Supporting Information

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Synthesis and Biological Evaluation of ortho-Aryl N-Hydroxycinnamides as Potent Histone Deacetylase (HDAC) 8 Isoform-Selective Inhibitors


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General. $^1$H NMR spectrum was obtained on a Bruker AV400 or AV500 spectrometer using standard pulse programs. Melting point was recorded on Fisher-Johns apparatus (uncorrected). MS data were measured on JEOL JMX-HX110 mass spectrometer (HREIMS and HRFABMS), JMS-SX102A mass spectrometer (EIMS and FABMS), and Finnigan Mat TSQ-7000 mass spectrometer (ESIMS). TLC analyses were carried out on silica gel plates (KG60-F254, Merck). Unless otherwise mentioned, all chemicals and materials were used as received from commercial suppliers without further purification.
Spectral Data and Procedure of compounds 4-7, 10-12, 15-17, 19-21, 23-26, and 28-32

**7-Benzylxoumarin (4a):** To a solution of 3 (4.86 g, 30.00 mmol) and K$_2$CO$_3$ (10.35 g, 75.00 mmol) in acetone (200 mL) was added benzyl chloride (6.90 mL, 60.00 mmol). The resulting was heated to 56 °C under N$_2$ overnight. After filtration to remove K$_2$CO$_3$, the filtrate was concentrated in vacuo. The residue was diluted with distd H$_2$O (100 mL) and then extracted with EtOAc (50 mL x 3). The organic layer was dried (Na$_2$SO$_4$), filtered and the solvent removed in vacuo. The residue was purified by silica gel chromatography (EtOAc: n-Hexane= 1:4) to give 4a (6.43 g, 85%) as a white solid: mp: 135-140 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$= 7.62 (d, $J$=9.5 Hz, 1H), 7.42 (m, 3H), 7.37 (d, $J$=8.7 Hz, 1H), 7.34 (m, 2H), 6.91 (d, $J$=8.7 Hz, 1H), 6.89 (s, 1H), 6.25 (d, $J$=9.5 Hz, 1H), 5.13 ppm (s, 2H); MS (EI, 70 ev) m/z: 252 [M]$^+$. 

**7-(4-Chlorobenzyloxy)coumarin (4b):** To a solution of 3 (5.16 g, 31.85 mmol) and K$_2$CO$_3$ (10.99 g, 79.63 mmol) in acetone (200 mL) was added 4-chlorobenzyl chloride (10.29 g, 63.70 mmol). Following the procedure as described for 4a gave 4b (7.47 g, 82%) as a white solid: mp: 120-125 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$= 7.63 (d, $J$=9.5 Hz, 1H), 7.37 (m, 5H), 6.90 (dd, ...
$J=2.4, 8.6 \text{ Hz, } 1H), 6.86 (d, J=2.4 \text{ Hz, } 1H), 6.26 (d, J=9.5 \text{ Hz, } 1H), 5.09 \text{ ppm (s, } 2H); \text{ MS (EI, 70 ev) } m/z: 286 [M]^+.$

7-(4-Bromobenzyloxy)coumarin (4c): To a solution of 3 (5.00 g, 30.86 mmol) and $K_2CO_3$ (10.65 g, 77.15 mmol) in acetone (200 mL) was added 4-bromobenzyl chloride (12.66 g, 61.72 mmol). Following the procedure as described for 4a gave 4c (8.02 g, 78%) as a white solid: mp: 140-145°C; $^1H$ NMR (500 MHz, CDCl$_3$): $\delta= 7.63 \text{ (d, } J=9.4 \text{ Hz, } 1H), 7.53 \text{ (d, } J=8.3 \text{ Hz, } 2H), 7.38 \text{ (d, } J=8.6 \text{ Hz, } 1H), 7.31 \text{ (d, } J=8.3 \text{ Hz, } 2H), 6.89 \text{ (d, } J=2.3, 8.6 \text{ Hz, } 1H), 6.85 \text{ (s, } 1H), 6.26 \text{ (d, } J=9.4 \text{ Hz, } 1H), 5.08 \text{ ppm (s, } 2H); \text{ MS (EI, 70 ev) } m/z: 333 [M]^+.$

