg, 4.69 mmol) was added at 0°C. After stirring for 4 hours, LiAlH₄ (100 mg, 2.64 mmol) was added again and stirred for an hour at rt. The reaction mixture was diluted with EtOAc, washed sequentially with 1 M HCl aq. and brine. The organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by silica-gel column chromatography (CHCl₃/MeOH = 100/1) to obtain 30 (1.20 g, quant).

HR-FD-MS (positive): Found \( m/z \) 297.1575 ([M]+, calcd. for C₁₅H₂₃NO₅ 297.1576); \(^1\)H-NMR (270 MHz, CDCl₃, rt): 1.53 (9H, s), 1.88-1.78 (2H, m), 2.74 (2H, t, \( J = 7.0 \) Hz), 3.58 (2H, t, \( J = 6.0 \) Hz), 3.84 (3H, s), 6.41 (1H, d, \( J = 8.3 \) Hz), 6.88 (1H, d, \( J = 8.3 \) Hz), 6.99 (1H, br s), 9.78 (1H, br s) ppm.

3-(3-Amino-2-hydroxy-4-methoxyphenyl)propanol (10). Compound 30 (22.9 mg, 0.077 mmol) was suspended in water (1.5 mL) and refluxed for two hours. The reaction mixture was extracted with EtOAc and the organic layer was washed with brine, dried over sodium sulfate and evaporated to obtain 10 (14 mg, 92%).

HR-FD-MS (positive): Found \( m/z \) 197.1032 ([M]+, calcd. for C₁₀H₁₅NO₃ 197.1052); \(^1\)H-NMR (270 MHz, CD₃OD, rt): 1.81-1.71 (2H, m), 2.61 (2H, t, \( J = 7.4 \) Hz), 3.53 (2H, t, \( J = 6.4 \) Hz), 3.79 (3H, s), 6.41 (1H, d, \( J = 8.4 \) Hz), 6.49 (1H, d, \( J = 8.4 \) Hz) ppm.

General procedure for the synthesis of 4-acylresorcinol (32c-g).\(^{23}\) Resorcinol (31, 10 mmol) was suspended in the corresponding chain length of acids (5 mL, C₄-C₈) and BF₃·Et₂O (20 mmol) was added. The mixture was stirred for 6 hours at 80°C. After cooling, water was added and the resulting
solution was extracted with EtOAC. Organic layer was washed with water, dried over sodium sulfate and evaporated to dryness. The residue was purified by silica-gel column chromatography (Hexane/EtOAc) to obtain 32c-g (83-92%).

\[
\text{1-(2,4-Dihydroxyphenyl)butan-1-one (32c). FD-MS (positive): m/z 180 ([M]^+); } \ \text{^1H NMR (500 MHz, acetone-d}_6, \text{ rt): 0.96 (3H, t, J = 7.3 Hz, H-4), 1.70 (2H, m, H-3), 2.92 (2H, t, J = 7.3 Hz, H-2), 6.31 (1H, d, J = 2.3 Hz, H-3')}, 6.41 (1H, dd, J = 8.9, 2.3 Hz, H-5'), 7.78 (1H, d, J = 8.9 Hz, H-6') \text{ ppm.}
\]

\[
\text{1-(2,4-Dihydroxyphenyl)pentan-1-one (32d). FD-MS (positive): m/z 194 ([M]^+); } \ \text{^1H NMR (500 MHz, acetone-d}_6, \text{ rt): 0.92 (3H, t, J = 7.3 Hz, H-5), 1.38 (2H, m, H-4), 1.66 (2H, m, H-3), 2.94 (2H, t, J = 7.4 Hz, H-2), 6.31 (1H, d, J = 2.4 Hz, H-3'), 6.41 (1H, dd, J = 8.9, 2.4 Hz, H-5'), 7.79 (1H, d, J = 8.9 Hz, H-6') \text{ ppm.}
\]

\[
\text{1-(2,4-Dihydroxyphenyl)hexan-1-one (32e). FD-MS (positive): m/z 208 ([M]^+); } \ \text{^1H NMR (500 MHz, acetone-d}_6, \text{ rt): 0.89 (3H, t, J = 7.3 Hz, H-6), 1.35 (4H, m, H-4, 5), 1.69 (2H, m, H-3), 2.94 (2H, t, J = 7.4 Hz, H-2), 6.31 (1H, d, J = 2.4 Hz, H-3'), 6.42 (1H, dd, J = 8.9, 2.4 Hz, H-5'), 7.80 (1H, d, J = 8.8 Hz, H-6') \text{ ppm.}
\]
1-(2,4-Dihydroxyphenyl)heptan-1-one (32f). FD-MS (positive): m/z 222 ([M]+); $^1$H NMR (500 MHz, acetone-$d_6$, rt): 0.88 (3H, $t$, $J = 6.9$ Hz, H-6), 1.31-1.41 (6H, $m$, H-4,5,6), 1.68 (2H, $m$, H-3), 2.96 (2H, $t$, $J = 7.4$ Hz, H-2), 6.31 (1H, $d$, $J = 2.4$ Hz, H-3’), 6.42 (1H, $dd$, $J = 8.9, 2.4$ Hz, H-5’), 7.81 (1H, $d$, $J = 8.9$ Hz, H-6’) ppm.

