Reagent controlled domino synthesis of skeletally diverse compound collections

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1 Supporting information

1.1 General

$^1$H NMR and $^{13}$C spectra were recorded on a Varian Mercury 600 or a Bruker DRX 500 spectrometer. NMR spectra were calibrated to the solvent signal of CDCl$_3$ (7.26 ppm and 77.0 ppm) and DMSO (2.49 ppm and 39.5 ppm). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, br = broad. GC-MS(EI) were measured on a Hewlett-Packard 6890 Series gas chromatograph connected to a Hewlett-Packard 5973 series mass spectrometer; column: H&W 19091σ-102 HP-5MS capillary: 25.0 m × 201 μm × 0.33 μm nominal. LC-MS was performed on a 1100 series from Hewlett-Packard connected to a Finnigan LCQ ESI-Spectrometer; column: VP 50 / 10 Nucleosil C18PPN-column (Macherey-Nagel); gradient: 90 / 10 (v / v) H$_2$O / acetonitrile (0.1% formic acid) to 10 / 90 (v / v) in 30 min, flow 1.00 ml / min. High resolution mass spectra (HR-MS) were measured on a finnigan MAT 8200 spectrometer. IR spectra were measured on a Bruker Vector 22 spectrometer with a diffuse reflectance head A527 from Spectra Tech. The optical rotation was determined with Perkin Elmer Polarimeter 241. TLC was performed on Merck silica gel 60F254 aluminium sheets using UV as a visualizing agent and a 0.5% aqueous potassium permanganate solution or an ethanolic solution of phosphomolybdic acid and heat as developing agents. For flash chromatography silica gel (40-60 μm) from Merck was used. All reactions were performed under an argon atmosphere with freshly distilled and dried solvents. All solvents were distilled using standard procedures. Unless otherwise noted, reagents were obtained from Aldrich, Acros, Fluka, Lancaster and Strem and used without further purification.
1.2 Synthesis of substituted pyridines without cleaving the TBS group

![Chemical structure diagram]

Representative procedure for the domino reactions leading to substituted pyridines:

(3R)-Ethyl 2-(4-(tert-butyldimethylsilyloxy)-3-methylbutyl)-5-(2-hydroxy-benzoyl) nicotinate (4a)

To a solution of chromonylidene-β-ketoester 1a (33.3 mg, 0.070 mmol) in MeOH (5 ml) was added ammonium fluoride (26.0 mg, 0.70 mmol, 10.0 eq.). The reaction mixture was stirred for 1h (TLC-control) at room temperature. The methanol was removed in vacuo, water was
added, and the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous MgSO₄, filtered and evaporated to give the crude pyridine. The residue was purified by column chromatography.

Yield = 27.8 mg (0.059 mmol, 87%); Rf = 0.42 (cyclohexane / EtOAc = 2 / 1); [α]D²⁰ = -3.1 ° (c =1.81, CHCl₃); ¹H–NMR (400 MHz, CDCl₃): δ(ppm) = 11.81 (s, 1H), 8.91 (d, J = 2.3 Hz, 1H), 8.45 (d, J = 2.3 Hz, 1H), 7.14-7.05 (m, 1H), 7.59-7.43 (m, 2H), 6.92 (ddd, J = 8.1 Hz, J = 7.2 Hz, J = 1.1 Hz, 1H), 4.41 (q, J = 7.2 Hz, 2H), 3.54 (dd, J = 9.8 Hz, J = 5.7 Hz, 1H), 3.43 (dd, J = 9.9 Hz, J = 6.5 Hz, 1H), 3.28 (ddd, J = 22.1 Hz, J = 10.7 Hz, J = 5.5 Hz, 1H), 1.94-1.81 (m, 1H), 1.78-1.64 (m, 1H), 1.60-1.46 (m, 1H), 1.41 (t, J = 7.1 Hz, 3H), 1.00 (d, J = 7.1 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ¹³C-NMR (100.6 MHz, CDCl₃): δ(ppm) = 198.3, 166.9, 165.7, 163.2, 151.2, 139.0, 137.0, 132.8, 130.8, 125.6, 119.1, 118.8, 118.7, 68.2, 61.7, 36.1, 34.8, 33.3, 25.9, 18.3, 16.6, 14.2, 14.1, -5.3; LC-MS(ESI): tᵣ = 9.69 min; calcd. for C₂₆H₃₇O₅Si 471.24, found 358.19 [M-SiMe₂tBu]⁺.

Ethyl 2-(4-(tert-butyldimethylsilyloxy)-butyl)-5-(2-hydroxybenzoyl) nicotinate (4c)

Yield = 23.91 mg (0.052 mmol, 79%); Rf = 0.41 (cyclohexane / EtOAc = 2 / 1); ¹H–NMR (400 MHz, CDCl₃): δ (ppm) = 11.79 (s, 1H), 8.90 (d, J = 2.1 Hz, 1H), 8.44 (d, J = 2.2 Hz, 1H), 7.61-7.46 (m, 2H), 7.09 (d, J = 8.3 Hz, 1H), 6.92 (d, J = 7.9 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 3.71-3.58 (m, 1H), 3.26 (t, J = 7.7 Hz, 2H), 1.88-1.74 (m, 2H), 1.71-1.58 (m, 2H), 1.39 (t, J = 7.2 Hz, 1H), 0.87 (s, 9H), 0.03 (s, 6H); ¹³C-NMR (100.6 MHz, CDCl₃): δ(ppm) = 198.3, 166.5, 165.7, 163.2, 151.2, 138.9, 137.0, 132.8, 130.9, 125.6, 119.1, 118.8, 118.7, 63.0, 61.7, 36.8, 32.8, 26.1, 25.9, 18.3, 14.1, -5.3; LC-MS(ESI): tᵣ = 9.20 min; calcd. for C₂₅H₃₅NO₅Si 457.23, found 344.20 [[M-SiMe₂tBu]⁺].
1.3 Procedure for the synthesis of substituted pyridines with TBS deprotection

Representative procedure for the domino reactions leading to substituted pyridines:

\[(3R)-\text{Ethyl} \ 2-(4\text{-hydroxy}-3\text{-methylbutyl})-5\text{-}(2\text{-hydroxybenzoyl}) \text{ nicotinate (5a)}\]

To a solution of chromonylidene-\(\beta\)-ketoester 1a (45.9 mg, 0.097 mmol) in MeOH (5 ml) was added ammonium fluoride (35.9 mg, 0.97 mmol, 10.0 eq.) at room temperature and the reaction mixture was stirred for 6h (TLC-control) at 60°C. The methanol was removed in \textit{vacuo}, water was added, and the mixture was extracted with EtOAc (2 \times 20ml). The combined organic phases were dried over anhydrous MgSO\(_4\), filtered and evaporated to give the crude pyridine. The residue was purified by column chromatography.

