Supporting Information

Synthesis of Rocaglamide Derivatives and Evaluation of Wnt Signal Inhibitory Activity

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Contents

S1~S23 Experimental data
S32~ ¹H and ¹³C NMR spectra.

General experimental procedure

NMR spectra were recorded on JEOL ECP400 and ECP600 spectrometers in a deuterated solvent whose chemical shift was taken as an internal standard. Mass spectra were obtained using AccuTOF LC-plus JMS-T100LP (JEOL). IR spectra were measured on ATR on a JASCO FT-IR 230 spectrophotometer. Column chromatography was performed using silica gel PSQ100B (Fuji Silysia Chemical Ltd., Kasugai, Japan) and silica gel 60N (Kanto Chemical Co., Inc., Tokyo, Japan). Photochemical reactions were carried out using HL-400B-8 (400 W, 33 A; mercury lamp) and HB400P-1 (400 W) (SEN Light Co., Osaka, Japan) with cooling system consists of TRL-117ST and TC-107E (THOMAS, KAGAKU Co., Ltd., Tokyo, Japan). Mercury lamp was cooled using glass container (Pyrex) (USHIO Inc., Tokyo, Japan) with water.

2-hydroxy-4,6-dimethoxyacetophenone (8)

The mixture of 2,4,6-trihydroxyacetophenone (4.0 g, 21.4 mmol), K₂CO₃ (16.0 g, 115.6 mmol), and methyl trifluoromethanesulfonate (6.6 mL, 59.9 mmol) in dry acetone (107 mL) was stirred
for 3 h under reflux condition. The reaction mixture was filtered on celite and then filtrate was concentrated. The resulting residue was diluted with H₂O and then extracted with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The crude oil was purified by silicagel column chromatography (hexane:AcOEt = 25:1) to afford 8 (3.61 g, 18.8 mmol, 88%).

IR (ATR): 3099, 3006, 2945, 2849, 1612, 1593, 1456, 1439, 1422, 1388, 1365, 1322, 1267, 1219, 1204, 1155, 1110, 1080, 1044, 1029, 997, 961, 941, 893, 835, 804 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ 14.04 (s, 1H), 6.06 (d, J = 2.2 Hz, 1H), 5.92 (d, J = 2.2 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 2.61 (s, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ 203.1, 167.5, 166.0, 162.9, 105.9, 93.4, 90.7, 55.5, 55.5, 32.9.


2-hydroxy-1-(2-hydroxy-4,6-dimethoxyphenyl)ethan-1-one (9)

A solution of 8 (400 mg, 2.0 mmol) in CH₂Cl₂ (5.2 mL) was cooled to 0 ºC and added triethylamine (832 µL, 6.0 mmol) and TBSOTf (1.1 mL, 5.6 mmol). The reaction mixture was stirred for 30 min and the reaction was quenched with sat. aq. NaHCO₃. The mixture was extracted with CH₂Cl₂ and separated organic layer was dried over Na₂SO₄. After filtration and concentration, the crude product was directly used for next reaction.

The crude product was dissolved in CH₂Cl₂ (10 mL) and cooled to 0 ºC. To the mixture was added NaHCO₃ (420 mg, 5.0 mmol) and mCPBA (552 mg, 3.2 mmol) and the reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with CH₂Cl₂ and washed with sat. aq. NaHCO₃ and water. The combined organic layer was dried over Na₂SO₄ and filtered. The solvent was concentrated and the crude product was directly used for next reaction.

The crude product was dissolved in THF (10 mL) and H₂O (1 mL) and TsOH·H₂O (37.6 mg, 0.2 mmol) was added to the mixture. Then the mixture was stirred for 9 h under reflux condition and the reaction was quenched with sat. aq. NaHCO₃. The mixture was extracted with EtOAc and dried over Na₂SO₄. After filtration and concentration, the resulting residue was purified by silicagel C.C. (hexane:AcOEt = 5:1→2:1) to afford 9 (290.9 mg, 69% in 3 steps).

IR (ATR): 3457, 2980, 2943, 2174, 2141, 1722, 1703, 1688, 1630, 1592, 1546, 1500, 1459, 1422, 1391, 1325, 1279, 1217, 1201, 1151, 1116, 1092, 999, 959, 938, 810 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ 13.20 (s, 1H), 6.08 (d, J = 2.2 Hz, 1H), 5.91 (d, J = 2.2 Hz, 1H),
4.69 (s, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.00 (brs, 1H).

\[^{13}\text{C}\-\text{NMR (100 MHz, CDCl}_3\):}\ \delta 201.9, 167.2, 167.1, 163.1, 103.3, 93.7, 90.9, 68.6, 55.7, 55.7.\]

ESI-HRMS [M+Na\(^+\):] calcd for C\(_{16}\)H\(_{12}\)NaO\(_5\) 235.0582, found 235.0590.

3-(benzyloxy)-4-methoxybenzoic acid (10)

To a solution of 3-hydroxy-4-methoxybenzoic acid (1.0 g, 6.0 mmol) in MeOH (11 mL) was added H\(_2\)SO\(_4\) (36 µL, 0.36 mmol) and the reaction mixture was stirred for 18 h under reflux condition. The reaction mixture was cooled to rt and concentrated \textit{in vacuo}. The resulting mixture was diluted with sat. aq. NaHCO\(_3\) and extracted with EtOAc. The organic layer was dried over Na\(_2\)SO\(_4\) and concentrated, and the residue was purified by silicagel flash C.C. (hexane:AcOEt = 5:1) to give methyl 3-hydroxy-4-methoxybenzoate (1.04 g, 95% yield).

\[^{1}\text{H}\-\text{NMR (400 MHz, CDCl}_3\):}\ \delta 7.62 (dd, \(J = 8.4, 2.0\) Hz, 1H), 7.59 (d, \(J = 2.0\) Hz, 1H), 6.87 (d, \(J = 8.4\) Hz, 1H), 5.66 (s, 1H), 3.94 (s, 3H), 3.88 (s, 3H).

\[^{13}\text{C}\-\text{NMR (100 MHz, CDCl}_3\):}\ \delta 166.8, 150.4, 145.2, 123.4, 122.8, 115.6, 109.8, 56.0, 51.9.

ESI-HRMS [M-H\(^-\):] calcd for C\(_9\)H\(_9\)O\(_4\) 181.0501, found 181.0527.

To a solution of methyl 3-hydroxy-4-methoxybenzoate (1.02 g, 5.6 mmol) in MeOH was added DBU (1.3 mL, 8.4 mmol) and benzyl bromide (736 µL, 6.2 mmol) and then the reaction mixture was stirred for 20 h under reflux condition. After removal of solvent, the resulting residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine and dried over Na\(_2\)SO\(_4\). After filtration and concentration, the residue was purified by crystallization to give methyl 3-(benzyloxy)-4-methoxybenzoate (1.21 g, 79% yield).

IR (ATR): 2942, 2184, 1962, 1707, 1584, 1509, 1436, 1384, 1341, 1293, 1261, 1207, 1176, 1127, 1006, 873, 847 cm\(^{-1}\).

\[^{1}\text{H}\-\text{NMR (400 MHz, CDCl}_3\):}\ \delta 7.68 (dd, \(J = 8.6, 2.0\) Hz, 1H), 7.61 (d, \(J = 2.0\) Hz, 1H), 7.48-7.30 (m, 5H), 6.90 (d, \(J = 8.6\) Hz, 1H), 5.17 (s, 2H), 3.93 (s, 3H), 3.87 (s, 3H).

\[^{13}\text{C}\-\text{NMR (100 MHz, CDCl}_3\):}\ \delta 166.8, 153.6, 147.7, 136.6, 128.6, 128.0, 127.5, 124.0, 122.5, 114.4, 110.7, 71.0, 56.0, 51.9.

ESI-HRMS [M+Na\(^+\):] calcd for C\(_{16}\)H\(_{16}\)NaO\(_4\) 295.0946, found 295.0871.

To a solution of 3-(benzyloxy)-4-methoxybenzoate (844 mg, 3.1 mmol) in THF (3.4 mL) was
added 1N NaOH (8.4 mL) and stirred for 3 h under reflux condition. The reaction was quenched with 1N HCl and the mixture was extracted with EtOAc. The combined organic layer was washed with brine and dried over Na$_2$SO$_4$. Filtration and concentration afforded 10 (800 mg, 98%).

IR (ATR): 2957, 2039, 1681, 1599, 1517, 1438, 1348, 1301, 1269, 1224, 1135, 1021 cm$^{-1}$.

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.77 (dd, $J = 8.4$, 2.2 Hz, 1H), 7.65 (d, $J = 2.2$ Hz, 1H), 7.48-7.30 (m, 5H), 6.93 (d, $J = 8.4$ Hz, 1H), 5.19 (s, 2H), 3.95 (s, 3H).

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 171.2, 154.3, 147.8, 136.5, 128.6, 128.1, 127.5, 124.9, 121.6, 114.7, 110.7, 71.0, 56.1.

ESI-HRMS [M+Na]$^+$: calcd for C$_{15}$H$_{14}$NaO$_4$ 281.0790, found 281.0793.