1-(2,4-Dihydroxyphenyl)octan-1-one (32g). FD-MS (positive): m/z 236 ([M]+); $^1$H NMR (500 MHz, acetone-$d_6$, rt): 0.87 (3H, $t$, $J = 6.9$ Hz, H-6), 1.29-1.36 (8H, $m$, H-4,5,6,7), 1.69 (2H, $m$, H-3), 2.95 (2H, $t$, $J = 7.4$ Hz, H-2), 6.31 (1H, $d$, $J = 2.4$ Hz, H-3’), 6.42 (1H, $dd$, $J = 8.9, 2.4$ Hz, H-5’), 7.81 (1H, $d$, $J = 8.9$ Hz, H-6’) ppm.

**General procedure for the synthesis of 4-acyl-2-nitroresorcinol (33).** Compound 32* (10 mmol) was dissolved in acetic acid (20 mL) and the mixture of 70% nitric acid aq. (1.4 mL) and acetic acid (10 mL) was added drop by drop. After stirring for 6 hours, the reaction mixture was diluted by water and extracted with EtOAc. The organic layer was washed by water, dried over sodium sulfate and evaporated to dryness. The residue was purified by silica-gel column chromatography (Hexane/EtOAc) to obtain 33a-g (12-27%).

*Commercial compound was used for 32a,b.
1-(2,4-Dihydroxy-3-nitrophenoxy)ethan-1-one (33a). HR-FD-MS (positive): Found m/z 197.0338 ([M]$^+$, calcd. for C$_8$H$_7$NO$_5$ 197.0324); $^1$H NMR (500 MHz, acetone-$d_6$, rt): 2.63 (3H, s, CH$_3$), 6.69 (1H, d, $J$ = 9.0 Hz, H-5), 7.99 (1H, d, $J$ = 9.0 Hz, H-6) ppm.

1-(2,4-Dihydroxy-3-nitrophenoxy)propan-1-one (33b). HR-FD-MS (positive): Found m/z 211.0496 ([M]$^+$, calcd. for C$_9$H$_9$NO$_5$ 211.0481); $^1$H NMR (500 MHz, acetone-$d_6$, rt): 1.64 (3H, t, $J$ = 7.2 Hz, CH$_3$), 3.09 (2H, q, $J$ = 7.2 Hz, CH$_2$), 6.69 (1H, d, $J$ = 9.0 Hz, H-5), 8.0 (1H, d, $J$ = 9.0 Hz, H-6) ppm.

1-(2,4-Dihydroxy-3-nitrophenoxy)butan-1-one (33c). HR-FD-MS (positive): Found m/z 225.0653 ([M]$^+$, calcd. for C$_{10}$H$_{11}$NO$_5$, 225.0637); $^1$H NMR (500 MHz, acetone-$d_6$, rt): 0.98 (3H, t, $J$ = 7.3 Hz, H-4), 1.73 (2H, m, H-3), 3.03 (2H, t, $J$ = 7.3 Hz, H-2), 6.69 (1H, d, $J$ = 8.9 Hz, H-5$'$), 8.03 (1H, d, $J$ = 8.9 Hz, H-6$'$) ppm.

1-(2,4-Dihydroxy-3-nitrophenoxy)pentan-1-one (33d). HR-FD-MS (positive): Found m/z 239.0806 ([M]$^+$, calcd. for C$_{11}$H$_{13}$NO$_5$, 239.0794); $^1$H NMR (500 MHz, acetone-$d_6$, rt): 0.93 (3H, t, $J$ = 7.3 Hz,
H-5), 1.41 (2H, m, H-4), 1.71 (2H, m, H-3), 3.05 (2H, t, J = 7.3 Hz, H-2), 6.69 (1H, d, J = 8.9 Hz, H-5\textsuperscript{\prime}), 8.04 (1H, d, J = 8.9 Hz, H-6\textsuperscript{\prime}) ppm.

1-(2,4-Dihydroxy-3-nitrophenyl)hexan-1-one (33e). HR-FD-MS (positive): Found m/z 253.0960 ([M]\textsuperscript{+}, calcd. for C\textsubscript{12}H\textsubscript{15}NO\textsubscript{5}, 253.0950); \textsuperscript{1}H NMR (500 MHz, acetone-\textit{d}_6, rt): 0.89 (3H, t, J = 7.4 Hz, H-6), 1.37 (4H, m, H-4,5), 1.71 (2H, m, H-3), 3.05 (2H, t, J = 7.4 Hz, H-2), 6.69 (1H, d, J = 9.0 Hz, H-5\textsuperscript{\prime}), 8.04 (1H, d, J = 9.0 Hz, H-6\textsuperscript{\prime}) ppm.