Yield = 24.7 mg (0.069 mmol, 71%); \(R_f = 0.40\) (cyclohexane / EtOAc = 2 / 1); \([\alpha]_D^{20} = -4.9^\circ\) (c =2.01, CHCl\(_3\)); \(^1\)H–NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) = 11.76 (s, 1H), 8.89 (d, \(J = 2.2\) Hz, 1H), 8.47 (d, \(J = 2.2\) Hz, 1H), 7.61-7.44 (m, 2H), 7.08 (dd, \(J = 8.4, J = 0.8\) Hz, 1H), 6.96-6.85 (m, 1H), 4.39 (q, \(J = 7.1\) Hz, 2H), 3.57 (dd, \(J = 5.6\) Hz, \(J = 4.4\) Hz, 2H), 3.32-3.21 (m, 2H), 1.82-1.73 (m, 2H), 1.74-1.61 (m, 1H), 1.38 (t, \(J = 7.1\) Hz, 3H), 0.99 (d, \(J = 6.6\) Hz, 3H); \(^13\)C–NMR (100.6 MHz, CDCl\(_3\)): \(\delta\) (ppm) = 198.1, 166.8, 165.5, 163.2, 151.2, 139.2, 137.1, 132.7, 131.0, 125.3, 119.1, 118.8, 118.7, 67.2, 61.9, 35.6, 34.1, 32.8, 16.7, 14.1; LC-MS (ESI): \(t_R = 10.93\) min; calcd. for C\(_{20}\)H\(_{23}\)NO\(_5\) 357.16, found 358.23 [M+H]\(^+\).

Derivates were synthesizes by following the procedure for 5a

\[(3S)-\text{Methyl} \ 2-(4\text{-hydroxy}-3\text{-methylbutyl})-5\text{-}(2\text{-hydroxybenzoyl}) \text{ nicotinate (5b)}\]
Yield = 17.3 mg (0.050 mmol, 87%); R_f = 0.41 (cyclohexane / EtOAc = 2 / 1); [α]_D = -1.7 ° (c = 1.78, CHCl₃); ¹H–NMR (400 MHz, CDCl₃): δ (ppm) = 11.76 (s, 1H), 8.94-8.88 (m, 1H), 8.50-8.46 (m, 1H), 7.60-7.48 (m, 2H), 7.09 (d, J = 8.4 Hz, 1H), 6.94-6.87 (m, 1H), 3.93 (d, J = 5.8 Hz, 3H), 3.65-3.51 (m, 2H), 3.33-3.23 (m, 2H), 1.91-1.74 (m, 3H), 1.75-1.62 (m, 1H), 1.01 (d, J = 7.2 Hz, 3H); ¹³C-NMR (100.6 MHz, CDCl₃): δ(ppm) = 198.0, 167.0, 165.9, 163.2, 151.4, 139.3, 137.1, 132.7, 131.0, 124.8, 119.1, 118.7, 118.7, 67.2, 52.7, 35.6, 34.2, 32.8, 16.7; LC-MS (ESI): t_R = 9.08 min; calcd. for C₁₉H₂₁NO₅ 343.1420, found 344.18 [M+H]^+.

Ethyl 5-(2-hydroxybenzoyl)-2-(4-hydroxybutyl) nicotinate (5c)

Yield = 19.6 mg (0.057 mmol, 76%); R_f = 0.40 (cyclohexane / EtOAc = 2 / 1); ¹H–NMR (400 MHz, CDCl₃): δ (ppm) = 11.77 (s, 1H), 8.89 (d, J = 2.2 Hz, 1H), 8.50-8.41 (m, 1H), 7.61-7.47 (m, 2H), 7.08 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 0.7 Hz, 1H), 4.46-4.30 (q, J = 7.1 Hz, 2H), 3.72 (t, J = 6.1 Hz, 2H), 3.34-3.23 (m, 2H), 1.92-1.66 (m, 5H), 1.39 (dt, J = 7.1 Hz, J = 0.7 Hz, 3H); ¹³C-NMR (100.6 MHz, CDCl₃): δ(ppm) = 198.1, 166.4, 165.6, 163.2, 151.2, 139.1, 137.0, 132.7, 131.0, 125.4, 119.1, 118.8, 118.7, 62.1, 61.8, 36.2, 32.2, 25.6, 14.1; LC-MS (ESI): t_R = 9.08 min; calcd. for C₁₉H₂₁NO₅ 343.14, found 344.20 [M+H]^+.

1.4 General procedure for hydrolysis of substituted pyridines

To a solution of ester 5 in THF/MeOH 2:1 (v/v) was added 2N NaOH solution (5.0 eq.) at 0°C and the reaction mixture was stirred for 16h (TLC-control). The reaction mixture was acidified with 25% HCl to pH 3-4. After water was added, the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous MgSO₄, filtered and evaporated to give the crude acid. The residue was purified by column chromatography.
(3R)-2-(4-Hydroxy-3-methylbutyl)-5-(2-hydroxybenzoyl) nicotinic acid (6a)

Yield = 13.5 mg (0.041 mmol, 67%); \( R_f = 0.32 \) (EtOAc / MeOH = 5 / 3); \( \left[ \alpha \right]_{D}^{20} = -6.7^\circ \) (c = 1.56, DMSO); \(^1\)H–NMR (400 MHz, DMSO-\( d_6 \)): \( \delta \) (ppm) = 10.56 (brs, 1H), 8.86 (d, \( J = 2.2 \) Hz, 1H), 8.32 (d, \( J = 2.2 \) Hz, 1H), 7.58 (dd, \( J = 8.8 \) Hz, \( J = 2.6 \) Hz, 1H), 7.52 (d, \( J = 2.6 \) Hz, 1H), 6.94 (d, \( J = 8.8 \) Hz, 1H), 3.31-3.16 (m, 3H), 3.10 (ddd, \( J = 12.8 \) Hz, \( J = 10.5 \) Hz, \( J = 5.8 \) Hz, 1H), 1.75 (ddd, \( J = 10.6 \) Hz, \( J = 7.4 \) Hz, \( J = 5.3 \) Hz, 1H), 1.52 (dd, \( J = 12.8 \) Hz, \( J = 6.7 \) Hz, 1H), 1.45-1.33 (m, 1H), 0.87 (d, \( J = 6.6 \) Hz, 3H); \(^1\)C-NMR (100.6 MHz, DMSO-\( d_6 \)): \( \delta \) (ppm) = 192.7, 167.1, 166.5, 155.2, 151.4, 138.6, 135.8, 132.1, 130.0, 126.8, 125.8, 119.0, 110.4, 66.1, 35.5, 33.9, 33.0, 16.5.