Compound 11, 16a-d

General procedure

To a solution of 9 (300 mg, 1.4 mmol) in CH$_2$Cl$_2$ (14 mL) was added 15a (538 mg, 4.2 mmol), DMAP (59 mg, 0.48 mmol) and EDC·HCl (1.2 g, 6.3 mmol). The reaction mixture was stirred at rt for 8 h and then diluted with water. The mixture was extracted with CH$_2$Cl$_2$ and the organic layer was dried over Na$_2$SO$_4$. After filtration and concentration, the resulting residue was purified by silicagel chromatography (hexane:AcOEt = 3:1) to afford 16a (605 mg, 1.4 mmol, quant.).

2-(2-((3-(benzyloxy)-4-methoxybenzoyl)oxy)-4,6-dimethoxyphenyl)-2-oxoethyl 3-(benzyloxy)-4-methoxybenzoate (11): 90%

IR (ATR): 2936, 2840, 1718, 1600, 1512, 1455, 1420, 1344, 1290, 1265, 1201, 1175, 1130, 1098, 1019 cm$^{-1}$.

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.79 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.71 (d, $J = 2.0$ Hz, 1H), 7.63 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.54 (d, $J = 2.0$ Hz, 1H), 7.44-7.25 (m, 10H), 6.89 (d, $J = 8.4$ Hz, 1H), 6.80 (d, $J = 8.4$ Hz, 1H), 6.43 (d, $J = 2.0$ Hz, 1H), 6.36 (d, $J = 2.0$ Hz, 1H), 5.20 (s, 2H), 5.14 (s, 2H), 5.02 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H).
$^{13}$C-NMR (100 MHz CDCl$_3$): $\delta$ 194.1, 165.5, 164.6, 162.9, 159.7, 154.1, 153.7, 151.2, 147.8, 147.6, 136.5, 128.5, 127.9, 127.6, 125.1, 124.3, 122.0, 121.4, 114.8, 114.4, 113.5, 110.7, 110.6, 100.8, 96.3, 70.9, 70.8, 69.4, 67.0, 56.0, 55.7.

ESI-HRMS [M+Na]$^+$: calcd for C$_{40}$H$_{36}$NaO$_{11}$ 715.2155, found 715.2067.

3,5-dimethoxy-2-(2-((thiophene-2-carbonyl)oxy)acetyl)phenyl thiophene-2-carboxylate (16a); quant.

IR (ATR): 3102, 2943, 2841, 1717, 1608, 1573, 1522, 1457, 1412, 1360, 1332, 1248, 1220, 1197, 1152, 1094, 1053, 1022 cm$^{-1}$.

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.93 (dd, $J = 3.9$, 1.5 Hz, 1H), 7.77 (dd, $J = 3.7$, 1.1 Hz, 1H), 7.61 (dd, $J = 5.0$, 1.5 Hz, 1H), 7.52 (dd, $J = 4.8$, 1.1 Hz, 1H), 7.12 (dd, $J = 5.0$, 3.9, 1H), 7.05 (dd, $J = 4.8$, 3.7 Hz, 1H), 6.43 (d, $J = 2.2$ Hz, 1H), 6.38 (d, $J = 2.2$ Hz, 1H), 5.22 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H).

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 193.2, 163.1, 161.4, 160.2, 159.9, 150.8, 135.1, 133.9, 133.7, 133.1, 132.7, 132.3, 128.0, 127.7, 113.2, 100.9, 96.5, 56.0, 55.7.

ESI-HRMS [M+Na]$^+$: calcd for C$_{20}$H$_{16}$NaO$_7$S$_2$ 455.0235, found 455.0203.

2-(2-((furan-2-carbonyl)oxy)-4,6-dimethoxyphenyl)-2-oxoethyl furan-2-carboxylate (16b); quant.

IR (ATR): 3141, 2944, 2851, 1734, 1609, 1566, 1470, 1421, 1391, 1361, 1334, 1295, 1228, 1173, 1105, 1013 cm$^{-1}$.

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.62 (dd, $J = 2.0$, 0.8 Hz, 1H), 7.55 (dd, $J = 1.6$, 0.8 Hz, 1H), 7.35 (dd, $J = 3.6$, 0.8, 1H), 7.18 (dd, $J = 3.6$, 0.8 Hz, 1H), 6.53 (dd, $J = 3.6$, 1.6 Hz, 1H), 6.47 (dd, $J = 3.6$, 2.0 Hz, 1H), 6.41 (d, $J = 2.4$ Hz, 1H), 6.38 (d, $J = 2.4$ Hz, 1H), 5.26 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H).

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 192.5, 163.3, 160.1, 157.8, 156.5, 150.6, 147.3, 146.5, 144.1,

2-(2-((15-bromothiophene-2-carbonyl)oxy)-4,6-dimethoxyphenyl)-2-oxoethyl 5-bromothiophene-2-carboxylate (16c); 91%

IR (ATR): 1732, 1608, 1415, 1227, 1100 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ 7.67 (d, J = 3.9 Hz, 1H), 7.53 (d, J = 3.9 Hz, 1H), 7.09 (d, J = 3.9 Hz, 1H), 7.04 (d, J = 3.9 Hz, 1H), 6.40 (d, J = 2.3 Hz, 1H), 6.38 (d, J = 2.3 Hz, 1H), 5.18 (s, 2H), 3.86 (s, 3H), 3.82 (s, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ 192.5, 163.3, 160.3, 160.0, 159.2, 150.7, 135.3, 134.2, 134.1, 133.4, 131.1, 130.9, 121.8, 120.7, 112.9, 101.1, 96.7, 69.7, 56.1, 55.8.

ESI-MS [M+Na]⁺: calcd for C₇₀H₆₁BrO₇S₂ 612.8425, found 612.8486, C₇₀H₆₁Br₂O₂S₂ 610.8445, found 610.8394, C₇₀H₆₁Br₂O₂S₂ 614.8405 found 614.8307.

2-(2-((15-bromofuran-2-carbonyl)oxy)-4,6-dimethoxyphenyl)-2-oxoethyl 5-bromofuran-2-carboxylate (16d); 95%

IR (ATR): 3154, 2943, 2845, 1731, 1682, 1608, 1567, 1459, 1421, 1358, 1332, 1286, 1228, 1206, 1142, 1106, 1015 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ 7.27 (d, J = 3.7 Hz, 1H), 7.12 (d, J = 3.7 Hz, 1H), 6.48 (d, J = 3.3 Hz, 1H), 6.42 (d, J = 3.3 Hz, 1H), 6.39 (s, 2H), 5.24 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ 192.0, 163.4, 160.2, 156.7, 155.3, 150.5, 145.7, 145.2, 128.8, 127.8, 122.2, 120.8, 114.3, 114.0, 112.6, 101.1, 96.7, 69.4, 56.1, 55.8.

ESI-HRMS [M+Na]⁺: calcd for C₇₀H₆₁Br₂O₂S₂ 582.8882, found 582.8861, C₇₀H₆₁Br₂NaO₈ 578.8902, found 578.8956, C₇₀H₆₁Br₂NaO₈ 582.8861, found 582.8852.

Compound 12, 17a-d
**General procedure**

To a solution of 16a (578 mg, 1.3 mmol) in THF (38 mL) was added of LHMDS (1.3 M, 3.1 mL, 4.0 mmol) at -20°C in dropwise manner. The reaction mixture was stirred for 2 h and the reaction was quenched using sat. aq. NaHCO₃. The resulting mixture was extracted using EtOAc. The combined organic layers were then washed with brine, dried over Na₂SO₄ and filtered. The solvent was evaporated *in vacuo* and the resulting residue was purified by silicagel chromatography (hexane:AcOEt = 3:1) to afford 17a (432 mg, 1.0 mmol, 75 %).

1-(3-(benzyloxy)-4-methoxyphenyl)-3-(2-hydroxy-4,6-dimethoxyphenyl)-1,3-dioxopropan-2-yl 3-(benzyloxy)-4-methoxybenzoate (12) (used to next step without purification.)

IR (ATR): 2945, 1718, 1681, 1598, 1513, 1426, 1270, 1216, 1159, 1114, 1020 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ 13.26 (s, 1H), 7.76 (d, J = 2.0 Hz, 1H), 7.74 (d, J = 1.6 Hz, 1H), 7.64-7.59 (m, 2H), 7.43-7.20 (m, 11H), 6.91 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.08 (d, J = 2.0 Hz, 1H), 5.76 (d, J = 2.0 Hz, 1H), 5.21-5.09 (m, 4H), 3.94 (s, 3H), 3.90 (s, 3H), 3.79 (s, 3H).

¹³C-NMR (100 MHz CDCl₃): δ 194.3, 189.8, 167.7, 166.9, 165.1, 161.5, 154.4, 154.3, 148.0, 147.8, 136.5, 136.3, 128.6, 128.5, 128.1, 128.0, 127.7, 127.6, 127.5, 124.9, 123.8, 121.1, 114.8, 113.0, 110.8, 104.4, 94.1, 91.0, 71.0, 70.7, 56.1, 56.1, 55.7, 55.1.


1-(2-hydroxy-4,6-dimethoxyphenyl)-1,3-dioxo-3-(thiophen-2-yl)propan-2-yl thiophene-2-carboxylate (17a); 85%.