1-(2,4-Dihydroxy-3-nitrophenyl)heptan-1-one (33f). HR-FD-MS (positive): Found m/z 267.1118 ([M]\textsuperscript{+}, calcd. for C\textsubscript{13}H\textsubscript{17}NO\textsubscript{5}, 267.1107); \textsuperscript{1}H NMR (500 MHz, acetone-\textit{d}_6, rt): 0.88 (3H, t, J = 7.4 Hz, H-6), 1.28-1.42 (6H, m, H-4,5,6), 1.71 (2H, m, H-3), 3.06 (2H, t, J = 7.4 Hz, H-2), 6.7 (1H, d, J = 9.0 Hz, H-5\textsuperscript{\prime}), 8.04 (1H, d, J = 9.0 Hz, H-6\textsuperscript{\prime}) ppm.

1-(2,4-Dihydroxy-3-nitrophenyl)-1-octanone (33g). HR-FD-MS (positive): Found m/z 281.1267 ([M]\textsuperscript{+}, calcd. for C\textsubscript{14}H\textsubscript{19}NO\textsubscript{5}, 281.1263); \textsuperscript{1}H NMR (500 MHz, acetone-\textit{d}_6, rt): 0.87 (3H, t, J = 6.9 Hz, H-6), 1.28-1.36 (8H, m, H-4,5,6,7), 1.71 (2H, m, H-3), 3.06 (2H, t, J = 7.4 Hz, H-2), 6.7 (1H, d, J = 9.1 Hz, H-5\textsuperscript{\prime}), 8.04 (1H, d, J = 9.1 Hz, H-6\textsuperscript{\prime}) ppm.
General procedure for the synthesis of 4-acyl-2-aminoresorcinol (11). Compound 33 was dissolved in MeOH and 10% Pd on charcoal was added. The mixture was stirred for 10 min under hydrogen atmosphere. The reaction mixture was passed through Celite® pad and evaporated to give 11 (>90%) as a solid.

\[ \text{HO} \begin{array}{c} \text{O} \\
\text{H}_2\text{N} \\
\text{HO} \end{array} \text{H}_2\text{N} \begin{array}{c} \text{O} \\
\text{OH} \end{array} \]

1-(3-Amino-2,4-dihydroxyphenyl)ethan-1-one (11a). HR-FD-MS (positive): Found m/z 167.0589 ([M]^+, calcd. for C_8H_9NO_3 167.0582); \(^1\)H NMR (500 MHz, DMSO-d_6, rt): 1.88 (3H, s, CH_3), 6.39 (1H, d, J = 8.7 Hz, H-5), 7.13 (1H, d, J = 8.7 Hz, H-6) ppm.

\[ \text{HO} \begin{array}{c} \text{O} \\
\text{H}_2\text{N} \\
\text{HO} \end{array} \text{H}_2\text{N} \begin{array}{c} \text{O} \\
\text{OH} \end{array} \]

1-(3-Amino-2,4-dihydroxyphenyl)-1-propanone (11b). HR-FD-MS (positive): Found m/z 181.0730 ([M]^+, calcd. for C_9H_11NO_3, 181.0739); \(^1\)H NMR (500 MHz, DMSO-d_6, rt) δ (ppm): 1.07 (3H, t, J = 7.3 Hz, CH_3), 2.94 (2H, q, J = 7.3 Hz, CH_2), 6.38 (1H, d, J = 8.8 Hz, H-5), 7.15 (1H, d, J = 8.8 Hz, H-6) ppm.

\[ \text{HO} \begin{array}{c} \text{O} \\
\text{H}_2\text{N} \\
\text{HO} \end{array} \text{H}_2\text{N} \begin{array}{c} \text{O} \\
\text{OH} \end{array} \]

1-(3-Amino-2,4-dihydroxyphenyl)butan-1-one (11c). HR-FD-MS (positive): Found m/z 195.0869 ([M]^+, calcd. for C_10H_13NO_3, 195.0895); \(^1\)H NMR (500 MHz, DMSO-d_6, rt): 0.91 (3H, t, J = 7.3 Hz, H-4), 1.62 (2H, m, H-3), 2.87 (2H, t, J = 7.3 Hz, H-2), 6.38 (1H, d, J = 8.8 Hz, H-5), 7.16 (1H, d, J = 8.8 Hz, H-6') ppm.
1-(3-Amino-2,4-dihydroxyphenyl)pentan-1-one (**11d**). HR-FD-MS (positive): Found m/z 209.1097 ([M]$^+$, calcd. for C$_{11}$H$_{15}$NO$_3$, 209.1052); $^1$H NMR (500 MHz, DMSO-$d_6$, rt): 0.89 (3H, t, $J$ = 7.3 Hz, H-5), 1.32 (2H, m, H-4), 1.57 (2H, m, H-3), 2.87 (2H, t, $J$ = 7.3 Hz, H-2), 6.35 (1H, d, $J$ = 8.8 Hz, H-5’), 7.15 (1H, d, $J$ = 8.8 Hz, H-6’) ppm.

1-(3-Amino-2,4-dihydroxyphenyl)hexan-1-one (**11e**). HR-FD-MS (positive): Found m/z 223.1118 ([M]$^+$, calcd. for C$_{12}$H$_{17}$NO$_3$, 223.1208); $^1$H NMR (500 MHz, DMSO-$d_6$, rt): 0.85 (3H, t, $J$ = 7.4 Hz, H-6), 1.29 (4H, m, H-4,5), 1.59 (2H, m, H-3), 2.87 (2H, t, $J$ = 7.4 Hz, H-2), 6.35 (1H, d, $J$ = 8.8 Hz, H-5’), 7.15 (1H, d, $J$ = 8.8 Hz, H-6’) ppm.