(3S)-2-(4-Hydroxy-3-methylbutyl)-5-(2-hydroxybenzoyl) nicotinic acid (6b)

Yield = 7.5 mg (0.023 mmol, 79%); \( R_f = 0.35 \) (cyclohexane / EtOAc = 2 / 1); \( \left[ \alpha \right]_{D}^{20} = 4.5^\circ \) (c = 0.98, DMSO); \(^1\)H–NMR (400 MHz, DMSO-\( d_6 \)): \( \delta \) (ppm) = 10.42 (brs, 1H), 8.86 (d, \( J = 2.2 \) Hz, 1H), 8.33 (d, \( J = 2.2 \) Hz, 1H), 7.50-7.45 (m, 1H), 7.42 (dd, \( J = 7.7 \) Hz, \( J = 1.4 \) Hz, 1H), 6.98 (dd, \( J = 7.8 \) Hz, \( J = 4.6 \) Hz, 2H), 3.29 (dd, \( J = 10.4 \) Hz, \( J = 5.9 \) Hz, 1H), 3.24-3.17 (m, 2H), 3.16-3.07 (m, 1H), 1.76 (dd, \( J = 7.5 \) Hz, \( J = 5.4 \) Hz, 1H), 1.54 (d, \( J = 6.1 \) Hz, 1H), 1.47-1.34 (m, 1H), 0.89 (d, \( J = 6.6 \) Hz, 3H); \(^1\)C-NMR (100.6 MHz, DMSO-\( d_6 \)): \( \delta \) (ppm) = 196.1, 170.1, 164.4, 157.0, 147.9, 137.2, 134.9, 133.3, 130.1, 124.6, 118.9, 116.8, 65.9, 35.4, 33.4, 33.0, 16.8; LC-MS (ESI): \( t_R = 8.80 \) min; calcd. for \( C_{18}H_{19}NO_5 \) 329.13, found 330.17 [M+H]+.

5-(2-Hydroxybenzoyl)-2-(4-hydroxybutyl) nicotinic acid (6c)

Yield = 14.6 mg (0.046 mmol, 79%); \( R_f = 0.35 \) (cyclohexane / EtOAc = 2 / 1); \(^1\)H–NMR (400 MHz, DMSO-\( d_6 \)): \( \delta \) (ppm) = 10.42 (brs, 1H), 8.87 (d, \( J = 2.2 \) Hz, 1H), 8.34 (d, \( J = 2.2 \) Hz, 1H), 7.52-7.38 (m, 2H), 7.04-6.89 (m, 2H), 3.40 (t, \( J = 6.5 \) Hz, 2H), 3.22-3.11 (m,
2H), 1.76-1.64 (m, 2H), 1.52-1.40 (m, 2H); $^{13}$C-NMR (100.6 MHz, DMSO-$d_6$): $\delta$(ppm) = 194.6, 167.1, 165.6, 156.8, 151.1, 138.7, 134.0, 130.7, 130.6, 125.9, 124.0, 119.4, 116.8, 60.5, 35.8, 32.4, 25.7; LC-MS (ESI): $t_R = 8.34$ min; calcd. for C$_{17}$H$_{17}$NO$_5$ 315.1107, found 316.19 [M+H]$^+$. 

\[
\text{5-(2-Hydroxy-5-isopropylbenzoyl)-2-(4-hydroxybutyl) nicotinic acid (6d)}
\]

Yield = 14.6 mg (0.41 mmol, 74%); $R_f = 0.33$ (cyclohexane / EtOAc = 2 / 1); $^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$(ppm) = 10.20 (s, 1H), 8.86 (d, $J = 2.2$ Hz, 1H), 8.33 (d, $J = 2.2$ Hz, 1H), 7.35 (dd, $J = 8.5$ Hz, $J = 2.3$ Hz, 1H), 7.26 (d, $J = 2.2$ Hz, 1H), 6.91 (d, $J = 8.4$ Hz, 1H), 3.39 (t, $J = 6.5$ Hz, 2H), 3.18-3.12 (m, 2H), 2.90-2.78 (m, 1H), 1.74-1.65 (m, 2H), 1.46 (dd, $J = 14.8$ Hz, $J = 6.8$ Hz, 2H), 1.16 (d, $J = 6.9$ Hz, 6H); $^{13}$C-NMR (100.6 MHz, DMSO-$d_6$): $\delta$(ppm) = 194.8, 167.2, 165.7, 155.0, 151.3, 139.2, 138.6, 132.1, 130.6, 127.8, 125.7, 123.5, 116.8, 60.5, 35.9, 32.4, 32.3, 25.7, 23.8; LC-MS (ESI): $t_R = 9.46$ min; calcd. for C$_{20}$H$_{23}$NO$_5$ 357.15, found 358.22 [M+H]$^+$. 

\[
\text{Supplementary Material (ESI) for Chemical Communications}
\]

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1.5 Synthesis of substituted pyridines with shorter alkyl chains

![Chemical Structure]

To a solution of chromonylidene-β-ketoester 7a (45.9 mg, 0.097 mmol) in MeOH (5 ml) was added ammonium fluoride (35.9 mg, 0.97 mmol, 10.0 eq.) at room temperature and the reaction mixture was stirred for 6h (TLC-control) at 60°C. The methanol was removed in vacuo, water was added, and the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous MgSO₄, filtered and evaporated to give the crude pyridine. The residue was purified by column chromatography.

Yield = 233.0 mg (0.817 mmol, 78%); Rf = 0.39 (cyclohexane / EtOAc = 2 / 1); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.79 (s, 1H), 8.88 (d, J = 2.2 Hz, 1H), 8.49 (d, J = 2.2 Hz, 1H), 7.63-7.45 (m, 2H), 7.09 (dd, J = 8.4 Hz, J = 1.0 Hz, 1H), 6.91 (ddd, J = 8.2, J = 7.2 Hz, J = 1.1 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 2.93 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H); ¹³C-NMR (100.6 MHz, CDCl₃): δ (ppm) = 198.2, 165.5, 163.2, 163.1, 151.2, 138.8, 137.0, 132.8,

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</table>

ᵃ) isolated yields; b) yield from 8.