7-(4-Methoxybenzyloxy)coumarin (4d): To a solution of 3 (4.85 g, 29.94 mmol) and $K_2CO_3$ (10.33 g, 74.85 mmol) in acetone (200 mL) was added 4-methoxybenzyl chloride (8.14 mL, 59.88 mmol). Following the procedure as described for 4a gave 4d (6.84 g, 81%) as a white solid: mp: 131-135°C; $^1H$ NMR (500 MHz, CDCl$_3$): $\delta= 7.63 \text{ (d, } J=9.5 \text{ Hz, } 1H), 7.36 \text{ (m, } 3H), 6.93 \text{ (d, } J=8.6 \text{ Hz, } 2H), 6.90 \text{ (d, } J=8.6 \text{ Hz, } 2H), 6.24 \text{ (d, } J=9.5 \text{ Hz, } 1H), 5.05 \text{ (s, } 2H), 3.82 \text{ ppm (s, } 3H); \text{ MS (EI, 70 ev) } m/z: 282 [M]^+.$

7-[(Naphthalen-4-yl)methoxy]coumarin (4e): To a solution of 3 (4.45 g, 27.47 mmol) and $K_2CO_3$ (9.48 g, 68.67 mmol) in acetone (220 mL) was added 1-(chloromethyl)naphthalene (8.30 mL, 54.94 mmol). Following the procedure
as described for 4a gave 4e (6.22 g, 75%) as a white solid: mp: 135-150 °C; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \textsuperscript{δ} = 8.03 (d, \textit{J}=8.1 Hz, 1H), 7.91 (d, \textit{J}=7.8 Hz, 1H), 7.88 (d, \textit{J}=8.1 Hz, 1H), 7.63 (d, \textit{J}=9.5 Hz, 1H), 7.60 (m, 1H), 7.56 (m, 2H), 7.48 (t, \textit{J}=7.8 Hz, 1H), 7.39 (d, \textit{J}=8.6 Hz, 1H), 7.00 (d, \textit{J}=2.2 Hz, 1H), 6.96 (dd, \textit{J}=2.2, 8.6 Hz, 1H), 6.26 (d, \textit{J}=9.5 Hz, 1H), 5.56 ppm (s, 2H); MS (EI, 70 ev) \textit{m/z}: 302 [M\textsuperscript{+}].

7-(Trifluoromethoxybenzyloxy)coumarin (4f): To a solution of 3 (4.50 g, 27.78 mmol) and K\textsubscript{2}CO\textsubscript{3} (7.67 g, 55.56 mmol) in acetone (220 mL) was added 1-(chloromethyl)-4-(trifluoromethoxy)benzene (11.70 g, 55.56 mmol). Following the procedure as described for 4a gave 4f (7.47 g, 80%) as a white solid: mp: 100-105 °C; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \textsuperscript{δ} = 7.64 (d, \textit{J}=9.5 Hz, 1H), 7.47 (d, \textit{J}=8.5 Hz, 2H), 7.39 (d, \textit{J}=8.6 Hz, 1H), 7.25 (d, \textit{J}=8.5 Hz, 2H), 6.91 (dd, \textit{J}=2.3, 8.6 Hz, 1H), 6.87 (d, \textit{J}=2.3 Hz, 1H), 6.26 (d, \textit{J}=9.5 Hz, 1H), 5.12 ppm (s, 2H); MS (EI, 70 ev) \textit{m/z}: 336 [M\textsuperscript{+}].

(E)-Ethyl 4-benzyloxy-2-hydroxycinnamate (5a): To a solution of 4a (5.54 g, 22.00 mmol) in anhydrous EtOH (50 mL) was added NaOEt (3.12 g, 44.00 mmol) in anhydrous EtOH (50 mL) dropwise during 1 h. The resulting solution was heated to 78 °C under N\textsubscript{2} at for 6 h. The reaction was diluted with distd H\textsubscript{2}O (200 mL), acidified with 1N HCl\textsubscript{(aq)} to pH 4-5 and extracted with EtOAc
(100 mL x 3). The organic layer was dried (Na₂SO₄), filtered and the solvent removed in vacuo. The residue was purified by silica gel chromatography (EtOAc: n-Hexane= 1: 4) to give 5a (4.92 g, 75%) as a white solid: mp: 120-130 °C; ¹H NMR (500 MHz, [D₆] DMSO): δ 10.33 (s, 1H), 7.77 (d, J=16.2 Hz, 1H), 7.52 (d, J=9.3 Hz, 1H), 7.40 (m, 5H), 7.33 (d, J=9.3 Hz, 1H), 6.51 (s, 1H), 6.44 (d, J=16.2 Hz, 1H), 5.08 (s, 2H), 4.14 (q, J=7.1 Hz, 2H), 1.22 ppm (t, J=7.2 Hz, 3H); MS (EI, 70 ev) m/z: 298 [M]⁺.