1-(3-Amino-2,4-dihydroxyphenyl)heptan-1-one (**11f**). HR-FD-MS (positive): Found m/z 237.1349 ([M]$^+$, calcd. for C$_{13}$H$_{19}$NO$_3$, 237.1365); $^1$H NMR (500 MHz, DMSO-$d_6$, rt): 0.84 (3H, t, $J$ = 7.4 Hz, H-7), 1.27 (6H, m, H-4,5,6), 1.59 (2H, m, H-3), 2.88 (2H, t, $J$ = 7.3 Hz, H-2), 6.37 (1H, d, $J$ = 8.8 Hz, H-5’), 7.15 (1H, d, $J$ = 8.8 Hz, H-6’) ppm.
1-(3-Amino-2,4-dihydroxyphenyl)octan-1-one (11g). HR-FD-MS (positive): Found m/z 251.1484 ([M]$^+$, calcd. for C$_{14}$H$_{21}$NO$_3$, 251.1521); $^1$H NMR (500 MHz, DMSO-$d_6$, rt): 0.84 (3H, $t$, $J$ = 7.4 Hz, H-8), 1.24 (8H, $m$, H-4,5,6,7), 1.59 (2H, $m$, H-3), 2.86 (2H, $t$, $J$ = 7.3 Hz, H-2), 6.35 (1H, $d$, $J$ = 8.8 Hz, H-5$'$), 7.14 (1H, $d$, $J$ = 8.8 Hz, H-6$'$) ppm.

General procedure for the synthesis of Alkyl 2,4-dihydroxy-3-nitrobenzoate (34b-g). Compound 34a$^{24}$ (1 mmol) was suspended in an alcohol (5 mL) and conc. H$_2$SO$_4$ (0.25 mL) was added. After refluxing for 24 hours, the reaction mixture was cooled, water was added and extracted by EtOAc. The organic layer was washed by water, dried over sodium sulfate and evaporated. The residue was purified by silica-gel column chromatography (Hexane/EtOAc) to obtain 34b-g (35-83%).

Ethyl 2,4-dihydroxy-3-nitrobenzoate (34b). HR-FD-MS (positive): Found m/z 227.0414 ([M]$^+$, calcd. for C$_9$H$_9$NO$_6$, 227.0430); $^1$H NMR (500 MHz, acetone-$d_6$, rt): 1.39 (3H, $t$, $J$ = 7.1 Hz, CH$_3$), 4.43 (2H, $q$, $J$ = 7.1 Hz, OCH$_2$), 6.71 (1H, $d$, $J$ = 9.2 Hz, H-5), 7.88 (1H, $d$, $J$ = 9.2 Hz, H-6) ppm.

Propyl 2,4-dihydroxy-3-nitrobenzoate (34c). HR-FD-MS (positive): Found m/z 241.0607 ([M]$^+$, calcd. for C$_{10}$H$_{11}$NO$_6$, 241.0586); $^1$H NMR (acetone-$d_6$): 1.0 (3H, $t$, $J$ = 7.4 Hz, CH$_3$), 1.79 (2H, $m$, CH$_2$), 4.31 (2H, $t$, $J$ = 6.6 Hz, OCH$_2$), 6.64 (1H, $d$, $J$ = 9.0 Hz, H-5), 7.81 (1H, $d$, $J$ = 9.0 Hz, H-6)
**Butyl 2,4-dihydroxy-3-nitrobenzoate (34d).** HR-FD-MS (positive): Found m/z 255.0751 ([M]$^+$, calcd. for C$_{11}$H$_{13}$NO$_6$, 255.0743); $^1$H NMR (500 MHz, acetone-$d_6$, rt): 0.95 (3H, $t$, $J = 7.4$ Hz, CH$_3$), 1.46 (2H, $m$, CH$_2$), 1.75 (2H, $m$, CH$_2$), 4.36 (2H, $J = 6.6$ Hz, OCH$_2$), 6.63 (1H, $d$, $J = 9.0$ Hz, H-5), 7.8 (1H, $d$, $J = 9.0$ Hz, H-6) ppm.

**Pentyl 2,4-dihydroxy-3-nitrobenzoate (34e).** HR-FD-MS (positive): Found m/z 269.0932 ([M]$^+$, calcd. for C$_{12}$H$_{15}$NO$_6$, 269.0899); $^1$H NMR (500 MHz, acetone-$d_6$, rt): 0.9 (3H, $t$, $J = 7.1$ Hz, CH$_3$), 1.4 (4H, $m$, CH$_2$), 1.78 (2H, $m$, CH$_2$), 4.38 (2H, $J = 6.6$ Hz, OCH$_2$), 6.7 (1H, $d$, $J = 9.0$ Hz, H-5), 7.88 (1H, $d$, $J = 9.0$ Hz, H-6) ppm.