IR (ATR): 3103, 2943, 1715, 1671, 1624, 1577, 1521, 1463, 1414, 1359, 1274, 1244, 1217, 1159, 1114, 1091, 861, 821 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ 13.17 (s, 1H), 7.91 (d, J = 4.4 Hz, 1H), 7.83 (d, J = 4.2 Hz, 1H),
7.72 (d, \( J = 5.3 \) Hz, 1H), 7.61 (d, \( J = 5.3 \) Hz, 1H), 7.21 (s, 1H), 7.17 (dd, \( J = 5.3, 4.4 \) Hz, 1H), 7.11 (dd, \( J = 5.3, 4.2 \) Hz, 1H), 6.09 (d, \( J = 2.4 \) Hz, 1H), 5.83 (d, \( J = 2.4 \) Hz, 1H), 3.80 (s, 3H), 3.41 (s, 3H).

\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \( \delta \) 192.9, 183.7, 167.7, 167.1, 161.5, 160.9, 141.7, 134.9, 133.8, 133.4, 131.9, 128.5, 128.0, 104.4, 94.1, 91.0, 78.1, 55.7, 55.2.

ESI-HRMS [M+Na]: calcd for C\(_{20}\)H\(_{16}\)NaO\(_7\)S\(_2\) 455.0235, found 455.0196.

1-(furan-2-yl)-3-(2-hydroxy-4,6-dimethoxyphenyl)-1,3-dioxopropan-2-yl furan-2-carboxylate (17b); 70%.

IR (ATR): 3136, 2945, 1728, 1682, 1609, 1567, 1463, 1438, 1420, 1392, 1347, 1296, 1275, 1248, 1215, 1158, 1105, 1048, 1011 cm\(^{-1}\).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta \) 13.15 (s, 1H), 7.64 (dd, \( J = 1.8, 0.7 \) Hz, 1H), 7.61 (dd, \( J = 1.8, 0.9 \) Hz, 1H), 7.36 (dd, \( J = 3.7, 0.7 \) Hz, 1H), 7.29 (dd, 3.7, 0.9 Hz, 1H), 7.19 (s, 1H), 6.60 (dd, 3.7, 1.8 Hz, 1H), 6.51 (dd, 3.7, 1.8 Hz, 1H), 6.09 (d, \( J = 2.6 \) Hz, 1H), 5.82 (d, \( J = 2.6 \) Hz, 1H), 3.80 (s, 3H), 3.43 (s, 3H).

\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \( \delta \) 192.7, 179.4, 167.8, 167.2, 161.3, 157.2, 150.9, 147.24, 147.21, 143.7, 119.7, 118.9, 112.8, 112.1, 104.3, 94.1, 91.0, 55.7, 55.3.

ESI-HRMS [M+Na]: calcd for C\(_{20}\)H\(_{16}\)NaO\(_9\) 423.0692, found 423.0672.

1-(5-bromo thiophen-2-yl)-3-(2-hydroxy-4,6-dimethoxyphenyl)-1,3-dioxopropan-2-yl 5-bromothiophene-2-carboxylate (17c); 86%

IR (ATR): 2925, 2970, 1720, 1671, 1412, 1330, 1238, 1217, 1160, 1115, 1090, 896 cm\(^{-1}\).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta \) 13.1 (s, 1H), 7.65 (d, \( J = 3.9 \) Hz, 1H), 7.55 (d, \( J = 3.9 \) Hz, 1H), 7.14 (d, \( J = 4.2 \) Hz, 1H), 7.08 (d, \( J = 4.2 \) Hz, 1H), 7.08 (s, 1H), 6.08 (d, \( J = 2.3 \) Hz, 1H), 5.83 (d, \( J = 2.3 \) Hz, 1H), 3.79 (s, 3H), 3.47 (s, 3H).
\[ ^{13}\text{C-NMR} \ (100 \text{ MHz, CDCl}_3): \delta \ 192.2, 182.4, 167.8, 167.3, 161.4, 159.7, 142.9, 135.3, 133.6, 132.8, 131.2, 124.2, 122.1, 104.3, 94.2, 91.2, 77.7, 55.8, 55.3. \]

ESI-MS \([\text{M}+\text{Na}]^+\): calcd for C\(_{20}\)H\(_{14}\)\(^79\)Br\(^{81}\)BrNaO\(_7\)S \(612.8425\), found 612.8362.

\[ \text{C\(_{20}\)H\(_{14}\)\(^79\)Br\(_2\)NaO\(_7\)S} \ 610.8445, \text{found 610.8397}. \]

\[ \text{C\(_{20}\)H\(_{14}\)\(^81\)Br\(_2\)NaO\(_7\)S} \ 614.8405, \text{found 614.8322}. \]

1-(5-bromofuran-2-yl)-3-(2-hydroxy-4,6-dimethoxyphenyl)-1,3-dioxopropan-2-yl-5-bromofuran-2-carboxylate (17d); 65%.

IR (ATR): 3146, 2924, 2850, 2159, 1730, 1683, 1613, 1578, 1451, 1421, 1359, 1275, 1248, 1214, 1159 \text{ cm}^{-1}.

\[ ^1\text{H-NMR} \ (400 \text{ MHz, CDCl}_3): \delta \ 13.06 \ (s, 1\text{H}), 7.29 \ (d, J = 4.0 \text{ Hz, 1H}), 7.23 \ (d, J = 3.5 \text{ Hz, 1H}), 7.08 \ (s, 1\text{H}), 6.56 \ (d, J = 4.0 \text{ Hz, 1H}), 6.47 \ (d, J = 3.5 \text{ Hz, 1H}), 6.08 \ (d, J = 2.2 \text{ Hz, 1H}), 5.83 \ (d, J = 2.2 \text{ Hz, 1H}), 3.79 \ (s, 3\text{H}), 3.50 \ (s, 3\text{H}). \]

\[ ^{13}\text{C-NMR} \ (100 \text{ MHz, CDCl}_3): \delta \ 192.0, 177.8, 167.8, 167.3, 161.4, 156.0, 152.3, 144.8, 129.6, 128.9, 121.9, 121.1, 115.0, 114.2, 104.2, 94.1, 91.1, 76.9, 55.7, 55.4. \]

ESI-HRMS \([\text{M}+\text{Na}]^+\): calcd for C\(_{20}\)H\(_{14}\)\(^79\)Br\(^{81}\)BrNaO\(_9\) \(580.8882\), found 580.8869.

\[ \text{C\(_{20}\)H\(_{14}\)\(^79\)Br\(_2\)NaO\(_9\)} \ 578.8902, \text{found 578.8945}. \]

\[ \text{C\(_{20}\)H\(_{14}\)\(^81\)Br\(_2\)NaO\(_9\)} \ 582.8861, \text{found 582.8855}. \]

Compound 13, 19a-d

**General procedure**

To a solution of 17a (404 mg, 0.93 mmol) in 12 mL of glacial acetic acid was added 246 \(\mu\)L of sulfuric acid. The resulting mixture was stirred at rt for 22 h. The reaction was quenched with cool water and filtered. Then resulting residue was added EtOH and stirred for a few hours under reflux condition. The reaction mixture was concentrated and resulting crude product 18a (307 mg) was used for next reaction without further purification.

To a solution of crude product 18a (307 mg) in EtOH (3.7 mL) was added 1\(\text{N}\) NaOH (890 \(\mu\)L). The reaction mixture was heated at 80 °C and stirred for 5 h. The reaction was quenched with 1\(\text{N}\) HCl and filtered by Kiriyama funnel. The residue was washed with cooled EtOH and the solvent was evaporated in vacuo to afford 19a (149 mg, 0.5 mmol, 66% from 17a).
2-(3-(benzyloxy)-4-methoxyphenyl)-3-hydroxy-5,7-dimethoxy-4H-chromen-4-one (13); 75% in 3 steps from 11.

IR (ATR): 2938, 1615, 1514, 1496, 1456, 1437, 1335, 1259, 1213, 1160, 1020 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ 7.83 (d, J = 2.0 Hz, 1H), 7.80 (dd, J = 8.4, 2.0 Hz, 1H), 7.51-7.49 (m, 2H), 7.39-7.28 (m, 3H), 6.99 (d, J = 8.4 Hz, 1H), 6.46 (d, J = 2.0 Hz, 1H), 6.32 (d, J = 2.0 Hz, 1H), 5.23 (s, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 3.90 (s, 3H).

¹³C-NMR (100 MHz CDCl₃): δ 171.9, 164.3, 160.5, 158.9, 147.9, 142.0, 137.5, 136.9, 128.5, 128.0, 127.6, 123.6, 121.2, 113.0, 111.4, 106.2, 95.6, 92.3, 71.3, 56.4, 56.0, 55.8.


To a solution of 13 (30 mg, 0.069 mmol) in THF (950 µL) and EtOH (950 µL) was added Pd(OH)₂ on activated carbon (3 mg). Under balloon pressure of hydrogen, the reaction mixture was stirred for 2 h. The reaction mixture was filtered through a celite and the solvent was removed in vacuo to afford a yellow-white solid 14 (23.8 mg, quant.).

IR (ATR): 3422, 3242, 2952, 2882, 1722, 1614, 1512, 1437, 1334, 1250, 1210, 1159, 1034 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ 7.84 (dd, J = 8.8, 2.0 Hz, 1H), 7.78 (d, J = 2.0 Hz, 1H), 6.98 (d, J = 8.8 Hz, 1H), 6.56 (d, J = 2.4 Hz, 1H), 6.35 (d, J = 2.4 Hz, 1H), 5.69 (brs, 1H), 3.98 (s, 3H), 3.98 (s, 3H), 3.92 (s, 3H).