(E)-Ethyl 4-(4-chlorobenzyloxy)-2-hydroxycinnamate (5b): To a solution of 4b (6.26 g, 21.89 mmol) in anhydrous EtOH (60 mL) was added NaOEt (3.10 g, 43.78 mmol) in anhydrous EtOH (50 mL) dropwise during 1 h. Following the procedure as described for 5a gave 5b (5.23 g, 72%) as a white solid: mp: 133-140 °C; ¹H NMR (500 MHz, CDCl₃): δ 7.95 (d, J=16.2 Hz, 1H), 7.39 (d, J=8.7 Hz, 1H), 7.35 (dd, J=2.3, 9.0 Hz, 4H), 6.66 (s, 1H), 6.53 (dd, J=2.3, 8.7 Hz, 1H), 6.52 (d, J=16.2 Hz, 1H), 6.44 (d, J=2.3 Hz, 1H), 5.01 (s, 2H), 4.27 (q, J=7.1 Hz, 2H), 1.34 ppm (t, J=7.1 Hz, 3H); MS (EI, 70 ev) m/z: 332 [M]⁺.

(E)-Ethyl 4-(4-bromobenzyloxy)-2-hydroxycinnamate (5c): To a solution of 4c (7.15 g, 21.47 mmol) in anhydrous EtOH (60 mL) was added NaOEt (3.04 g, 42.94 mmol) in anhydrous EtOH (50 mL) dropwise during 1 h. Following the procedure as described for 5a gave 5c (6.02 g, 74%) as a white solid: mp:
138-145 °C; ¹H NMR (500 MHz, [D₆]acetone): δ = 9.31 (s, 1H), 7.90 (d, J=16.1 Hz, 1H), 7.57 (d, J=8.3 Hz, 2H), 7.53 (d, J=8.5 Hz, 1H), 7.42 (d, J=8.3 Hz, 2H), 6.58 (d, J=8.5 Hz, 1H), 6.57 (d, J=2.1 Hz, 1H), 6.47 (d, J=16.1 Hz, 1H), 5.11 (s, 2H), 4.17 (q, J=7.1 Hz, 2H), 1.26 ppm (t, J=7.1 Hz, 3H); MS (EI, 70 ev) m/z: 379 [M]+.

(E)-Ethyl 2-hydroxy-4-(4-methoxybenzyloxy)cinnamate (5d): To a solution of 4d (6.60 g, 23.40 mmol) in anhydrous EtOH (60 mL) was added NaOEt (3.31 g, 46.81 mmol) in anhydrous EtOH (50 mL) dropwise during 1 h. Following the procedure as described for 5a gave 5d (5.91 g, 77%) as a white solid: mp: 135-150 °C; ¹H NMR (500 MHz, [D₆]acetone): δ = 9.28 (s, 1H), 7.91 (d, J=16.0 Hz, 1H), 7.51 (d, J=8.5 Hz, 1H), 7.38 (d, J=8.6 Hz, 2H), 6.94 (d, J=8.6 Hz, 2H), 6.58 (d, J=8.5 Hz, 1H), 6.56 (d, J=2.1 Hz, 1H), 6.46 (d, J=16.0 Hz, 1H), 5.02 (s, 2H), 4.17 (q, J=7.1 Hz, 2H), 1.26 ppm (t, J=7.1 Hz, 3H); MS (EI, 70 ev) m/z: 328 [M]+.