Ethyl-5-(2-hydroxybenzoyl)-2-methylnicotinate (8a)

To a solution of chromonylidene-β-ketoester 7a (45.9 mg, 0.097 mmol) in MeOH (5 ml) was added ammonium fluoride (35.9 mg, 0.97 mmol, 10.0 eq.) at room temperature and the reaction mixture was stirred for 6h (TLC-control) at 60°C. The methanol was removed in vacuo, water was added, and the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous MgSO₄, filtered and evaporated to give the crude pyridine. The residue was purified by column chromatography.

Yield = 233.0 mg (0.817 mmol, 78%); Rf = 0.39 (cyclohexane / EtOAc = 2 / 1); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.79 (s, 1H), 8.88 (d, J = 2.2 Hz, 1H), 8.49 (d, J = 2.2 Hz, 1H), 7.63-7.45 (m, 2H), 7.09 (dd, J = 8.4 Hz, J = 1.0 Hz, 1H), 6.91 (ddd, J = 8.2, J = 7.2 Hz, J = 1.1 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 2.93 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H); ¹³C-NMR (100.6 MHz, CDCl₃): δ (ppm) = 198.2, 165.5, 163.2, 163.1, 151.2, 138.8, 137.0, 132.8,
1.6 General procedure for hydrolysis of substituted pyridines with shorter alkyl chains

To a solution of ester 8 in THF/MeOH 2:1 (v/v) was added 2N NaOH solution (5.0 eq.) at 0°C and the reaction mixture was stirred for 16h (TLC control). The reaction mixture was acidified with 25% HCl to pH 3-4. After water was added, the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous MgSO₄, filtered and evaporated to give the crude acid. The residue was purified by column chromatography.

5-(2-Hydroxybenzoyl)-2-methylnicotinic acid (9a)

Yield = 14.3 mg (0.056 mmol, 94%); R_f = 0.34 (EtOAc / MeOH = 5 / 3); ^1H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 10.52 (br s, 1H), 8.83 (d, J = 2.2 Hz, 1H), 8.36 (d, J = 2.2 Hz, 1H), 7.52-7.38 (m, 2H), 6.98 (m, 2H), 2.80 (s, 3H); ^13C-NMR (100.6 MHz, DMSO-d_6): δ (ppm) = 194.7, 167.0, 162.4, 156.8, 151.3, 138.4, 133.9, 130.7, 130.5, 125.6, 124.0, 119.4, 116.8, 24.6; LC-HRMS (ESI): t_R = 2.07 min; calcd. for C_{14}H_{12}NO_{4} 258.07608, found 258.07605 [M+H]+.

5-(2-Hydroxy-5-methylbenzoyl)-2-methylnicotinic acid (9b)

Yield = 12.1 mg (0.045 mmol, 97%); R_f = 0.37 (EtOAc / MeOH = 5 / 3); ^1H-NMR (400 MHz, DMSO-d_6): δ (ppm) = 10.52 (br s, 1H), 8.82 (d, J = 2.3 Hz, 1H), 8.35 (d, J = 2.3 Hz, 1H), 7.28 (ddd, J = 8.3 Hz, J = 2.3 Hz, J = 0.6 Hz, 1H), 7.23-7.19 (m, 1H), 6.89 (d, J = 8.3 Hz, 1H), 2.80 (s, 3H), 2.24 (s, 3H); ^13C-NMR (100.6 MHz, DMSO-d_6): δ (ppm) = 194.7, 167.0, 162.3, 154.7, 151.3, 138.4, 133.9, 130.7, 130.5, 125.6, 124.0, 119.4, 116.8, 24.6; LC-HRMS (ESI): t_R = 2.07 min; calcd. for C_{14}H_{12}NO_{4} 258.07608, found 258.07605 [M+H]+.
125.6, 123.7, 116.7, 24.6, 19.8; LC-HRMS (ESI): $t_R = 2.37$ min; calcd. for $\text{C}_{13}\text{H}_{14}\text{NO}_4$ 272.09173, found 272.09170 $[\text{M+H}]^+$.  

![Chemical structure](image)

5-(3,5-Dichloro-2-hydroxybenzoyl)-2-methylnicotinic acid (9c)

Yield = 13.7 mg (0.042 mmol, 100%); $R_f = 0.47$ (EtOAc / MeOH = 5 / 3); $^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ (ppm) = 10.60 (br s, 1H), 8.84 (d, $J = 2.3$ Hz, 1H), 8.36 (d, $J = 2.3$ Hz, 1H), 7.80 (d, $J = 2.6$ Hz, 1H), 7.43 (d, $J = 2.6$ Hz, 1H), 2.81 (s, 3H); $^{13}$C-NMR (100.6 MHz, DMSO-$d_6$): $\delta$ (ppm) = 192.5, 166.9, 163.1, 151.6, 150.8, 138.4, 132.5, 129.9, 128.4, 127.8, 125.8, 123.6, 123.2, 24.7; LC-HRMS (ESI): $t_R = 2.74$ min; calcd. for $\text{C}_{14}\text{H}_{10}\text{Cl}_2\text{NO}_4$ 325.99814, found 325.99847 $[\text{M+H}]^+$. 
1.7 Procedure for synthesis of substituted phenols

![Chemical structure](image)

Substance $R_1$ $R_2$ $R_3$ $R_4$ Yield [%] $a$ Yield [%] $b$

| Substance | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield [%] $a$ | Yield [%] $b$
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<td>d</td>
<td>i)</td>
<td>Et</td>
<td>H</td>
<td>H</td>
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</tbody>
</table>

- $a$) isolated yield; $b$) yield from 13.

Methyl 2-hydroxy-5-(2-hydroxybenzoyl)-3-methylbenzoate (13a)

To a solution of chromonylidene-$\beta$-ketoester 7a (516.4 mg, 1.804 mmol) in DMF (5 ml) was added caesium fluoride (548.0 mg, 0.097 mmol, 2.0 eq.) at room temperature and the reaction mixture was stirred for 2-4h (TLC-control) at 80°C. After addition of EtOAc and brine, the biphasic mixture was several times extracted with brine. The combined organic phases were dried over anhydrous MgSO$_4$, filtered and evaporated to give the crude phenol. The residue was purified by column chromatography.