**Hexyl 2,4-dihydroxy-3-nitrobenzoate (34f).** HR-FD-MS (positive): Found m/z 283.1084 ([M]$^+$, calcd. for C$_{13}$H$_{17}$NO$_6$, 283.1056); $^1$H NMR (500 MHz, acetone-$d_6$, rt): 0.89 (3H, $t$, $J = 7.1$ Hz, CH$_3$), 1.29-1.47 (6H, $m$, CH$_2$), 1.79 (2H, $m$, CH$_2$), 4.37 (2H, $J = 6.6$ Hz, OCH$_2$), 6.68 (1H, $d$, $J = 9.1$ Hz, H-5), 7.86 (1H, $d$, $J = 9.1$ Hz, H-6) ppm.
**Heptyl 2,4-dihydroxy-3-nitrobenzoate (34g).** HR-FD-MS (positive): Found m/z 297.1211 ([M]⁺, calcd. for C₁₄H₁₉NO₆, 297.1212); ¹H NMR (500 MHz, acetone-d₆, rt): 0.86 (3H, t, J = 7.1 Hz, CH₃), 1.29-1.48 (8H, m, CH₂), 1.78 (2H, m, CH₂), 4.37 (2H, J = 6.6 Hz, OCH₂), 6.7 (1H, d, J = 9.0 Hz, H-5), 7.88 (1H, d, J = 9.0 Hz, H-6) ppm.

**General procedure for the synthesis of Alkyl 3-amino-2,4-dihydroxybenzoate (12).** Compound 34 was dissolved in MeOH and 10% Pd on charcoal was added. The mixture was stirred for 10 min under hydrogen atmosphere. The reaction mixture was passed through Celite® pad and evaporated to give 12 (>90%) as a solid.

**Methyl 3-amino-2,4-dihydroxybenzoate (12a).** HR-FD-MS (positive): Found m/z 183.0506 ([M]⁺, calcd. for C₈H₉NO₄, 183.0532); ¹H NMR (500 MHz, DMSO-d₆, rt): 3.34 (3H, s, OMe), 6.38 (1H, d, J = 8.9 Hz, H-5), 7.02 (1H, d, J = 8.9 Hz, H-6) ppm.

**Ethyl 3-amino-2,4-dihydroxybenzoate (12b).** HR-FD-MS (positive): Found m/z 197.0710 ([M]⁺, calcd. for C₉H₁₁NO₄, 197.0688); ¹H NMR (500 MHz, DMSO-d₆, rt): 1.3 (3H, t, J = 7.1 Hz, CH₃), 4.3 (2H, q, J = 7.1 Hz, OCH₂), 6.37 (1H, d, J = 8.7 Hz, H-5), 7.03 (1H, d, J = 8.7 Hz, H-6) ppm.
**Propyl 3-amino-2,4-dihydroxybenzoate (12c).** HR-FD-MS (positive): Found m/z 211.0837 ([M]$^+$, calcd. for C$_{10}$H$_{13}$NO$_4$, 211.0845); $^1$H NMR (500 MHz, DMSO-$d_6$, rt): 0.94 (3H, t, $J = 7.3$ Hz, CH$_3$), 1.68 (2H, m, CH$_2$), 4.17 (2H, $t$, $J = 6.5$ Hz, OCH$_2$), 6.25 (1H, $d$, $J = 8.7$ Hz, H-5), 6.99 (1H, $d$, $J = 8.7$ Hz, H-6) ppm.

**Butyl 3-amino-2,4-dihydroxybenzoate (12d).** HR-FD-MS (positive): Found m/z 225.1003 ([M]$^+$, calcd. for C$_{11}$H$_{15}$NO$_4$, 225.1001); $^1$H NMR (500 MHz, DMSO-$d_6$, rt): 0.91 (3H, t, $J = 7.3$ Hz, CH$_3$), 1.39 (2H, m, CH$_2$), 1.66 (2H, m, CH$_2$), 4.23 (2H, $J = 6.5$ Hz, OCH$_2$), 6.30 (1H, $d$, $J = 8.7$ Hz, H-5), 6.99 (1H, $d$, $J = 8.7$ Hz, H-6) ppm.

**Pentyl 3-amino-2,4-dihydroxybenzoate (12e).** HR-FD-MS (positive): Found m/z 239.1175 ([M]$^+$, calcd. for C$_{12}$H$_{17}$NO$_4$, 239.1158); $^1$H NMR (500 MHz, DMSO-$d_6$, rt): 0.88 (3H, t, $J = 7.0$ Hz, CH$_3$), 1.34 (4H, m, CH$_2$), 1.68 (2H, m, CH$_2$), 4.24 (2H, $J = 6.6$ Hz, OCH$_2$), 6.37 (1H, $d$, $J = 8.7$ Hz, H-5), 7.02 (1H, $d$, $J = 8.7$ Hz, H-6) ppm.
**Hexyl 3-amino-2,4-dihydroxybenzoate (12f).** HR-FD-MS (positive): Found m/z 253.1308 ([M]+, calcd. for C13H19NO4, 253.1314); 1H NMR (500 MHz, DMSO-d6, rt): 0.85 (3H, m, CH3), 1.28-1.36 (6H, m, CH2), 1.67 (2H, m, CH2), 4.23 (2H, J = 6.4 Hz, OCH2), 6.34 (1H, d, J = 8.7 Hz, H-5), 7.01 (1H, d, J = 8.7 Hz, H-6) ppm.