(E)-Ethyl 2-hydroxy-4-[(naphthalen-4-yl)methoxy]cinnamate (5e): To a solution of 4e (6.00 g, 19.87 mmol) in anhydrous EtOH (60 mL) was added NaOEt (2.81 g, 39.74 mmol) in anhydrous EtOH (50 mL) dropwise during 1 h. Following the procedure as described for 5a gave 5e (5.12 g, 74%) as a white solid: mp: 139-144 °C; ¹H NMR (500 MHz, [D₆]DSMO): δ = 10.34 (s, 1H), 8.05
(d, J=8.0 Hz, 1H), 7.97 (d, J=7.6 Hz, 1H), 7.93 (d, J=8.7 Hz, 1H), 7.79 (d,
J=16.1 Hz, 1H), 7.64 (t, J=6.9 Hz, 1H), 7.57 (m, 3H), 7.51 (t, J=7.6 Hz, 1H),
6.61 (dd, J=2.1, 8.7 Hz, 1H), 6.57 (d, J=2.1 Hz, 1H), 6.46 (d, J=16.1 Hz, 1H),
5.53 (s, 2H), 4.14 (q, J=7.1 Hz, 2H), 1.23 ppm (t. J=7.1 Hz, 3H); MS (EI, 70 ev)
m/z: 348 [M]+.

(E)-Ethyl 2-hydroxy-4-(trifluoromethoxy)cinnamate (5f): To a solution of 4f
(7.17 g, 22.95 mmol) in anhydrous EtOH (60 mL) was added NaOEt (3.25 g, 45.89 mmol) in anhydrous EtOH (50 mL) dropwise during 1 h. Following the
procedure as described for 5a gave 5f (6.93 g, 79%) as a white solid: mp:
139-145 °C; 1H NMR (500 MHz, [D₄]MeOH): δ= 7.88 (d, J=16.1 Hz, 1H), 7.51
(d, J=8.6 Hz, 2H), 7.41 (d, J=8.7 Hz, 1H), 7.27 (d, J=8.2 Hz, 2H), 6.52 (dd,
J=2.7, 8.6 Hz, 1H), 6.46 (d, J=2.7 Hz, 1H), 6.44 (d, J=16.1 Hz, 1H), 5.08 (s, 2H), 4.20 (q, J=7.2 Hz, 2H), 1.30 ppm (t, J=7.2 Hz, 3H); MS (EI, 70 ev) m/z:
382 [M]+.

(E)-Ethyl 4-benzyloxy-2-methoxycinnamate (6a): To a solution of 5a (4.77 g,
16.00 mmol) and K₂CO₃ (5.52 g, 40.00 mmol) in acetone (50 mL) was added
DMS (3.03 mL, 32.00 mmol). The resulting mixture was heated to 56 °C under
N₂ overnight. After filtration to remove K₂CO₃, the filtrate was concentrated in
vacuo. The residue was diluted with distd H₂O (100 mL) and extracted with
EtOAc (50 mL x 3). The organic layer was dried (Na$_2$SO$_4$), filtered and the solvent removed in vacuo. The residue was purified by silica gel chromatography (EtOAc: $n$-Hexane= 1: 6) to give 6a (4.39 g, 88%) as a white solid: mp: 62-70 °C; $^1$H NMR (500 MHz, [D$_6$]DMSO): δ= 7.79 (d, J=16.1 Hz, 1H), 7.63 (d, J=8.6 Hz, 1H), 7.45 (d, J=7.3 Hz, 2H), 7.39 (t, J=7.3 Hz, 2H), 7.33 (d, J=7.3 Hz, 1H), 6.71 (d, J=1.4 Hz, 1H), 6.51 (s, 1H), 6.65 (d, J=8.6 Hz, 1H), 6.47 (d, J=16.1 Hz, 1H), 5.16 (s, 2H), 4.14 (q, J=7.1 Hz, 2H), 3.84 (s, 3H), 1.22 ppm (t, J=7.1 Hz, 3H); MS (ESI+) m/z: 351 [M+K]$^+$.  

(E)-Ethyl 4-(4-chlorobenzyloxy)-2-methoxycinnamate (6b): To a solution of 5b (5.00 g, 15.06 mmol) and K$_2$CO$_3$ (5.20 g, 37.65 mmol) in acetone (50 mL) was added DMS (2.85 mL, 30.12 mmol). Following the procedure as described for 6a gave 6b (4.43 g, 85%) as a white solid: mp: 95-105 °C; $^1$H NMR (500 MHz, CDCl$_3$): δ=7.89 (d, J=16.1 Hz, 1H), 7.52 (d, J=8.3 Hz, 2H), 7.43 (d, J=8.4 Hz, 1H), 7.30 (d, J=8.4 Hz, 2H), 6.53 (d, J=8.4 Hz, 1H), 6.52 (s, 1H), 6.43 (d, J=16.1 Hz, 1H), 5.04 (s, 2H), 4.25 (q, J=7.1 Hz, 2H), 3.85 (3H, s), 1.33 ppm (t, J=7.1 Hz, 3H); MS (EI, 70 ev) m/z: 346 [M]+.  