Yield: = 346.0 mg (1.209 mmol, 67%); $R_f = 0.34$ (cyclohexane / EtOAc = 2 / 1); $^1$HNMR (400 MHz, CDCl$_3$): $\delta$ (ppm) = 11.85 (s, 1H), 11.47 (s, 1H), 8.09 (dd, $J = 2.2$ Hz, $J = 0.5$ Hz, 1H), 7.74-7.68 (m, 1H), 7.58 (dd, $J = 8.1$ Hz, $J = 1.6$ Hz, 1H), 7.49 (ddd, $J = 8.8$ Hz, 1H), 7.32 (t, $J = 7.3$ Hz, 2H), 7.20 (d, $J = 8.2$ Hz, 2H), 4.41 (q, $J = 7.2$ Hz, 2H), 3.75-3.66 (m, 4H), 3.59 (s, 3H).
$J = 7.2 \text{ Hz}, J = 1.7 \text{ Hz}, \text{ 1H}$), $7.06 \text{ (dd, } J = 8.4 \text{ Hz, } J = 1.6 \text{ Hz, } \text{ 1H}), 6.93-6.86 \text{ (m, } \text{ 1H}), 3.95 \text{ (s, } \text{ 3H}), 2.32 \text{ (s, } \text{ 3H}); ^{13}\text{C-NMR (100.6 MHz, CDCl}_3\text{): } \delta \text{ (ppm) } = 199.2, 170.3, 163.1, 162.9, 136.8, 135.9, 132.9, 130.0, 128.2, 127.3, 119.0, 118.6, 118.3, 111.1, 52.5, 15.6; \text{ GC-MS(EI): } t_R = 8.79 \text{ min; m / z (rel. Int. [%]): 286 (75) [M$^+$], 271 (21), 253 (32), 239 (6), 226 (11), 197 (18), 161 (30), 134 (84), 121 (100).  

![Chemical Structure](image)

(2$S$)-Ethyl 2-hydroxy-3-(3-hydroxy-2-methylpropyl)-5-(2-hydroxybenzoyl)benzoate (13d)

Yield: = 17.1 mg (0.047 mmol, 56%); $R_f = 0.25$ (cyclohexane / EtOAc = 2 / 1); $[\alpha]_{D}^{20} = 6.2^\circ$ (c = 1.51, CHCl$_3$); $^1$H–NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) = 11.87 (s, 1H), 11.79 (s, 1H), 8.18 (d, $J = 2.3$ Hz, 1H), 7.70 (d, $J = 2.2$ Hz, 1H), 7.59 (dd, $J = 8.0$ Hz, $J = 1.6$ Hz, 1H), 7.52 (ddd, $J = 8.7$ Hz, $J = 7.2$ Hz, $J = 1.7$ Hz, 1H), 7.09 (dd, $J = 8.4$ Hz, $J = 0.9$ Hz, 1H), 6.91 (ddd, $J = 8.1$ Hz, $J = 7.3$ Hz, $J = 1.2$ Hz, 1H), 4.45 (q, $J = 7.1$ Hz, 2H), 3.48 (dd, $J = 6.4$ Hz, $J = 5.7$ Hz, 2H), 2.91-2.85 (m, 1H), 2.61 (dd, $J = 13.5$ Hz, $J = 7.0$ Hz, 1H), 2.05 (m, 1H), 1.45-1.38 (t, $J = 7.1$ Hz, 3H), 0.98 (d, $J = 6.8$ Hz, 3H); $^{13}$C-NMR (100.6 MHz, CDCl$_3$): $\delta$ (ppm) = 199.4, 170.1, 163.0, 162.9, 137.6, 136.1, 132.9, 130.3, 129.4, 128.5, 119.1, 118.6, 118.5, 112.6, 66.8, 62.1, 36.3, 32.8, 16.6, 14.1; LC-MS (ESI): $t_R = 11.93$ min; calcd. for C$_{20}$H$_{22}$O$_6$ 358.14, found 359.12 [M+H$^+$].

### 1.8 General procedure for hydrolysis of substituted phenols

To a solution of ester 6 in THF/MeOH 2:1 (v/v) was added 2N NaOH solution (5.0 eq.) at 0°C and the reaction mixture was stirred for 16h (TLC control). The reaction mixture was acidified with 25% HCl to pH 3-4. After water was added, the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous MgSO$_4$, filtered and evaporated to give crude acid. The residue was purified by column chromatography.
2-Hydroxy-5-(2-hydroxybenzoyl)-3-methylbenzoic acid (14a)

Yield: 24.6 mg (0.090 mmol, 89%); Rf = 0.45 (EtOAc / MeOH = 5 / 2); ¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) = 10.23 (brs, 1H), 7.99 (d, J = 2.2 Hz, 1H), 7.81 (dd, J = 2.2 Hz, J = 0.9 Hz, 1H), 7.39 (ddd, J = 8.3 Hz, J = 7.3 Hz, J = 1.7 Hz, 1H), 7.30 (dd, J = 7.6 Hz, J = 1.7 Hz, 1H), 7.07-6.79 (m, 1H), 2.23 (s, 3H); ¹³C-NMR (100.6 MHz, DMSO-d₆): δ (ppm) = 194.9, 171.9, 163.3, 156.1, 136.1, 132.6, 130.7, 129.8, 128.0, 126.2, 125.1, 119.0, 116.5, 111.6, 15.2; LC-HRMS (ESI): tᵣ = 2.86 min; calcd. for C₁₅H₁₃O₅ 273.07575, found 273.07581 [M+H]⁺.

2-Hydroxy-5-(2-hydroxy-5-methylbenzoyl)-3-methylbenzoic acid (14b)

Yield: 17.8 mg (0.062 mmol, 92%); Rf = 0.46 (EtOAc / MeOH = 5 / 2); ¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) = 9.91 (brs, 1H), 8.02-7.97 (m, 1H), 7.80 (dd, J = 2.3 Hz, J = 0.9 Hz, 1H), 7.22-7.16 (m, 1H), 7.08 (d, J = 2.1 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 2.22 (s, 6H); ¹³C-NMR (100.6 MHz, DMSO-d₆): δ (ppm) = 195.0, 171.9, 163.3, 153.8, 136.1, 133.1, 130.7, 129.7, 128.1, 127.6, 126.1, 125.0, 116.3, 111.7, 19.8, 15.2; LC-HRMS (ESI): tᵣ = 3.03 min; calcd. for C₁₆H₁₅O₅ 287.09140, found 287.09143 [M+H]⁺.
1.9 Procedures for synthesis of intermediate in benzopyran formation

To a solution of chromonylidene-β-ketoester **1** (1.0 eq.) in MeOH (5 ml) was added PPTS (8.0 eq.) at room temperature and the reaction mixture was stirred for 1 h (TLC-control) at 65°C. The methanol was removed in vacuo, water was added, and the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous MgSO₄, filtered and evaporated to give crude chromane. The residue was purified by column chromatography.