¹³C-NMR (100 MHz CDCl₃): δ 171.9, 164.3, 160.5, 158.9, 147.7, 145.6, 141.9, 137.7, 124.4, 120.5, 113.1, 110.5, 106.2, 95.7, 92.4, 56.4, 56.0, 55.8.


3-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-5,7-dimethoxy-4H-chromen-4-one (14)

3-hydroxy-5,7-dimethoxy-2-(thiophen-2-yl)-4H-chromen-4-one (19a); 66%.
IR (ATR): 1614, 1557, 1436, 1370, 1325, 1237, 1213, 1158, 1107, 1032, 808 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ 7.91 (d, J = 4.0 Hz, 1H), 7.56 (d, J = 5.2 Hz, 1H), 7.21 (dd, J = 5.2, 4.0 Hz, 1H), 6.54 (d, J = 2.0 Hz, 1H), 6.35 (d, J = 2.0 Hz, 1H), 3.97 (s, 3H), 3.92 (s, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ 171.3, 164.4, 160.6, 158.7, 140.0, 136.6, 133.0, 128.7, 128.2, 128.0, 106.4, 95.8, 92.5, 56.4, 55.8.


2-(furan-2-yl)-3-hydroxy-5,7-dimethoxy-4H-chromen-4-one (19b); 92%.

IR (ATR): 3296, 2922, 2850, 1602, 1568, 1490, 1456, 1435, 1363, 1306, 1267, 1240, 1214, 1157, 1133, 1076, 1055, 997, 977, 938, 915, 885, 846, 820 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ 7.65 (dd, J = 1.8, 0.9 Hz, 1H), 7.23 (dd, J = 3.7, 0.9 Hz, 1H), 6.62 (dd, J = 3.7, 1.8 Hz, 1H), 6.58 (d, J = 2.2 Hz, 1H), 6.35 (d, J = 2.2 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ 171.2, 164.4, 160.6, 158.6, 138.5, 135.9, 114.1, 112.5, 106.5, 95.9, 92.6, 56.4, 55.8.


2-(5-bromothiophen-2-yl)-3-hydroxy-5,7-dimethoxy-4H-chromen-4-one (19c); 55%

IR (ATR): 2921, 1608, 1439, 1232, 1159, 1130, 1053 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ 7.60 (d, J = 3.9 Hz, 1H), 7.14 (d, J = 3.9 Hz, 1H), 6.50 (d, J = 2.3 Hz, 1H), 6.34 (d, J = 2.3 Hz, 1H), 3.96 (s, 3H), 3.90 (s, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ 171.2, 164.6, 160.6, 158.6, 138.5, 136.1, 134.2, 130.8, 128.1, 116.8, 106.4, 95.9, 92.5, 56.5, 55.9, 53.4.

406.9388, found 406.9372.

2-(5-bromofuran-2-yl)-3-hydroxy-5,7-dimethoxy-4H-chromen-4-one (19d); 55%.

IR (ATR): 3414, 1616, 1489, 1455, 1244, 1217, 1163, 1128, 1008, 923, 815 cm⁻¹.

¹H-NMR (400 MHz, CDCl₃): δ 7.14 (brs, 1H), 7.14 (d, J = 3.5 Hz, 1H), 6.59 (d, J = 2.2 Hz, 1H), 6.52 (d, J = 3.5 Hz, 1H), 6.34 (d, J = 2.2 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ 171.0, 164.5, 160.5, 158.6, 146.0, 136.1, 134.8, 124.7, 116.4, 114.4, 106.5, 96.0, 92.6, 56.4, 55.9.

ESI-HRMS [M+H]+: C₁₅H₁₂O₁⁸¹BrO₆ calcd 368.9797, found for 368.9747.

Compound 5, 22a-d

**General procedure**

To solution of 3-hydroxychromone (19a; 91 mg, 0.30 mmol) in dry acetonitrile (4.7 mL) and dry MeOH (3.2 mL) was added methyl cinnamate (610 µL, 3.9 mmol). The reaction mixture was irradiated (400 W mercury lamp) at 0 °C for 2 h. The solvent was removed *in vacuo* and the resulting residue was purified by silicagel column chromatography (hexane:AcOEt = 10:1→2:1→1:1) to afford a mixture containing 20a (95.7 mg).

To a mixture containing 20a (95.7 mg) in dry MeOH (7 mL) was added NaOMe (31 mg, 0.57 mmol). The reaction mixture was stirred for 2 h under reflux condition. The reaction was quenched with sat. aq. NH₄Cl and the mixture was extracted with EtOAc. The combined organic layer was washed with brine and dried over Na₂SO₄. After filtration and concentration, the resulting residue was purified by silicagel column chromatography (hexane:AcOEt = 2:1) to afford inseparable keto-enol isomers of 21a (55.9 mg, 0.12 mmol, 53% in 2 steps from 19a).

A mixture of tetramethylammonium triacetoxyborohydride (189 mg, 0.72 mmol) and acetic acid (70 µL, 1.2 mmol) in dry acetonitrile (3.1 mL) was stirred at rt for 5 min. The mixture was added to a solution of keto-enol tautomers 21a (55.9 mg, 0.12 mmol) in dry acetonitrile (2.1 mL) and the mixture was stirred at rt for 2 h. The reaction was quenched with sat. aq. NH₄Cl and the mixture was extracted with CH₂Cl₂. The combined organic layer was washed with brine and dried over Na₂SO₄. After filtration and concentration, the resulting residue was purified by silicagel column chromatography (hexane:AcOEt = 3:2) to afford 22a (45.9 mg, 0.098 mmol,
methyl (1R*,2R*,3S*,3aR*,8bS*)-1,8b-dihydroxy-3a-(3-hydroxy-4-methoxyphenyl)-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxylate (5); 35% in 3 steps.

IR (ATR): 3490, 2951, 2842, 1740, 1622, 1597, 1512, 1499, 1454, 1437, 1340, 1266, 1216, 1200, 1146, 1120, 1059, 1030 cm⁻¹.

¹H-NMR (400 MHz, CD₂OD): δ 7.05-7.00 (m, 3H), 6.91 (d, J = 8.0 Hz, 2H), 6.71 (d, J = 2.0 Hz, 1H), 6.65 (dd, J = 8.4, 2.0 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 6.22 (d, J = 2.0 Hz, 1H), 6.16 (d, J = 2.0 Hz, 1H), 4.85 (m, 1H), 4.21 (d, J = 14.2 Hz, 1H), 3.97 (dd, J = 14.2, 6.0 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.71 (s, 3H).

¹H-NMR (400 MHz, CDCl₃): δ 7.10-7.03 (m, 3H), 6.94-6.92 (m, 2H), 6.82 (d, J = 2.2 Hz, 1H), 6.67 (dd, J = 8.4, 2.2 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 6.28 (d, J = 1.8 Hz, 1H), 6.11 (d, J = 1.8 Hz, 1H), 5.43 (brs, 1H), 4.99 (d, J = 6.6 Hz, 1H), 4.33 (d, J = 14.3 Hz, 1H), 3.95 (dd, J = 14.3, 6.6 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 3.65 (s, 3H), 3.58 (brs, 1H), 1.86 (brs, 1H).

¹³C-NMR (100 MHz, CD₂OD): δ 172.6, 165.2, 162.2, 159.3, 147.7, 146.0, 139.2, 130.0, 129.1, 128.5, 127.2, 120.7, 116.6, 111.2, 109.2, 102.7, 95.1, 93.1, 90.0, 80.6, 56.4, 56.2, 56.1, 56.0, 52.5, 52.2.

¹³C-NMR (100 MHz, CDCl₃): δ 170.6, 164.1, 160.9, 157.0, 145.7, 144.6, 137.0, 127.8, 127.7, 127.6, 126.5, 119.7, 114.4, 109.5, 107.5, 101.8, 93.7, 92.6, 89.4, 79.5, 55.8, 55.7, 55.0, 52.0, 50.5.


methyl (1R*,2R*,3S*)-1,8b-dihydroxy-6,8-dimethoxy-3-phenyl-3a-(thiophen-2-yl)-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxylate (22a); 43% in 3 steps.
IR (ATR): 2950, 2844, 1735, 1597, 1499, 1455, 1436, 1339, 1276, 1216, 1200, 1146, 1116, 1033 cm\(^{-1}\).

\(^{1}\)H-NMR (400 MHz, CDCl\(_3\)) : \(\delta\) 7.13-7.09 (m, 4H), 7.02-6.99 (m, 2H), 6.89 (dd, \(J = 3.5, 1.1\) Hz, 1H), 6.87 (dd, \(J = 5.1, 3.5\) Hz, 1H), 6.28 (d, \(J = 1.8\) Hz, 1H), 6.14 (d, \(J = 1.8\) Hz, 1H), 4.97 (dd, \(J = 6.2, 1.8\) Hz, 1H), 4.33 (d, \(J = 14.3\) Hz, 1H), 3.92 (ddd, \(J = 14.3, 6.2, 1.1\) Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.65 (s, 3H), 3.43 (dd, \(J = 1.8, 1.1\) Hz, 1H), 2.01 (s, 1H).