(E)-Ethyl 4-(4-bromobenzyloxy)-2-methoxycinnamate (6c): To a solution of 5c (5.86 g, 15.46 mmol) and K$_2$CO$_3$ (5.34 g, 38.65 mmol) in acetone (50 mL) was added DMS (2.93 mL, 30.92 mmol). Following the procedure as described
for 6a gave 6c (4.88 g, 81%) as a white solid: mp: 97-104 °C; 1H NMR (500 MHz, CDCl₃): δ= 7.89 (d, J=16.1 Hz, 1H), 7.43 (d, J=8.4 Hz, 1H), 7.37 (s, 4H), 6.54 (dd, J=2.2, 8.4 Hz, 1H), 6.51 (d, J=2.2 Hz, 1H), 6.43 (d, J=16.1 Hz, 1H), 5.05 (s, 2H), 4.25 (q, J=7.1 Hz, 2H), 1.33 ppm (t, J=7.1 Hz, 3H); MS (EI, 70 ev) m/z: 390 [M]+.

(E)-Ethyl 4-(4-methoxybenzylxyloxy)-2-methoxycinnamate (6d): To a solution of 5d (5.60 g, 17.07 mmol) and K₂CO₃ (5.90 g, 42.68 mmol) in acetone (80 mL) was added DMS (3.24 mL, 34.14 mmol). Following the procedure as described for 6a gave 6d (4.79 g, 82%) as a white solid: mp: 93-100 °C; 1H NMR (500 MHz, CDCl₃): δ= 7.90 (d, J=16.1 Hz, 1H), 7.43 (d, J=8.5 Hz, 1H), 7.35 (d, J=8.4 Hz, 2H), 6.93 (d, J=8.4 Hz, 2H), 6.56 (dd, J=1.6, 8.5 Hz, 1H), 6.52 (s, 1H), 6.43 (d, J=16.1 Hz, 1H), 5.00 (s, 2H), 4.25 (q, J=7.0 Hz, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 1.26 ppm (t, J=7.0 Hz, 3H); MS (EI, 70 ev) m/z: 342 [M]+.

(E)-Ethyl 4-[(naphthalen-4-yl)methoxy]-2-methoxycinnamate (6e): To a solution of 5e (5.00 g, 14.37 mmol) and K₂CO₃ (4.97 g, 35.92 mmol) in acetone (80 mL) was added DMS (2.73 mL, 28.74 mmol). Following the procedure as described for 6a gave 6e (4.16 g, 80%) as a white solid: mp: 96-110 °C; 1H NMR (500 MHz, [D₆]DMSO): δ= 8.07 (d, J=8.2 Hz, 1H), 7.96 (d, J=7.6 Hz, 1H), 7.94 (d, J=8.2 Hz, 1H), 7.80 (d, J=16.1 Hz, 1H), 7.69 (t, J=6.9 Hz, 1H), 7.66 (d,
\[ J=8.6 \text{ Hz, 1H}, \ 7.55 \ (m, 2H), \ 7.51 \ (t, J=7.6 \text{ Hz, 1H}), \ 6.79 \ (d, J=1.8 \text{ Hz, 1H}), \ 6.76 \ (dd, J=1.8, 8.6 \text{ Hz, 1H}), \ 6.47 \ (d, J=16.1 \text{ Hz, 1H}), \ 5.61 \ (s, 2H), \ 4.15 \ (q, J=7.1 \text{ Hz, 2H}), \ 3.86(s, 3H), \ 1.23 \text{ ppm (t, J=7.1 Hz, 3H)}; \ MS (EI, 70 \text{ ev}) \frac{m}{z}: 362 [M]^+ . \]