**Heptyl 3-amino-2,4-dihydroxybenzoate (12g).** HR-FD-MS (positive): Found m/z 267.1448 ([M]+, calcd. for C14H21NO4, 267.1471); 1H NMR (500 MHz, DMSO-d6, rt): 0.84 (3H, m, CH3), 1.26-1.31 (8H, m, CH2), 1.67 (2H, m, CH2), 4.22 (2H, t, J = 6.3 Hz, OCH2), 6.32 (1H, d, J = 8.6 Hz, H-5), 6.99 (1H, d, J = 8.6 Hz, H-6) ppm.

**4-Methoxymethyl-2-nitroresorcinol (35).** Compound 34a (241.0 mg, 1.13 mmol) was dissolved in THF (15 mL) and DIPEA (1.2 mL, 7.06 mmol), MOMCl (0.4 mmol, 5.32 mmol) was added. After stirring for an hour under argon atmosphere, the reaction mixture was diluted with 1 M HCl aq. and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and evaporated. The obtained crude mixture of mono- and di-methoxymethylated product was then dissolved in the mixture of dry THF (13 mL) and dry Et2O (13 mL). The solution was cooled to 0°C and LiAlH4 (112.2 mg, 2.37 mmol) was added slowly and stirred under argon atmosphere for 20 min. The reaction mixture was quenched by the addition of methanol, diluted with 1 M HCl aq. and
extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and evaporated. The residue was dissolved in methanol (15 mL) and conc. HCl aq. (1.2 mL) was added. After stirring for 30 min at 60°C, the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and evaporated. The residue was purified by silica-gel chromatography (Hexane/EtOAc) to obtain 35 (175.1 mg, 79% from 34a).

HR-FD-MS (positive): Found m/z 199.0484 ([M]^+, calcd. for C₈H₉NO₅ 197.0481); ¹H-NMR (270 MHz, acetone-d₆, rt): 3.35 (3H, s), 4.43 (2H, s), 6.63 (1H, d, J = 8.3 Hz), 7.51 (1H, d, J = 8.3 Hz) ppm; ¹³C-NMR (67.5 MHz, acetone-d₆, rt): 58.5, 69.3, 109.4, 119.3, 126.7, 137.8, 153.6, 155.4 ppm

2-Amino-4-methylresorcinol (13). To the solution of 35 (175.1 mg, 0.889 mmol) in methanol (18 mL), Boc₂O (0.4 mL, 1.785 mmol) and 10% Pd/C was added. The mixture was stirred overnight under hydrogen atmosphere and then passed through Celite® pad. The filtrate was evaporated and partially purified by silica-gel chromatography (Hexane/EtOAc) as the byproduct was unable to be separated from the desired product. The crude product was then dissolved in 4 M HCl in 1,4-dioxane (3.2 mL). After stirring for 30 min, the reaction mixture was evaporated and purified by preparative TLC (CHCl₃/MeOH = 8/1) to obtain 13 (13.1 mg, 11% from 35).

HR-FD-MS (positive): Found m/z 139.0630 ([M]^+, calcd. for C₇H₉NO₂ 139.0633); ¹H-NMR (270 MHz, acetone-d₆, rt): 2.10 (3H, s), 6.23 (1H, d, J = 8.2 Hz), 6.35 (1H, d, J = 8.2 Hz) ppm; ¹³C-NMR (67.5 MHz, acetone-d₆, rt): 16.0, 108.0, 117.5, 121.0, 124.4, 145.2, 145.9 ppm
**N-(tert-Butoxycarbonyl)-3-amino-2,4-dihydroxyacetophenone (36).**

To the solution of 33a (1.544 g, 7.831 mmol) in THF (35 mL), Boc₂O (3.325 g, 15.23 mmol) and 10% Pd/C was added and stirred overnight under hydrogen atmosphere. The reaction mixture was passed through Celite® pad and evaporated. The residue was purified by silica-gel column chromatography (Hexane/EtOAc) to obtain 36 (1.093 g, 52%).

HR-ESI-MS (positive): Found m/z 290.0997 ([M+Na]⁺, calcd. for C₁₃H₁₇O₅NNa 290.0999); ¹H-NMR (270 MHz, CDCl₃, rt): 1.54 (9H, s), 2.56 (3H, s), 6.51 (1H, d, J = 9.0 Hz), 7.13 (1H, s), 7.42 (1H, d, J = 9.0 Hz), 10.96 (1H, s), 13.48 (1H, s) ppm; ¹³C-NMR (67.5 MHz, CDCl₃, rt): 26.1, 28.1, 83.2, 110.9, 112.6, 113.8, 127.4, 154.5, 154.7, 156.2, 203.0 ppm.

**N-(tert-Butoxycarbonyl)-3-amino-2-hydroxy-4-(methoxymethoxy)acetophenone (37).** To the solution of 36 (814.2 mg, 3.0 mmol) in DMF (25 mL), i-Pr₂NEt (0.79 mL, 4.6 mmol) and MOMCl (0.79 mL, 4.6 mmol) was added at 0ºC. After stirring for 2 hours at 0ºC, cold water was added and the mixture was extracted by EtOAc. The organic layer was washed with brine, dried over sodium sulfate and evaporated. The residue was purified by silica-gel column chromatography (Hexane/EtOAc) to obtain 37 (872.8 mg, 92%).