\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) : \(\delta\) 170.4, 164.2, 160.9, 157.1, 137.4, 136.5, 127.8, 127.7, 126.8, 126.4, 125.9, 125.6, 107.0, 101.6, 93.5, 93.0, 89.4, 79.0, 55.8, 55.7, 55.0, 52.0, 50.1.

ESI-HRMS [M+Na\(^{+}\)] : calcd for C\(_{25}\)H\(_{24}\)NaO\(_7\)S 491.1140, found 491.1099.

methyl (1\(R^*,2R^*,3S^*,3aS^*,8bS^*)\)-3a-(furan-2-yl)-1,8b-dihydroxy-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1\(H\)-cyclopenta[b]benzofuran-2-carboxylate (22b); 13\% in 3 steps.

IR(ATR): 3505, 2950, 2844, 1742, 1625, 1600, 1499, 1455, 1437, 1344, 1285, 1216, 1201, 1147, 1122, 1083, 1033, 914, 813 cm\(^{-1}\).

\(^{1}\)H-NMR (400 MHz, CDCl\(_3\)) : \(\delta\) 7.30 (dd, \(J = 0.8, 2.0\) Hz, 1H), 7.17-7.08 (m, 5H), 6.26 (d, \(J = 2.0\) Hz, 1H), 6.18 (dd, \(J = 0.8, 3.4\) Hz, 1H), 6.13 (dd, \(J = 2.0, 3.4\) Hz, 1H), 6.12 (d, \(J = 2.0\) Hz, 1H), 4.94 (d, \(J = 6.0\) Hz, 1H), 4.30 (dd, \(J = 6.0, 14.0\) Hz, 1H), 4.17 (d, \(J = 14.0\) Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.64 (s, 3H), 3.42 (brs, 1H), 2.01 (s, 1H).

\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) : \(\delta\) 170.6, 164.2, 161.3, 156.9, 149.4, 142.6, 136.6, 127.8, 127.6, 126.8, 110.1, 109.6, 107.0, 100.2, 94.3, 92.9, 89.6, 79.3, 55.8, 55.7, 54.2, 52.0, 50.1.

ESI-HRMS [M+Na\(^{+}\)] : calcd for C\(_{25}\)H\(_{24}\)NaO\(_8\) 475.1369, found 475.1365.
methyl(1\(R^*\),2\(R^*\),3\(S^*\),3a\(S^*\),8b\(S^*\))-3a-(5-bromothiophen-2-yl)-1,8b-dihydroxy-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1\(H\)-cyclopenta[b]benzofuran-2-carboxylate (22c); 55% in 3 steps.

IR (ATR): 3507, 1743, 1599, 1499, 1437, 1201, 1117, 885, 811 cm\(^{-1}\).  
\(^1\)H-NMR (400 MHz, pyridine-\(d_5\)): \(\delta\) 7.42 (d, \(J = 7.4\) Hz, 2H), 7.19 (t, \(J = 7.4\) Hz, 2H), 7.06 (t, \(J = 7.4\) Hz, 1H), 6.95 (d, \(J = 3.9\) Hz, 1H), 6.87 (d, \(J = 3.9\) Hz, 1H), 6.46 (br, 1H), 6.29 (br, 1H), 5.58 (d, \(J = 4.9\) Hz, 1H), 5.15 (d, \(J = 14.1\) Hz, 1H), 4.53 (dd, \(J = 14.1, 4.9\) Hz, 1H), 3.72 (s, 3H), 3.61 (s, 3H), 3.59 (s, 3H).  
\(^{13}\)C-NMR (100 MHz, pyridine-\(d_5\)) : \(\delta\) 171.3, 163.9, 161.8, 159.0, 143.3, 139.0, 129.9, 128.6, 128.2, 127.5, 126.9, 111.2, 108.7, 102.4, 94.8, 93.0, 89.3, 80.2, 56.1, 55.6, 55.3, 52.4, 51.6.  
ESI-MS [M+Na]\(^+\) : calcd for C\(_{25}\)H\(_{23}\)BrO\(_7\)S 567.0246, found 569.0238. C\(_{25}\)H\(_{23}\)BrO\(_7\)S 571.0225, found 571.0225.

methyl (1\(R^*\),2\(R^*\),3\(S^*\),3a\(S^*\),8b\(S^*\))-3a-(5-bromofuran-2-yl)-1,8b-dihydroxy-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1\(H\)-cyclopenta[b]benzofuran-2-carboxylate (22d); 32% in 3 steps.

IR (ATR): 3483, 2951, 2842, 1738, 1625, 1600, 1505, 1455, 1437, 1376, 1343, 1284, 1201, 1148, 1116, 1073, 1034, 915, 813 cm\(^{-1}\).  
\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.20-7.10 (m, 5H), 6.24 (d, \(J = 2.0\) Hz, 1H), 6.14 (d, \(J = 3.2\) Hz, 1H), 6.12 (d, \(J = 2.0\) Hz, 1H), 6.02 (d, \(J = 3.2\) Hz, 1H), 4.92 (d, \(J = 6.0\) Hz, 1H), 4.26 (dd, \(J = 14.2, 6.0\) Hz, 1H), 4.18 (d, \(J = 14.2\) Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.65 (s, 3H), 3.31 (brs, 1H).  
\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 170.6, 164.3, 161.2, 157.0, 151.2, 136.3, 127.9, 127.7, 127.0, 121.9, 112.0, 111.6, 106.8, 99.9, 94.2, 93.0, 89.6, 79.1, 55.8, 55.7, 54.1, 52.0, 49.9.
ESI-HRMS [M+Na]: calcd for C_{25}H_{23}^{79}\text{Br}NaO_8 553.0474, found 553.0470. calcd for C_{25}H_{23}^{81}\text{Br}NaO_8 555.0454, found 555.0448.

Compound 4, 23a-d

General procedure

Rocaglamide derivative 22a (10.3 mg, 0.022 mmol) was dissolved in 4.7 mL of a 5:1 mixture of dry THF and distilled water. Lithium hydroxide monohydrate (13.8 mg, 0.33 mmol) was added and the reaction mixture was stirred at rt for 23 h. The mixture was diluted with CH_2Cl_2 and washed with 1N HCl and the organic layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and filtered. Concentration in vacuo gave rocagloic acid 23a (9.7 mg, 0.021 mmol, 97%).

(1R*,2R*,3S*,3aR*,8bS*)-1,8b-dihydroxy-3a-(3-hydroxy-4-methoxyphenyl)-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-2-carboxylic acid (4); quant.

IR (ATR): 2934, 2842, 1725, 1597, 1499, 1428, 1333, 1268, 1216, 1199, 1146, 1120, 1030 cm\(^{-1}\).

\(^1\)H-NMR (400 MHz, Py-d_5): \(\delta\) 7.56 (s, 1H), 7.54 (d, \(J = 4.8\) Hz, 2H), 7.17 (d, \(J = 5.8\) Hz, 1H), 7.11 (t, \(J = 4.8\) Hz, 2H), 6.96 (t, \(J = 4.8\) Hz, 1H), 6.70 (d, \(J = 5.8\) Hz, 1H), 6.48 (d, \(J = 1.2\) Hz, 1H), 6.27 (d, \(J = 1.2\) Hz, 1H), 5.82 (d, \(J = 3.2\) Hz, 1H), 5.36 (d, \(J = 9.2\) Hz, 1H), 4.80 (dd, \(J = 9.2, 3.2\) Hz, 1H), 3.73 (s, 3H), 3.63 (s, 3H), 3.52 (s, 3H).

\(^1\)H-NMR (400 MHz, CDCl_3): \(\delta\) 7.09-7.04 (m, 3H), 6.94-6.92 (m, 2H), 6.78 (d, \(J = 2.0\) Hz, 1H), 6.63 (dd, \(J = 8.6, 2.0\) Hz, 1H), 6.58 (d, \(J = 8.6\) Hz, 1H), 6.25 (d, \(J = 2.0\) Hz, 1H), 6.09 (d, \(J = 2.0\) Hz, 1H), 4.98 (d, \(J = 6.6\) Hz, 1H), 4.26 (d, \(J = 14.1\) Hz, 1H), 3.92 (dd, \(J = 14.1, 6.6\) Hz, 1H), 3.81 (s, 6H), 3.76 (s, 3H).

\(^{13}\)C-NMR (100 MHz, Py-d_5): 173.7, 163.7, 162.4, 159.0, 147.1, 146.6, 140.5, 131.3, 129.0, 128.0, 126.2, 120.0, 117.3, 110.9, 109.8, 103.2, 95.3, 92.4, 89.3, 81.0, 56.4, 55.59, 55.56, 55.3
\( ^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \( \delta \) 174.2, 164.0, 160.8, 157.0, 145.7, 144.5, 136.7, 127.8, 127.7, 127.5, 126.5, 119.6, 114.4, 109.5, 107.3, 101.7, 93.6, 92.6, 89.4, 79.3, 55.7, 55.7, 54.9, 50.2.

ESI-HRMS [M+Na]\(^+\): calcd for C\(_{27}\)H\(_{26}\)NaO\(_5\) 517.1475, found 517.1456.