(3S,E)-Methyl 2-(3-methyl-3,4-dihydro-2H-pyran-6-yl)-3-(4-oxo-4H-chromen-3-yl)acrylate (17a)

R_f = 0.30 (cyclohexane / EtOAc = 2 / 1); ^1H-NMR (400 MHz, CDCl₃): δ (ppm) = 8.41 (d, J = 1.0 Hz, 1H), 8.27-8.23 (m, 1H), 7.82 (d, J = 1.0 Hz, 1H), 7.73-7.63 (m, 1H), 7.48-7.39 (m, 2H), 4.83 (dd, J = 4.8 Hz, J = 2.9 Hz, 1H), 4.10 (ddd, J = 10.4 Hz, J = 3.4 Hz, J = 1.8 Hz, 1H), 3.79 (s, 3H), 2.31-2.13 (m, 1H), 2.10-2.00 (m, 1H), 1.85-1.72 (m, 1H), 1.00 (d, J = 6.8 Hz, 3H); ^13C-NMR (100.6 MHz, CDCl₃): δ (ppm) = 175.7, 166.6, 155.9, 153.4, 146.9, 133.8, 133.6, 132.3, 129.4, 126.3, 126.2, 125.6, 125.3, 118.1, 118.0, 117.7, 102.7, 101.9, 71.9, 52.3, 52.2, 29.4, 28.7, 26.8, 26.8, 17.2, 17.0.
1.10 Procedures for the synthesis of benzopyrans

Representative procedure for the domino reactions leading to benzopyrans with *trans* esterification:

**Methyl 3,4-Dihydro-(3R)-methyl-6-(2-hydroxybenzoyl)-2H-chromene-8-carboxylate** (18b)

To a solution of chromonylidene-β-ketoester I (33.3 mg, 0.070 mmol) in MeOH (5 ml) was added PPTS (140.7 mg, 0.56 mmol, 8.0 eq.) at room temperature and the reaction mixture was stirred for 36 h (TLC-control) at 65°C. The methanol was removed in *vacuo*, water was added, and the mixture was extracted with EtOAc (2 × 20 ml). The combined organic phases

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</table>

ᵃ) isolated yield; b) yield from 18

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Supplementary Material (ESI) for Chemical Communications
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were dried over anhydrous MgSO\textsubscript{4}, filtered and evaporated to give crude product which was further purified by column chromatography.

Yield: = 17.9 mg (0.055 mmol, 78%); R\textsubscript{f} = 0.39 (cyclohexane / EtOAc = 2 / 1); \([\alpha]_{D}^{20} = 17.4^\circ\), (c = 1.74, CHCl\textsubscript{3}); \textsuperscript{1}\textsuperscript{H}-NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) (ppm) = 11.85 (s, 1H), 8.00 (d, \(J = 2.2\) Hz, 1H), 7.60 (dd, \(J = 6.2\) Hz, \(J = 1.8\) Hz, 2H), 7.54-7.46 (m, 1H), 7.06 (d, \(J = 8.4\) Hz, 1H), 6.94-6.85 (m, 1H), 4.42 (ddd, \(J = 10.8\) Hz, \(J = 3.4\) Hz, \(J = 2.2\) Hz, 1H), 3.85 (s, 3H), 2.93 (ddd, \(J = 16.4\) Hz, \(J = 4.9\) Hz, \(J = 1.7\) Hz, 1H), 2.54 (dd, \(J = 16.2\) Hz, \(J = 10.2\) Hz, 1H), 2.33-2.16 (m, 1H), 1.09 (d, \(J = 6.7\) Hz, 3H); \textsuperscript{13}\textsuperscript{C}-NMR (100.6 MHz, CDCl\textsubscript{3}): \(\delta\) (ppm) = 199.2, 165.7, 162.9, 157.7, 136.0, 134.8, 133.0, 131.6, 128.9, 123.6, 119.1, 118.8, 118.6, 118.3, 72.8, 52.1, 33.4, 26.2, 16.7; LC-MS(ESI): \(t_{R} = 10.47\) min; calcd. for C\textsubscript{19}H\textsubscript{18}O\textsubscript{5} 326.12, found 327.12 [M+H]\textsuperscript{+}.

Representative procedure for the domino reactions leading to benzopyrans:

\[
\text{Methyl 3,4-Dihydro-(3S)-methyl-6-(2-hydroxybenzoyl)-2H-chromene-8-carboxylate (18a)}
\]

To a solution of chromonylidene-\textbeta-ketoester (1.0 eq.) in MeOH (5 ml) was added PPTS (8.0 eq.) at room temperature and the reaction mixture was stirred for 24 h at 65°C. The methanol was removed in vacuo, water was added, and the mixture was extracted with EtOAc (2 \(\times\) 20ml). The combined organic phases were dried over anhydrous MgSO\textsubscript{4}, filtered and evaporated to give crude chromane. The residue was purified by column chromatography.

Yield: = 16.3 mg (0.050 mmol, 63%); R\textsubscript{f} = 0.38 (cyclohexane / EtOAc = 2 / 1); \([\alpha]_{D}^{20} = -79.3^\circ\) (c = 2.46, CHCl\textsubscript{3}); \textsuperscript{1}\textsuperscript{H}-NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) (ppm) = 11.85 (s, 1H), 8.00 (d, \(J = 2.2\) Hz, 1H), 7.62-7.56 (m, 2H), 7.52-7.46 (m, 1H), 7.05 (d, \(J = 8.4\) Hz, 1H), 6.92-6.82 (m, 1H), 4.41 (ddd, \(J = 10.8\) Hz, \(J = 3.4\) Hz, \(J = 2.2\) Hz, 1H), 3.90-3.80 (m, 4H), 2.97-2.87 (m, 1H), 2.53 (dd, \(J = 16.2\) Hz, \(J = 10.1\) Hz, 1H), 2.29-2.14 (m, 1H), 1.08 (d, \(J = 6.7\) Hz, 3H); \textsuperscript{13}\textsuperscript{C}-NMR (100.6 MHz, CDCl\textsubscript{3}): \(\delta\) (ppm) = 199.2, 165.7, 162.9, 157.7, 135.9, 134.8, 133.0, 131.6, 128.9, 123.6, 119.0, 118.7, 118.6, 72.8, 52.1, 33.4, 26.2, 16.7; LC-MS(ESI): \(t_{R} = 10.71\) min; calcd. for C\textsubscript{19}H\textsubscript{18}O\textsubscript{5} 326.16, found 327.12 [M+H]\textsuperscript{+}.
1.11 General procedure for hydrolysis of substituted benzopyrans

To a solution of ester 18 in THF/MeOH 2:1 (v/v) was added 2N NaOH solution (5.0 eq.) at 0°C and the reaction mixture was stirred for 16h (TLC control). The reaction mixture was acidified with 25% HCl to pH 3-4. After water was added, the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous MgSO₄, filtered and evaporated to give crude acid. The residue was purified by column chromatography.