HR-ESI-MS (positive): Found m/z 334.1264 ([M+Na]⁺, calcd. for C₁₅H₂₁O₆NNa 334.1261); ¹H-NMR (270 MHz, CDCl₃, rt): 1.49 (9H, s), 2.57 (3H, s), 3.61 (3H, s), 5.26 (2H, s), 6.71 (1H, d, J = 9.1 Hz), 7.60 (1H, d, J = 9.1 Hz), 12.81 (1H, s) ppm; ¹³C-NMR (67.5 MHz, CDCl₃, rt): 26.3, 28.2, 56.4, 80.1, 94.5, 105.5, 114.9, 115.1, 129.7, 153.6, 158.3, 159.1, 203.0 ppm.
3′-((tert-Butoxycarbonyl)amino)-2′-hydroxy-4′-(methoxymethoxy)-4-((2-(benzyloxycarbonyl)amino)ethoxy)chalcone (39). Compound 37 (742.3 mg, 2.384 mmol) and 38 (841.6 mg, 2.812 mmol) was dissolved in 1,4-dioxane (20 mL) and 50% NaOH aq. (20 mL) was added at 0°C. After stirring for 7 days under argon atmosphere, the reaction mixture was acidified by 1 M HCl aq. and extracted by EtOAc. The organic layer was washed with water and then brine. The layer was dried over sodium sulfate and evaporated. The residue was purified by silica-gel column chromatography (Hexane/EtOAc) to obtain 39 (554.4 mg, 39%).

HR-ESI-MS (positive): Found m/z 615.2317 ([M+Na]+, calcd. for C₃₂H₃₆O₉N₂Na 615.2313);

^1^H-NMR (270 MHz, CDCl₃, rt): 1.51 (9H, s), 3.52 (3H, s), 3.63(2H, q, J = 4.9 Hz), 4.09 (2H, t, J = 4.9 Hz), 5.12 (2H, s), 5.29 (2H, s), 5.98 (1H, s), 6.75 (1H, d, J = 9.2 Hz), 6.92 (2H, d, J = 8.5 Hz), 7.35 (5H, m), 7.44 (1H, d, J = 15.3 Hz), 7.59 (2H, d, J = 8.5 Hz), 7.77 (1H, d, J = 9.2 Hz), 7.85 (1H, d, J = 15.3 Hz), 13.58 (1H, s) ppm; ^1^C-NMR (67.5 MHz, CDCl₃, rt): 28.2, 40.4, 56.5, 66.9, 67.0, 80.2, 94.5, 105.5, 114.9, 115.1, 115.4, 117.8, 127.8, 128.1, 128.2, 128.5, 128.6, 130.5, 136.2, 144.6, 153.7, 156.4, 158.2, 160.3, 160.7, 192.3 ppm.

1-(3-(tert-Butoxycarbonyl)amino-2-hydroxy-4-(methoxymethoxy)phenyl)-3-(4-(2-((3-(chlorosulfonyl)benzoyl)amino)ethoxy)phenyl)propan-1-one (40). To the solution of 39 (224.7 mg, 0.3792 mmol) in MeOH (5 mL), 10% Pd/C was added and stirred for 2.5 hours under hydrogen atmosphere. The reaction mixture was passed through Celite® pad and evaporated. The residue was dissolved in CH₂Cl₂ (10 mL) and pyridine (0.09 mL, 1.1 mmol), 3-(chlorosulfonyl)benzoyl chloride (0.12 mL, 0.76 mmol) was added at 0°C. After stirring for 1.5 hours under argon atmosphere, the reaction
mixture was evaporated and the residue was purified by silica-gel column chromatography (CHCl₃) to obtain 40 (125.6 mg, 50%).

HR-FD-MS (positive): Found m/z 662.1718 ([M]+, calcd. for C₃₁H₃₅O₁₀N₂SCl 662.1701); ¹H-NMR (270 MHz, CDCl₃, rt): 1.49 (9H, s), 2.99 (2H, t, J = 7.4 Hz), 3.20 (2H, t, J = 7.4 Hz), 3.50 (3H, s), 3.89 (2H, q, J = 5.0 Hz), 4.16 (2H, t, J = 5.0 Hz), 5.25 (2H, s), 5.91 (1H, s), 6.68 (1H, d, J = 9.1 Hz), 6.85 (2H, d, J = 8.6 Hz), 7.15 (2H, d, J = 8.6 Hz), 7.59 (1H, d, J = 9.1 Hz), 7.72 (1H, t, J = 7.9 Hz), 8.18-8.14 (2H, m), 8.42 (1H, t, J = 1.7 Hz), 12.84 (1H, s) ppm; ¹³C-NMR (67.5 MHz, CDCl₃, rt): 28.0, 28.2, 29.3, 39.9, 56.5, 66.5, 77.2, 80.2, 94.5, 105.6, 114.6, 114.7, 115.0, 125.5, 128.9, 129.5, 130.2, 133.6, 133.7, 136.2, 144.7, 153.7, 156.8, 158.2, 159.2, 164.9, 204.0 ppm.