IR (ATR): 3472, 1717, 1599, 1499, 1200, 1148, 1118 cm\(^{-1}\).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.09-7.06 (m, 4H), 6.98-6.96 (m, 2H), 6.85-6.83 (m, 2H), 6.24 (d, \( J = 1.8 \) Hz, 1H), 6.10 (d, \( J = 1.8 \) Hz, 1H), 4.94 (dd, \( J = 5.9, 1.8 \) Hz, 1H), 4.24 (d, \( J = 13.9 \) Hz, 1H), 3.87 (dd, \( J = 13.9, 5.9 \) Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H).

\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \( \delta \) 174.1 164.2, 160.8, 157.0, 137.2, 136.2, 127.8, 127.7, 126.9, 126.4, 126.0, 125.6, 106.8, 101.5, 93.4, 93.0, 89.4, 78.8, 55.78, 55.72, 54.9, 49.7.

ESI-HRMS [M+Na]\(^+\): calcd for C\(_{24}\)H\(_{22}\)NaO\(_5\) 477.0984, found 477.0972.

\((1R^*,2R^*,3S^*,3aS^*,8bS^*)\)-1,8b-dihydroxy-6,8-dimethoxy-3-phenyl-3a-(furan-2-yl)-2,3,3a,8b-tetrahydro-1\(H\)-cyclopenta[b]benzofuran-2-carboxylic acid (23a); 97%.

\((1R^*,2R^*,3S^*,3aS^*,8bS^*)\)-3a-(furan-2-yl)-1,8b-dihydroxy-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1\(H\)-cyclopenta[b]benzofuran-2-carboxylic acid (23b); 87%.
IR (ATR): 3373, 2938, 1716, 1602, 1501, 1454, 1217, 1200, 1148, 1122 cm\(^{-1}\).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta 7.29 \text{ (d, } J = 2.0 \text{ Hz, } 1\text{H}), 7.15-7.09 \text{ (m, 5H), 6.24 \text{ (d, } J = 2.0 \text{ Hz, } 1\text{H}), 6.16 \text{ (d, } J = 3.2 \text{ Hz, } 1\text{H), 6.13 \text{ (dd, } J = 2.0, 3.2 \text{ Hz, } 1\text{H), 6.10 \text{ (d, } J = 2.0 \text{ Hz, } 1\text{H), 4.95 \text{ (d, } J = 6.0 \text{ Hz, } 1\text{H), 4.28 \text{ (dd, } J = 6.0, 14.2 \text{ Hz, } 1\text{H), 4.12 \text{ (d, } J = 14.2 \text{ Hz, } 1\text{H), 3.82 \text{ (s, } 3\text{H), 3.80 \text{ (s, } 3\text{H).}}}

\(^1\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta 174.3, 164.3, 161.2, 156.9, 149.2, 142.6, 136.3, 127.9, 127.7, 126.9, 110.1, 109.6, 106.8, 100.1, 94.2, 92.9, 89.6, 79.1, 55.8, 55.7, 54.1, 49.7.

ESI-HRMS [M+Na]\(^+\): calcd for C\(_{24}\)H\(_{22}\)NaO\(_8\) 461.1212, found 461.1143.

\((1R^*,2R^*,3S^*,3aS^*,8bS^*)-3\text{-a-(5-bromothiophen-2-yl)}-1,8b\text{-dihydroxy-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[h]benzofuran-2-carboxylic acid (23c); 66\%}

IR (ATR): 3450, 1725, 1599, 1501, 1217, 1146, 1118 cm\(^{-1}\).

\(^1\)H-NMR (400 MHz, pyridine-\(d_5\)): \(\delta 7.56-7.54 \text{ (m, 2H), 7.21-7.17 \text{ (m, 2H), 7.04 \text{ (t, } J = 7.4 \text{ Hz, } 1\text{H), 6.97 \text{ (d, } J = 3.9 \text{ Hz, } 1\text{H), 6.87 \text{ (d, } J = 3.9 \text{ Hz, } 1\text{H), 6.49 \text{ (d, } J = 1.9 \text{ Hz, } 1\text{H), 6.31 \text{ (d, } J = 1.9 \text{ Hz, } 1\text{H), 5.77 \text{ (d, } J = 4.7 \text{ Hz, } 1\text{H), 5.30 \text{ (d, } J = 14.0 \text{ Hz, } 1\text{H), 4.68 \text{ (dd, } J = 14.0, 4.7 \text{ Hz, } 1\text{H), 3.73 \text{ (s, } 3\text{H), 3.63 \text{ (s, } 3\text{H).}}}

\(^1\)C-NMR (100 MHz, pyridine-\(d_5\)): \(\delta 173.3, 163.8, 162.0, 159.0, 143.7, 139.6, 129.8, 128.8, 128.1, 127.4, 126.7, 111.0, 109.0, 102.7, 94.9, 92.9, 89.3, 80.4, 56.4, 55.6, 55.3, 52.8.

ESI-MS [M+Na]\(^+\): calcd for C\(_{24}\)H\(_{21}\)BrNaO\(_7\)S 555.0089, found 555.0072. C\(_{24}\)H\(_{21}\)BrNaO\(_7\)S 557.0069, found 557.0047.

\((1R^*,2R^*,3S^*,3aS^*,8bS^*)-3\text{-a-(5-bromofuran-2-yl)}-1,8b\text{-dihydroxy-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[h]benzofuran-2-carboxylic acid (23d); quant.}

S18
IR (ATR): 3477, 2944, 2024, 1717, 1626, 1503, 1455, 1200, 1148, 1117 cm⁻¹.

¹H-NMR (400 MHz, CD₃OD): δ 7.20-7.06 (m, 5H), 6.23 (d, J = 1.8 Hz, 1H), 6.16 (d, J = 1.8 Hz, 1H), 6.09 (d, J = 3.4 Hz, 1H), 6.01 (d, J = 3.4 Hz, 1H), 4.77 (d, J = 5.2 Hz, 1H), 4.17 (dd, J = 13.8, 5.2 Hz, 1H), 4.09 (d, J = 13.8 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H).

¹³C-NMR (100 MHz CD₃OD): δ 174.2, 165.4, 162.6, 159.5, 154.3, 138.8, 129.1, 128.6, 127.5, 122.0, 112.3, 112.3, 101.2, 108.2, 95.7, 93.3, 89.8, 79.8, 56.1, 55.9, 55.7, 52.2.

ESI-HRMS [M+Na]⁺: calc for C₂₄H₂₁⁷⁹BrNaO₈ 539.0318, found 539.0265, C₂₄H₂₁⁸¹BrNaO₈ 541.0297, found 541.0243.

**Reporter gene assay and transfection for Wnt signal inhibitory activity**

A cell-based assay method was previously described (Li et al., 2009, *Chem. Asian J.* 4, 540–547). This assay was used to evaluate TCF/β-catenin transcriptional activity. Assay cells (STF/293 cells) were seeded into 96-well plates (3 x 10⁴ cells/well). After 24 h, the cells were treated with compounds combined with 15 mM LiCl for another 24 h. The cells were then lysed, and luciferase activity was measured using the Luciferase Assay System (Promega) on a Luminoskan Ascent (Thermo). To eliminate the nonspecific inhibition of TOP activity, FOP activity was also evaluated. HEK293 cells were plated on 24-well plates (1 x 10⁵ cells/well) and incubated for 24 h. Using Lipofectamine 2000, the cells were transiently transfected with 500 ng/well of the luciferase reporter construct (SuperFOPflash), and 25 ng/well of pRL-CMV (Promega, USA) for normalization. Compounds combined with 15 mM LiCl were then added to the cells 12 h post-transfection. After being incubated for 24 h with the compounds, cells were lysed and luciferase activity was measured using PICAGENE Dual Seapansy (Toyo Ink) with Luminoskan Ascent (Thermo).

**Viability assay**

STF/293 (3 x 10⁴ cells/well), AGS, HCT116, SW480, DLD1, RKO and HEK293 cells (5 x 10⁵ cells/well) were seeded into 96-well plates for 24 h. Compounds were then added and incubated as described. The viability of cells was measured using the fluorometric microculture cytotoxicity assay (FMCA) (Lindhagen et al., 2008, *Nat. Protoc.* 3, 1364–1369). After being
incubated with the compounds, cells were washed with PBS and then added to fluorescein diacetate (Wako, Japan) in PBS. Cells were incubated for 1 h and fluorescence was measured using a Fluoroskan (Ascent).

**Figure 2** Comparison of coupling constant of synthetic compound 5 with reported value.

![Coupling Constants](image)

Table 1 Comparison of data of synthetic compound 5 with reported value.