3,4-Dihydro-(3S)-methyl-6-(2-hydroxybenzoyl)-2H-chromene-8-carboxylic acid (19a)

Yield: = 5.8 mg (0.019 mmol, 90%); R₇ = 0.38 (EtOAc / MeOH = 5 / 2); [α]D²⁰ = 17.4 ° (c = 0.69, DMSO); ¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) = 10.18 (s, 1H), 7.80 (d, J = 2.1 Hz, 1H), 7.63 (d, J = 1.6 Hz, 1H), 7.39 (dd, J = 11.1 Hz, J = 4.5 Hz, 1H), 7.31-7.24 (m, 1H), 6.96 (d, J = 8.2 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 4.31 (d, J = 10.4 Hz, 1H), 3.82 (t, J = 10.0 Hz, 1H), 2.89 (dd, J = 16.2 Hz, J = 4.2 Hz, 1H), 2.55-2.43 (m, 1H), 0.98 (d, J = 6.6 Hz, 3H); ¹³C-NMR (100.6 MHz, DMSO-d₆): δ (ppm) = 195.0, 166.5, 157.2, 156.1, 133.9, 132.5, 131.0, 129.8, 128.5, 125.1, 123.4, 119.8, 119.0, 116.5, 71.9, 32.4, 25.6, 16.3; LC-MS(ESI): tR = 9.74 min; calcd. for C₁₈H₁₆O₅ 312.10, found 313.11 [M+H]⁺.

3,4-Dihydro-(3S)-methyl-6-(5-bromo-2-hydroxybenzoyl)-2H-chromene-8-carboxylic acid (19c)

Yield: = 9.1 mg (0.025 mmol, 89%); R₇ = 0.32 (EtOAc / MeOH = 5 / 2); [α]D²⁰ = 9.0 ° (c = 2.16, DMSO); ¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) = 10.26 (s, 1H), 7.78 (d, J = 2.2 Hz, 1H), 7.62 (d, J = 2.1 Hz, 1H), 7.50 (dd, J = 8.7 Hz, J = 2.6 Hz, 1H), 7.37 (d, J = 2.5 Hz, 1H), 6.91 (d, J = 8.7 Hz, 1H), 4.34-4.23 (m, 1H), 3.88-3.75 (m, 1H), 2.88 (dd, J = 9.7 Hz, 1H), 2.62 (t, J = 7.5 Hz, 1H), 2.55-2.43 (m, 1H), 0.98 (d, J = 6.6 Hz, 3H); ¹³C-NMR (100.6 MHz, DMSO-d₆): δ (ppm) = 195.0, 166.5, 157.2, 156.1, 133.9, 132.5, 131.0, 129.8, 128.5, 125.1, 123.4, 119.8, 119.0, 116.5, 71.9, 32.4, 25.6, 16.3; LC-MS(ESI): tR = 9.74 min; calcd. for C₁₈H₁₁BrO₅ 331.05, found 332.05 [M+H]⁺.
$J = 16.2$ Hz, $J = 4.5$ Hz, 1H), 2.55-2.40 (m, 1H), 2.06 (dd, $J = 2.4$ Hz, $J = 1.5$ Hz, 1H), 0.97 (d, $J = 6.7$ Hz, 3H); $^{13}$C-NMR (100.6 MHz, DMSO-$d_6$): $\delta$ (ppm) = 192.8, 166.5, 157.6, 154.4, 134.3, 133.9, 131.2, 131.1, 128.4, 128.0, 123.5, 120.0, 118.6, 110.0, 72.0, 32.4, 25.6, 16.3; LC-MS(ESI): $t_R = 10.15$ min; calcd. for C$_{18}$H$_{15}$BrO$_5$ 390.01, found 391.06 [M+H]$^+$.  

1.12 General procedure for the conversion of ethyl bromoacetic ester with pyridine derivates

Pyridine derivate 8 (1.0°eq.), K$_2$CO$_3$ (1.0 eq.) and ethyl 2-bromoacetate (1.0 eq.) were dissolved in acetone (5 ml) and heated under an argon atmosphere for 10h at 50 °C. The acetone was removed in vacuo, water was added, and the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous MgSO$_4$, filtered and evaporated to give crude pyridine. The residue was purified by column chromatography.

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a) isolated yield; b) yield from 20.
Ethyl-5-(2-(2-ethoxy-2-oxoethoxy)-5-methylbenzoyl)-2-methyl nicotinate (20a)

Yield = 37.2 mg (0.097 mmol, 88%); Rf = 0.37 (PE / EtOAc = 2 / 1); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 8.85 (d, J = 2.2 Hz, 1H), 8.55 (d, J = 2.2 Hz, 1H), 7.29-7.11 (m, 2H), 6.68 (d, J = 8.4 Hz, 1H), 4.41 (s, 2H), 4.31 (q, J = 7.1 Hz, 2H), 4.06 (t, J = 7.1 Hz, 2H), 2.81 (s, 3H), 2.27 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H); ¹³C-NMR (100.6 MHz, CDCl₃): δ (ppm) = 193.6, 167.9, 166.0, 163.3, 153.6, 152.7, 138.8, 133.4, 131.6, 131.0, 130.8, 127.6, 125.4, 112.3, 65.6, 61.4, 61.2, 24.9, 20.2, 14.1, 13.9; GC-MS(EI): tᵣ = 10.08 min; m/z (rel. Int. [%]): 385 (20) [M⁺], 340 (29), 312 (79), 284 (76), 251 (70), 179 (100), 135 (96).

1.13 General procedure for hydrolysis to diacids

To a solution of ester 20 in THF/MeOH 2:1 (v/v) was added 2N NaOH solution (5.0 eq.) at 0°C and the reaction mixture was stirred for 16h (TLC control). The reaction mixture was acidified with 25% HCl to pH 3-4. After water was added, the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous MgSO₄, filtered and evaporated to give crude acid. The residue was purified by column chromatography.