\text{(E)-Ethyl 4-(trifluoromethoxy)-2-methoxycinnamate (6f):} To a solution of \textit{5f} (6.50 g, 17.02 mmol) and \( \text{K}_2\text{CO}_3 \) (5.87 g, 42.54 mmol) in acetone (80 mL) was added DMS (3.23 mL, 34.04 mmol). Following the procedure as described for \textit{6a} gave \textit{6f} (5.93 g, 88\%) as a white solid: mp: 72-78 °C; \( ^1\text{H NMR (500 MHz, [D}_4\text{]MeOH):} \delta= 7.88 \ (d, J=16.1 \text{ Hz, 1H}), \ 7.54 \ (d, J=8.5 \text{ Hz, 2H}), \ 7.49 \ (d, J=8.6 \text{ Hz, 1H}), \ 7.28 \ (d, J=8.5 \text{ Hz, 2H}), \ 6.64 \ (d, J=2.1 \text{ Hz, 1H}), \ 6.76 \ (dd, J=2.1, 8.6 \text{ Hz, 1H}), \ 6.47 \ (d, J=16.1 \text{ Hz, 1H}), \ 5.61 \ (s, 2H), \ 4.15 \ (q, J=7.1 \text{ Hz, 2H}), \ 3.86 \ (s, 3H), \ 1.23 \text{ ppm (t, J=7.1 Hz, 3H)}; \ MS (EI, 70 \text{ ev}) \frac{m}{z}: 396 [M]^+ . \]

\text{(E)-4-Benzylxy-2-methoxycinnamate (7a):} To a solution of \textit{6a} (4.00 g, 12.82 mmol) in MeOH (50 mL) was added \( \text{LiOH} \) (3.17 g, 128.21 mmol). The resulting mixture was heated to 63 °C under \( \text{N}_2 \) overnight. The reaction was diluted with distd \( \text{H}_2\text{O} \) (100 mL), acidified with 2N HCl to pH 5~6 and extracted with \( \text{EtOAc} \) (50 mL x 3). The organic layer was dried (\( \text{Na}_2\text{SO}_4 \)), filtered and the solvent removed in vacuo to give \textit{7a} (3.46 g, 95\%) as a white solid: mp: 142-150 °C; \( ^1\text{H NMR (500 MHz, [D}_6\text{]DMSO):} \delta= 7.73 \ (d, J=16.1 \text{ Hz, 1H}), \ 7.60 \ (d, J=8.6 \text{ Hz, 1H}), \ 7.55 \ (t, J=8.6 \text{ Hz, 1H}), \ 7.51 \ (t, J=7.6 \text{ Hz, 1H}), \ 6.79 \ (d, J=1.8 \text{ Hz, 1H}), \ 6.76 \ (dd, J=1.8, 8.6 \text{ Hz, 1H}), \ 6.47 \ (d, J=16.1 \text{ Hz, 1H}), \ 5.61 \ (s, 2H), \ 4.15 \ (q, J=7.1 \text{ Hz, 2H}), \ 3.86 \ (s, 3H), \ 1.23 \text{ ppm (t, J=7.1 Hz, 3H)}; \ MS (EI, 70 \text{ ev}) \frac{m}{z}: 396 [M]^+ . \]
$7H, 7.45 (d, J=7.3 Hz, 2H), 7.39 (t, J=7.2 Hz, 2H), 7.34 (d, J=7.2 Hz, 1H), 6.70 (d, J=2.2 Hz, 1H), 6.64 (dd, J=2.2, 8.6 Hz, 1H), 6.37 (d, J=16.1 Hz, 1H), 5.16 (s, 2H), 3.84 ppm (s, 3H); MS (EI, 70 ev) m/z: 284 [M]+.

(E)-4-(4-Chlorobenzyloxy)-2-methoxycinnamate (7b): To a solution of 6b (4.20 g, 12.14 mmol) in MeOH (50 mL) was added LiOH (3.00 g, 121.39 mmol). Following the procedure as described for 7a gave 7b (3.63 g, 94%) as a white solid: mp: 180-190 °C; $^{1}{H}$ NMR (500 MHz, [D$_6$]DMSO): δ= 7.72 (d, J=16.1 Hz, 1H), 7.59 (d, J=8.6 Hz, 1H), 7.47 (d, J=8.5 Hz, 2H), 7.44 (d, J=8.5 Hz, 2H), 6.69 (d, J=0.9 Hz, 1H), 6.62 (dd, J=1.9, 8.6 Hz, 1H), 6.36 (d, J=16.1 Hz, 1H), 5.15 (s, 2H), 3.83 ppm (s, 3H); MS (EI, 70 ev) m/z: 318 [M]+.