<table>
<thead>
<tr>
<th>position</th>
<th>(^1)H-NMR (\delta ) (J in Hz)</th>
<th>ref 10</th>
<th>(^13)C-NMR (\delta ) (J in Hz)</th>
<th>ref 10</th>
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<td></td>
<td></td>
</tr>
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<td>3.96 (dd, 6.3, 14.1)</td>
<td>4.01 (dd, 6.2, 14.2)</td>
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</tr>
<tr>
<td>3</td>
<td>4.22 (d, 14.1)</td>
<td>4.27 (d, 14.2)</td>
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<td>56.4</td>
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<tr>
<td>3a</td>
<td></td>
<td></td>
<td>102.7</td>
<td>102.8</td>
</tr>
<tr>
<td>4a</td>
<td></td>
<td>*</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6.27 (d, 2.0)</td>
<td>6.32 (d, 1.9)</td>
<td>90.0</td>
<td>90.0</td>
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<tr>
<td>6</td>
<td></td>
<td>*</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>6.16 (d, 2.0)</td>
<td>6.21 (d, 2.0)</td>
<td>93.1</td>
<td>93.1</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>*</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>8a</td>
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<td></td>
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<td>109.3</td>
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<td>95.1</td>
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<td>130.1</td>
</tr>
<tr>
<td>2’</td>
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<td>6.76 (d, 2.0)</td>
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<tr>
<td>3’</td>
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<td></td>
<td>146.0</td>
<td>146.0</td>
</tr>
<tr>
<td>4’</td>
<td></td>
<td>*</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>5’</td>
<td>6.62 (d, 8.4)</td>
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<td>111.2</td>
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<tr>
<td>6’</td>
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<td>120.7</td>
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<td>129.1</td>
</tr>
<tr>
<td>3”/5”</td>
<td>7.01 (m)</td>
<td>7.05 (m)</td>
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<td>128.5</td>
</tr>
<tr>
<td>4”</td>
<td>7.01 (m)</td>
<td>7.05 (m)</td>
<td>127.2</td>
<td>127.2</td>
</tr>
<tr>
<td>6-OMe</td>
<td>3.81 (s)</td>
<td>3.86 (s)</td>
<td>56.2, 56.1, 56.0</td>
<td>56.2, 56.1, 56.0</td>
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<td>8-OMe</td>
<td>3.82 (s)</td>
<td>3.87 (s)</td>
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</tr>
<tr>
<td>4’-OMe</td>
<td>3.70 (s)</td>
<td>3.76 (s)</td>
<td></td>
<td></td>
</tr>
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<td>172.6</td>
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<td>3.66 (s)</td>
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*147.7, 159.3, 162.2, 165.2 exchangeable
**147.8, 159.3, 162.2, 165.3 exchangeable (in CD\(_3\)OD)
Table 2 Comparison of data of synthetic compound 4 with reported value.

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<th>position</th>
<th>$^1$H-NMR $\delta$ (J in Hz)</th>
<th>ref 5 (400 MHz)</th>
<th>$^1$C-NMR $\delta$ (J in Hz)</th>
<th>ref 5 (100MHz)</th>
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</thead>
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<tr>
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<td>3</td>
<td>4.26 (d, 14.1)</td>
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<td>55.9</td>
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<tr>
<td>3a</td>
<td></td>
<td>101.7</td>
<td>101.7</td>
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</tr>
<tr>
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<td>161.1</td>
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<td>5</td>
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<tr>
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<td>163.9</td>
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</tr>
<tr>
<td>7</td>
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<td>6.13 (d, 2.0)</td>
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<td>92.4</td>
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<td>157.4</td>
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</tr>
<tr>
<td>1'</td>
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<td>127.5</td>
<td>127.7</td>
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</tr>
<tr>
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<td>114.4</td>
<td>114.6</td>
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<tr>
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<td>144.3</td>
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<td>4'</td>
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<td>145.8</td>
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<td>109.6</td>
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<td>6.71 (dd, 2.5, 8.5)</td>
<td>119.6</td>
<td>119.5</td>
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<tr>
<td>1''</td>
<td></td>
<td>136.7</td>
<td>136.5</td>
<td></td>
</tr>
<tr>
<td>2''/6''</td>
<td>7.09-7.04 (m)</td>
<td>7.14-7.06 (m)</td>
<td>127.7</td>
<td>128.2</td>
</tr>
<tr>
<td>3''/5''</td>
<td>6.94-6.92 (m)</td>
<td>7.14-7.06 (m)</td>
<td>127.8</td>
<td>128.8</td>
</tr>
<tr>
<td>4''</td>
<td>7.09-7.04 (m)</td>
<td>7.14-7.06 (m)</td>
<td>126.5</td>
<td>126.7</td>
</tr>
<tr>
<td>Ar-OMe</td>
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<td>3.86 (s)</td>
<td>55.7</td>
<td>55.6</td>
</tr>
<tr>
<td></td>
<td>3.81 (s)</td>
<td>3.84 (s)</td>
<td>55.7</td>
<td>55.6</td>
</tr>
<tr>
<td></td>
<td>3.76 (s)</td>
<td>3.77 (s)</td>
<td>54.9</td>
<td>55.6</td>
</tr>
<tr>
<td>CO$_2$H</td>
<td></td>
<td>174.2</td>
<td>173.2</td>
<td></td>
</tr>
</tbody>
</table>

(in CDCl$_3$)
Figure 3 TRAIL resistance overcoming activity of 5, 22c and 23c.
X-ray data for 22a

Figure 4. X-ray structure of compound 22a.

Table 3. Crystal data for 22a

**Chemical formula** $C_{25}H_{23}O_{7}S$

**Formula weight** 468.50

**Wavelength** 1.54178 Å

**Crystal size** 0.200 x 0.200 x 0.800 mm

**Crystal system** orthorhombic

**Space group** Pbc

**Unit cell dimensions**

\[ a = 9.8131(3) \text{ Å} \quad \alpha = 90^\circ \]

\[ b = 20.4457(5) \text{ Å} \quad \beta = 90^\circ \]

\[ c = 21.4000(6) \text{ Å} \quad \gamma = 90^\circ \]
Volume 4293.6(2) Å³
Z 8
Density (calculated) 1.450 g/cm³
Absorption coefficient 1.744 mm⁻¹
F(000) 1968

Table 4. Data collection and structure refinement for 22a

Theta range for data collection 4.13 to 68.11°
Index ranges -11<=h<=9, -24<=k<=23, -25<=l<=23
Reflections collected 14098
Independent reflections 3851 [R(int) = 0.0174]
Coverage of independent reflections 98.3%
Absorption correction multi-scan
Max. and min. transmission 0.7217 and 0.3359
Structure solution technique direct methods
Structure solution program SHELXS-97 (Sheldrick, 1997)
Refinement method Full-matrix least-squares on F²
Refinement program SHELXL-97 (Sheldrick, 1997)
Function minimized Σ w(Fo² - Fc²)²
Data / restraints / parameters 3851 / 0 / 355
Goodness-of-fit on F² 1.035
Final R indices 3510 data; I>2σ(I) R1 = 0.0374, wR2 = 0.0999
all data R1 = 0.0404, wR2 = 0.1030
Weighting scheme w=1/[σ²(Fo²)+(0.0672P)²+1.5656P] where P=(Fo²+2Fc²)/3
Largest diff. peak and hole 0.337 and -0.252 eÅ⁻³
R.M.S. deviation from mean 0.049 eÅ⁻³
X-ray data for 23c

Figure 5. X-ray structure of compound 23c.

Table 5. Crystal data for 23c

A. Crystal Data

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical Formula</td>
<td>C_{25}H_{21}BrO_8S</td>
</tr>
<tr>
<td>Formula Weight</td>
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<td>Crystal Color, Habit</td>
<td>colorless, platelet</td>
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<tr>
<td>Crystal Dimensions</td>
<td>0.200 X 0.030 X 0.010 mm</td>
</tr>
<tr>
<td>Crystal System</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Lattice Type</td>
<td>Primitive</td>
</tr>
<tr>
<td>Lattice Parameters</td>
<td>a = 11.1283(3) Å</td>
</tr>
<tr>
<td></td>
<td>b = 29.5193(7) Å</td>
</tr>
<tr>
<td></td>
<td>c = 7.7932(2) Å</td>
</tr>
<tr>
<td></td>
<td>b = 108.307(2) °</td>
</tr>
<tr>
<td></td>
<td>V = 2430.5(1) Å^3</td>
</tr>
<tr>
<td>Space Group</td>
<td>P2_1/c (#14)</td>
</tr>
</tbody>
</table>
Z value 4
D_{calc} 1.534 \text{ g/cm}^3
F_{000} 1144.00
m(CuKa) 35.352 \text{ cm}^{-1}

B. Intensity Measurements

Diffractometer R-AXIS RAPID
Radiation CuKa (\lambda = 1.54187 \text{ Å})
Voltage, Current 40kV, 30mA
Temperature -180.0^\circ \text{C}
Detector Aperture 460 x 256 mm
Data Images 30 exposures
w oscillation Range (c=54.0, f=0.0) 80.0 - 260.0^\circ
Exposure Rate 10.0 sec./^\circ
w oscillation Range (c=54.0, f=90.0) 80.0 - 260.0^\circ
Exposure Rate 10.0 sec./^\circ
w oscillation Range (c=54.0, f=180.0) 80.0 - 260.0^\circ
Exposure Rate 10.0 sec./^\circ
w oscillation Range (c=54.0, f=270.0) 80.0 - 260.0^\circ
Exposure Rate 10.0 sec./^\circ
w oscillation Range (c=0.0, f=0.0) 80.0 - 260.0^\circ
Exposure Rate 10.0 sec./^\circ
Detector Position 127.40 mm
Pixel Size 0.100 mm
2q_{\text{max}} 136.5^\circ
No. of Reflections Measured Total: 26111
Unique: 4455 (R_{int} = 0.2105)
Corrections Lorentz-polarization
Absorption (trans. factors: 0.564 - 0.965)
Secondary Extinction (coefficient: 1.17000e-003)
C. Structure Solution and Refinement