Azidononyl

3-((2-(4-(3-(3-(tert-butoxycarbonyl)amino-2-hydroxy-4-(methoxymethoxy)phenyl)-3-oxopropyl)phenoxycarbonyl)aminooxy)ethyl)carbamoylbenzenesulfonate (41). To the solution of 40 (772 mg, 1.17 mmol) in CH₂Cl₂ (25 mL), DMAP (281 mg, 2.32 mmol), 9-azidononanol (960 mg, 5.18 mmol) was added at 0°C. After stirring for an hour under argon atmosphere, the reaction mixture was evaporated and the residue was purified by silica-gel column chromatography (Hexane/EtOAc) to obtain 41 (307.5 mg, 33%).

HR-FD-MS (positive): Found m/z 811.3456 ([M]+, calcd. for C₄₀H₅₃O₁₁N₅S 811.3462); ¹H-NMR (270 MHz, CDCl₃, rt): 1.40-1.20 (10H, m), 1.43 (9H, s), 1.70-1.50 (4H, m), 2.99 (2H, t, J = 7.6 Hz), 3.22 (2H, t, J = 7.6 Hz), 3.24 (2H, t, J = 7.0 Hz), 3.45 (3H, s), 3.89 (2H, q, J = 5.1 Hz), 4.08 (2H, t, J = 6.5 Hz), 4.16 (2H, t, J = 5.1 Hz), 5.23 (2H, s), 6.67 (1H, d, J = 9.1 Hz), 6.87 (2H, d, J = 8.6 Hz), 7.17 (2H, d, J = 8.6 Hz), 7.65 (1H, t, J = 7.8 Hz), 7.66 (1H, d, J = 9.1 Hz), 8.03 (1H, dt, J = 1.7, 7.8 Hz), 8.09 (1H, dt, J = 1.7, 7.8 Hz), 8.28 (1H, t, J = 1.7 Hz), 12.77 (1H, s) ppm; ¹³C-NMR (67.5 MHz, CDCl₃, rt): 25.1, 26.4, 27.6, 27.7 (3C), 28.6, 28.8, 29.0, 39.6, 39.8, 51.2, 56.1, 66.2, 71.2, 82.1, 93.9,
104.8, 114.3, 114.4, 117.2, 126.3, 129.3, 129.5, 130.2, 130.3, 132.2, 133.2, 135.5, 136.6, 151.0, 156.8, 158.1, 159.6, 165.5, 203.9 ppm.

Azidononyl

3-((2-(4-(3-amino-2,4-dihydroxyphenyl)-3-oxopropyl)phenoxy)ethyl)carbamoylbenzenesulfonate (14). Compound 41 (66.8 mg, 0.0823 mmol) was dissolved in 4 M HCl in 1,4-dioxane (1 mL) and stirred for 2 hours at 0°C. The reaction mixture was evaporated and the residue was purified by silica-gel column chromatography (CHCl₃/MeOH) to obtain 14 (28.7 mg, 52%).

HR-ESI-MS (negative): Found m/z 666.2615 ([M⁻], calcd. for C₃₃H₄₀O₈N₅S 666.2603); ¹H-NMR (270 MHz, acetone-d₆, rt): 1.35-1.15 (10H, m, H-25,26,27,28,29), 1.65-1.45 (4H, m, H-24,30), 2.91 (2H, t, 7.6 Hz, H-9), 3.20 (2H, t, J = 7.6 Hz, H-8), 3.26 (2H, t, J = 6.8 Hz, H-31), 3.76 (2H, q, J = 5.6 Hz, H-15), 4.05 (2H, t, J = 6.4 Hz, H-23), 4.14 (2H, t, J = 5.6 Hz, H-14), 6.40 (1H, d, J = 8.8 Hz, H-6), 6.83 (2H, dd, J = 2.0, 8.6 Hz, H-12), 7.16 (2H, dd, J = 2.0, 8.6 Hz, H-11), 7.17 (1H, d, J = 8.8 Hz, H-5), 7.74 (1H, t, J = 7.9 Hz, H-19), 8.02 (1H, dt, J = 1.5, 7.9 Hz, H-20), 8.24 (1H, dt, J = 1.5, 7.9 Hz, H-18), 8.36 (1H, t, J = 1.5 Hz, H-22) ppm; ¹³C-NMR (125 MHz, acetone-d₆, rt): 25.9 (C-25), 27.3 (C-29), 29.4 (C-24, 26, 30), 29.6 (C-28), 29.9 (C-27), 30.2 (C-9), 40.2 (C-8), 40.3 (C-15), 51.9 (C-31), 67.0 (C-14), 72.1 (C-23), 107.6 (C-6), 113.8 (C-2), 115.3 (C-12), 120.6 (C-5), 124.3 (C-4), 127.2 (C-22), 130.2 (C-11), 130.6 (C-19), 130.9 (C-20), 133.4 (C-10, 18), 136.8 (C-21), 137.7 (C-17), 150.7 (C-1), 151.9 (C-3), 158.1 (C-13), 165.8 (C-16), 205.4 (C-7) ppm.
References