(E)-4-(4-Bromobenzyloxy)-2-methoxycinnamate (7c): To a solution of 6c (4.50 g, 11.54 mmol) in MeOH (50 mL) was added LiOH (2.85 g, 115.38 mmol). Following the procedure as described for 7a gave 7c (4.01 g, 96%) as a white solid: mp: 185-195 °C; $^{1}{H}$ NMR (500 MHz, [D$_6$]DMSO): δ= 7.73 (d, J=16.1 Hz, 1H), 7.60 (d, J=8.6 Hz, 2H), 7.59 (d, J=8.6 Hz, 1H), 7.41 (d, J=8.6 Hz, 2H), 6.69 (d, J=2.2 Hz, 1H), 6.62 (dd, J=2.2, 8.6 Hz, 1H), 6.37 (d, J=16.1 Hz, 1H), 5.14 (s, 2H), 3.84 ppm (s, 3H). MS (EI, 70 ev) m/z: 362 [M]+.

(E)-4-(4-Methoxybenzyloxy)-2-methoxycinnamate (7d): To a solution of 6d (4.20 g, 12.28 mmol) in MeOH (50 mL) was added LiOH (3.04 g, 122.81 mmol).
Following the procedure as described for **7a** gave **7d** (3.66 g, 95%) as a white solid: mp: 165-170 °C; ¹H NMR (500 MHz, [D₆]DMSO): δ= 7.73 (d, J=16.0 Hz, 1H), 7.58 (d, J=8.6 Hz, 1H), 7.38 (d, J=8.6 Hz, 2H), 6.94 (d, J=8.6 Hz, 2H), 6.68 (d, J=2.2 Hz, 1H), 6.62 (dd, J=2.2, 8.6 Hz, 1H), 6.36 (d, J=16.0 Hz, 1H), 5.07 (s, 2H), 3.84 (s, 3H), 3.75 ppm (s, 3H); MS (EI, 70 ev) m/z: 314 [M]+.

**(E)-4-[(Naphthalen-4-yl)methoxy]-2-methoxycinnamate (7e):** To a solution of **6e** (3.80 g, 10.50 mmol) in MeOH (40 mL) was added LiOH (2.60 g, 104.97 mmol). Following the procedure as described for **7a** gave **7e** (3.26 g, 93%) as a white solid: mp: 156-160 °C; ¹H NMR (500 MHz, [D₆]DMSO): δ= 12.09 (s, 1H), 8.09 (d, J=8.3 Hz, 1H), 7.98 (d, J=7.6 Hz, 1H), 7.94 (d, J=8.3 Hz, 1H), 7.76 (d, J=16.1 Hz, 1H), 7.70 (d, J=6.9 Hz, 1H), 7.63 (d, J=8.6 Hz, 1H), 7.57 (m, 2H), 7.53 (t, J=7.6 Hz, 1H), 6.79 (d, J=2.1 Hz, 1H), 6.75 (d, J=8.6 Hz, 1H), 6.38 (d, J=16.1 Hz, 1H), 5.54 (s, 2H), 3.86 ppm (s, 3H); MS (EI, 70 ev) m/z: 334 [M]+.

**(E)-4-(Trifluoromethoxy)-2-methoxycinnamate (7f):** To a solution of **6f** (5.50 g, 13.89 mmol) in MeOH (60 mL) was added LiOH (3.44 g, 138.89 mmol). Following the procedure as described for **7a** gave **7f** (4.70 g, 92%) as a white solid: mp: 159-165 °C; ¹H NMR (500 MHz, [D₆]DMSO): δ= 12.09 (s, 1H), 7.73 (d, J=16.1 Hz, 1H), 7.61 (d, J=8.3 Hz, 2H), 7.59 (d, J=8.7 Hz, 1H), 7.39 (d,
\[ J = 8.3 \text{ Hz,} 2H \), 6.71 (d, \( J = 2.0 \text{ Hz,} 1H \), 6.64 (dd, \( J = 2.0, 8.7 \text{ Hz,} 1H \), 6.37 (d, \( J = 16.1 \text{ Hz,} 1H \), 5.20 (s, 2H), 3.84 ppm (s, 3H); MS (EI, 70 ev) \( m/z: 368 \ [M]^+ \).