Structure Solution

Refinement

Function Minimized

Least Squares Weights

$w = \frac{1}{s^2(F_o^2) + (0.1860 \cdot P)^2 + 0.0000 \cdot P}$

where $P = (\text{Max}(F_o^2, 0) + 2F_c^2)/3$

$2\sigma_{\text{max}}$ cutoff

Anomalous Dispersion

All non-hydrogen atoms

No. Observations (All reflections)

No. Variables

Reflection/Parameter Ratio

Residuals: $R_1$ ($I > 2.00\sigma(I)$)

Residuals: $R$ (All reflections)

Residuals: $wR^2$ (All reflections)

Goodness of Fit Indicator

Max Shift/Error in Final Cycle

Maximum peak in Final Diff. Map

Minimum peak in Final Diff. Map

Direct Methods

Full-matrix least-squares on $F^2$

$S \cdot w (F_o^2 - F_c^2)^2$

136.5°
X-ray data for 23d

![Diagram of compound 23d]

**Figure 6.** X-ray structure of compound 23d.

**Table 6.** Crystal data for 23d

A. Crystal Data

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical Formula</td>
<td>$\text{C}<em>{25}\text{H}</em>{22}\text{BrCl}_3\text{O}_8$</td>
</tr>
<tr>
<td>Formula Weight</td>
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<td>Crystal Color, Habit</td>
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<td>Lattice Type</td>
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</tr>
<tr>
<td>Lattice Parameters</td>
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<tr>
<td></td>
<td>$b = 10.5843(4) \text{ Å}$</td>
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<td></td>
<td>$c = 14.6153(5) \text{ Å}$</td>
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<td></td>
<td>$a = 74.063(2)^\circ$</td>
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<td></td>
<td>$b = 80.510(2)^\circ$</td>
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<td></td>
<td>$g = 63.284(2)^\circ$</td>
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<td>Parameters</td>
<td>Values</td>
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<tr>
<td>$m(\text{CuKa})$</td>
<td>$54.275 \text{ cm}^{-1}$</td>
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</table>

**B. Intensity Measurements**

- **Diffractometer**: R-AXIS RAPID
- **Radiation**: CuKa ($\lambda = 1.54187 \text{ Å}$)
- **Voltage, Current**: 40kV, 30mA
- **Temperature**: -180.0°C
- **Detector Aperture**: 460 x 256 mm
- **Data Images**: 30 exposures
- **$\omega$ oscillation Range ($c=54.0$, $f=0.0$)**: 80.0 - 260.0°
- **Exposure Rate**: 4.0 sec./°
- **$\omega$ oscillation Range ($c=54.0$, $f=90.0$)**: 80.0 - 260.0°
- **Exposure Rate**: 4.0 sec./°
- **$\omega$ oscillation Range ($c=54.0$, $f=180.0$)**: 80.0 - 260.0°
- **Exposure Rate**: 4.0 sec./°
- **$\omega$ oscillation Range ($c=54.0$, $f=270.0$)**: 80.0 - 260.0°
- **Exposure Rate**: 4.0 sec./°
- **Detector Position**: 127.40 mm
- **Pixel Size**: 0.100 mm
- **$2\theta_{\text{max}}$**: 136.5°
- **No. of Reflections Measured**: Total: 13987
  Unique: 4644 ($R_{\text{int}} = 0.0629$)
- **Corrections**: Lorentz-polarization
  - Absorption
    (trans. factors: 0.617 - 0.762)
  - Secondary Extinction
    (coefficient: 2.40000e-004)
## C. Structure Solution and Refinement

<table>
<thead>
<tr>
<th>Structure Solution</th>
<th>Direct Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refinement</td>
<td>Full-matrix least-squares on $F^2$</td>
</tr>
<tr>
<td>Function Minimized</td>
<td>$Sw\ (Fo^2 - Fc^2)^2$</td>
</tr>
<tr>
<td>Least Squares Weights</td>
<td>$w = 1/ \left[ s^2(Fo^2) + (0.0000 \cdot P)^2 + 8.1150 \cdot P \right]$</td>
</tr>
<tr>
<td>2$q_{\text{max}}$ cutoff</td>
<td>136.5°</td>
</tr>
<tr>
<td>Anomalous Dispersion</td>
<td>All non-hydrogen atoms</td>
</tr>
<tr>
<td>No. Observations (All reflections)</td>
<td>4644</td>
</tr>
<tr>
<td>No. Variables</td>
<td>335</td>
</tr>
<tr>
<td>Reflection/Parameter Ratio</td>
<td>13.86</td>
</tr>
<tr>
<td>Residuals: R1 ($I&gt;2.00s(I)$)</td>
<td>0.0547</td>
</tr>
<tr>
<td>Residuals: R (All reflections)</td>
<td>0.1044</td>
</tr>
<tr>
<td>Residuals: wR2 (All reflections)</td>
<td>0.1490</td>
</tr>
<tr>
<td>Goodness of Fit Indicator</td>
<td>1.137</td>
</tr>
<tr>
<td>Max Shift/Error in Final Cycle</td>
<td>0.000</td>
</tr>
<tr>
<td>Maximum peak in Final Diff. Map</td>
<td>0.77 e⁻/Å³</td>
</tr>
<tr>
<td>Minimum peak in Final Diff. Map</td>
<td>-0.84 e⁻/Å³</td>
</tr>
</tbody>
</table>
Compound 8
Compound 8
Compound 9
Compound 9
Compound 10
Compound 10
Compound 11

![Chemical Structure of Compound 11]

S38
Compound 11
Compound 12
Compound 14
Compound 14
Compound 5
Compound 5

\[
\begin{align*}
&\text{MeO} &\text{HO} &\text{CO}_2\text{Me} \\
&\text{MeO} &\text{HO} &\text{OMe}
\end{align*}
\]
Compound 4
Compound 4
Compound 16a
Compound 16b

![Compound 16b](image)

**DFILE**: 21b-bcm.xls  
**COMM**: kkkv6.0-bcm_142017  
**DATIM**: 208.6-10-17 13:30:55  
**OBNUC**: 13C  
**EXMID**: single_part_4dec  
**OBFOQ**: 100.53 MHz  
**OBSET**: 5.35 kHz  
**OBSN**: 5.86 Hz  
**PONR**: 32758  
**FREQ**: 251088.92 Hz  
**SCANS**: 903  
**ACOTM**: 1.3009 sec  
**PD**: 1.0000 sec  
**PW1**: 3.17 usec  
**HRNUC**: 1H  
**CHM**: 232.2 c  
**SVVHT**: CDCl3  
**EXHT**: 77.00 ppm  
**BF**: 2.00 Hz  
**RGM**: 24
Compound 16c
Compound 16c

S53
Compound 16d

![Chemical structure of compound 16d](image)

**S54**
Compound 16d

The image shows a 1H NMR spectrum with various chemical shifts and peaks labeled. The spectrum includes peaks at 1H, 1O, 2H, 4H, 6H, 7H, 8H, and 9H. The molecule is depicted with labels for different chemical groups, including MeO, OMe, and Br.
Compound 17a
Compound 17a

\[ \text{Diagram of Compound 17a} \]

Table of NMR parameters:

- DFIRE: 22a-bcm.xls
- COMMENT: kkkk-44-bcm-340512
- DATUM: 2014-06-12 17:16:33
- OBHIC: 13K
- ENMOD: single_pulse_drec
- OBSLQ: 100.53 MHz
- OBSF: 5.35 kHz
- OBSF: 5.89 Hz
- POINT: 32708
- FREQU: 25188.92 Hz
- SCABS: 356
- ACOTM: 1.3005 s/sec
- PD: 1.0000 s/sec
- PW2: 8.1774 s/sec
- STMUC: 11
- CETMP: 23.6 c
- SLWHT: CDCl3
- RESL: 77.00 ppm
- BF: 2.00 Hz
- RSL: 24
Compound 17b
Compound 17c

**Spectrum Details**
- **Instrument:** proton
- **Frequency:** 300.79 MHz
- **Frequency Error:** 6.19 kHz
- **Polarization:** 4.74 Hz
- **Power:** 13384
- **Scans:** 8
- **ACQ Time:** 2.9473 sec
- **Delay:** 5.0000 sec
- **Gated:** 1H
- **Temperature:** 20.1 °C
- **Solvent:** CDCl3
- **Reference:** 7.24 ppm
- **RF:** 6.02 Hz
- **Gain:** 50

**Chemical Structure**

![Chemical Structure of Compound 17c]
Compound 17c

\[
\text{OH} \quad \text{O} \\
\text{OMe} \quad \text{MeO} \\
\text{O} \quad \text{O} \\
\text{S} \quad \text{S} \\
\text{Br} \quad \text{Br}
\]

**17c**
Compound 17d
Compound 17d
Compound 19a
Compound 19a
Compound 19b
Compound 19b
Compound 19c

$\text{MeO} \quad \text{O} \quad \text{S} \quad \text{Br}$

S68
Compound 19c

$$\text{O}_{\text{MeO}}\text{O}_{\text{MeO}}$$

19c

MeO

MeO

Br

S

0
25
50
75
100
125
150
175

PPM
Compound 19d
Compound 19d
Compound 22a
Compound 22a
Compound 22b

\[ \text{Compound 22b} \]

![NMR spectrum of Compound 22b](image-url)
Compound 22b
Compound 22d
Compound 23a
Compound 23a
Compound 23b
Compound 23b
Compound 23c
Compound 23c

23c
Compound 23d