5-(2-(Carboxymethoxy)-5-methylbenzoyl)-2-methylnicotinic acid (21a)

Yield = 18.6 mg (0.056 mmol, 100%); Rf = 0.43 (EtOAc / MeOH = 5 / 2); ¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) = 8.85 (d, J = 2.2 Hz, 1H), 8.38 (d, J = 2.2 Hz, 1H), 7.35 (ddd, J = 8.6 Hz, J = 2.3 Hz, J = 0.6 Hz, 1H), 7.26-7.23 (m, 1H), 6.97 (d, J = 8.6 Hz, 1H),
4.58 (s, 2H), 2.78 (s, 3H), 2.29 (s, 3H); $^{13}$C-NMR (100.6 MHz, DMSO-$d_6$): $\delta$ (ppm) = 193.6, 169.5, 167.0, 162.7, 153.3, 151.7, 138.3, 133.3, 130.4, 129.7, 127.0, 125.8, 112.8, 64.8, 24.7, 19.8; LC-HRMS (ESI): $t_R$ = 2.06 min; calcd. for C$_{17}$H$_{17}$NO$_6$ 330.09721, found 330.09718 [M+H]$^+$. 

1.14 General procedure for the synthesis of coumarin-derivates

Pyridine derivate 8 (1.0 eq.), carbonyl diimidazole (2.0 eq.), K$_2$CO$_3$ (1.0 eq.), DMAP (0.1 eq.), and 2-substituted-acetic acid (2.0 eq.) were dissolved in DMF (5 ml) and heated under an argon atmosphere for 6h at 80 °C. After addition of EtOAc and brine, the biphasic mixture was several times extracted with brine. The combined organic phases were dried over anhydrous MgSO$_4$, filtered and evaporated to give crude phenol. The residue was purified by column chromatography.

![Scheme](image)

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<th>$R^1$</th>
<th>$R^2$</th>
<th>$R^3$</th>
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<th>Yield [%] $^{a,b}$</th>
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<td>b</td>
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<td>$i$-Pr</td>
<td>Ph</td>
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<tr>
<td>c</td>
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<td>$i$-Pr</td>
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$^{a,b}$ Ref 1 (2008)
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a) isolated yield; b) yield from 22.

**Ethyl 2-methyl-5-(2-oxo-3-phenyl-2H-chromen-4-yl)nicotinate (22a)**

Yield = 67.9 mg (0.176 mmol, 100%); Rf = 0.42 (PE / EtOAc = 2 / 1); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 8.37 (d, J = 2.3 Hz, 1H), 8.05-7.95 (d, J = 2.3 Hz, 1H), 7.59-7.55 (m, 1H), 7.46-7.44 (m, 1H), 7.26-7.21 (m, 4H), 7.15-7.10 (m, 3H), 4.41-4.22 (q, J = 7.2 Hz, 2H), 2.38 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ¹³C-NMR (100.6 MHz, CDCl₃): δ (ppm) = 165.7, 160.6, 159.9, 153.2, 151.4, 146.9, 139.2, 133.0, 131.9, 130.4, 128.5, 128.2, 127.9, 126.9, 125.0, 124.5, 119.8, 117.1, 61.5, 24.7, 14.2; LC-HRMS (ESI): tᵣ = 2.80 min; calcd. for C₂₄H₂₀NO₄ 386.13868, found 386.13904 [M+H]^+.

1.15 General procedure for hydrolysis of coumarins

To a solution of ester 13 in THF/MeOH 2:1 (v/v) was added 2N NaOH solution (5.0 eq.) at 0°C and the reaction mixture was stirred for 16h (TLC control). The reaction mixture was acidified with 25% HCl to pH 3-4. After water was added, the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous MgSO₄, filtered and evaporated to give crude acid. The residue was purified by column chromatography.
2-Methyl-5-(2-oxo-3-phenyl-2H-chromen-4-yl)nicotinic acid (23a)

Yield = 13.1 mg (0.037 mmol, 97%); \( R_f = 0.37 \) (EtOAc / MeOH = 7 / 2); \(^1\)H-NMR (400 MHz, CH\(_3\)OH-\(d_4\)): \( \delta \) (ppm) = 8.22 (d, \( J = 2.2 \) Hz, 1H), 8.10 (d, \( J = 2.2 \) Hz, 1H), 7.56 (ddd, \( J = 8.4 \) Hz, \( J = 7.3 \) Hz, \( J = 1.6 \) Hz, 1H), 7.40 (dd, \( J = 8.3 \) Hz, 0.8 Hz, 1H), 7.25-7.19 (m, 1H), 7.18-7.11 (m, 3H), 7.08 (ddd, \( J = 7.3 \) Hz, \( J = 4.7 \) Hz, \( J = 1.6 \) Hz, 3H), 2.67 (s, 3H); \(^1\)C-NMR (100.6 MHz, CH\(_3\)OH-\(d_4\)): \( \delta \) (ppm) = 167.2, 159.8, 158.1, 152.4, 150.7, 146.8, 138.6, 133.6, 131.8, 130.3, 127.7, 127.7, 127.5, 126.9, 124.6, 119.8, 116.4, 24.1; LC-HRMS (ESI): \( t_R = 2.07 \) min; calcd. for C\(_{22}\)H\(_{16}\)NO\(_4\) 358.10738, found 358.10736 [M+H]\(^+\).

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\end{align*}
\]

5-(6-isopropyl-2-oxo-3-phenyl-2H-chromen-4-yl)-2-methylnicotinic acid (23b)

Yield = 11.2 mg (0.028 mmol, 97%); \( R_f = 0.39 \) (EtOAc / MeOH = 7 / 2); \(^1\)H-NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) (ppm) = 8.39 (d, \( J = 2.2 \) Hz, 1H), 8.03 (d, \( J = 2.2 \) Hz, 1H), 7.58 (dd, \( J = 8.6 \) Hz, \( J = 2.1 \) Hz, 1H), 7.47 (d, \( J = 8.5 \) Hz, 1H), 7.26-7.10 (m, 5H), 6.88 (d, \( J = 2.1 \) Hz, 1H), 2.95-2.80 (m, 1H), 2.67 (s, 3H), 1.10 (d, \( J = 6.9 \) Hz, 6H); \(^1\)C-NMR (100.6 MHz, DMSO-\(d_6\)): \( \delta \) (ppm) = 167.1, 159.9, 158.2, 150.9, 150.9, 146.8, 144.6, 138.8, 133.7, 130.4, 129.9, 127.7, 127.7, 127.5, 125.0, 124.0, 119.4, 116.5, 32.7, 24.1, 23.6; LC-HRMS (ESI): \( t_R = 2.57 \) min; calcd. for C\(_{25}\)H\(_{22}\)NO\(_4\) 400.15433, found 400.15287 [M+H]\(^+\).
Supplementary Material (ESI) for Chemical Communications
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8a

solvent: CDCl$_3$
solvent: CDCl₃
8e
solvent: CDCl$_3$
9a
solvent: DMSO
20a
solvent: CDCl₃
Supplementary Material (ESI) for Chemical Communications

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22a
solvent: CDCl₃