**\( (E)\)-Ethyl 2-hydroxy-4-methoxycinnamate (10):** To a solution of 9 (21.12 g, 120.00 mmol) in anhydrous EtOH (200 mL) was added NaOEt (16.96 g, 240.00 mmol) in anhydrous EtOH (100 mL) dropwise during 1 h at RT under \( N_2 \). The reaction mixture was heated to 78°C for 6 h. The reaction was diluted with distd H\(_2\)O (200 mL) at ice bath, acidified with 1N HCl\(_{\text{aq}}\) to pH 4-5 and extracted with EtOAc (50 mL x 3). The organic layer was dried (Na\(_2\)SO\(_4\)), filtered and the solvent removed in vacuo. The residue was purified by silica gel chromatography (EtOAc: \( n\)-Hexane= 1: 5) to give 10 (21.32 g, 80%) as a white solid: mp: 115-120°C; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta = 7.97 \ (d, \ J = 16.1 \text{ Hz,} 1H), 7.39 \ (d, \ J = 8.6 \text{ Hz,} 1H), 6.51 \ (d, \ J = 16.1 \text{ Hz,} 1H), 6.48 \ (d, \ J = 8.6 \text{ Hz,} 1H), 6.41 \ (s, 1H), 4.27 \ (q, \ J = 7.0 \text{ Hz,} 2H), 3.80 \ (s, 3H), 1.34 \text{ ppm (t,} \ J = 7.1 \text{ Hz,} 3H); MS (EI, 70 ev) \( m/z: 222.0 \ [M]^+ \).

**\( (E)\)-Ethyl 2-benzyloxy-4-methoxycinnamate (11a):** To a mixture of 10 (4.00 g, 18.02 mmol) and \( K_2\)CO\(_3\) (6.22 g, 45.05 mmol) in acetone (100 mL) was added benzyl chloride (4.15 mL, 36.04 mmol). The resulting mixture was heated to 56°C under \( N_2 \) overnight. After filtration to remove \( K_2\)CO\(_3\), the filtrate was concentrated in vacuo. The residue was diluted with EtOAc (100 mL) and
washed with distd H₂O (50 mL x 3). The organic layer was dried (Na₂SO₄),
filtered and the solvent removed in vacuo. The residue was purified by silica
gel chromatography (EtOAc: n-Hexane= 1: 6) to give 11a (4.27 g, 76%) as a
colorless liquid: ¹H NMR (500 MHz, [D₆]acetone): δ= 8.09 (d, J=16.1 Hz, 1H),
7.74 (d, J=8.6 Hz, 1H), 7.64 (d, J=7.4 Hz, 2H), 7.54 (t, J=7.4 Hz, 2H), 7.48 (d,
J=7.4 Hz, 1H), 6.84 (d, J=2.3 Hz, 1H), 6.72 (dd, J=8.6, 2.3 Hz, 1H), 6.57 (d,
J=16.1 Hz, 1H), 5.38 (s, 2H), 4.28 (q, J=7.1 Hz, 2H), 3.95 (s, 3H), 1.37 ppm (t,
J=7.1 Hz, 3H); MS (EI, 70 ev) m/z: 312.4 [M]+.

(E)-Ethyl 2-(4-chlorobenzyloxy)-4-methoxycinnamate (11b): To a mixture
of 10 (3.34 g, 15.05 mmol) and K₂CO₃ (5.19 g, 37.61 mmol) in acetone (80 mL)
was added 4-chlorobenzyl chloride (4.85 g, 30.01 mmol). Following the
procedure described for 11a gave 11b (3.85 g, 74%) as a white solid: mp:
103-105 °C; ¹H NMR (500 MHz, CDCl₃): δ= 7.97 (d, J=16.1 Hz, 1H), 7.48 (d,
J=8.6 Hz, 1H), 7.36 (brs, 4H), 6.52 (dd, J=8.6, 2.1 Hz, 1H), 6.45 (d, J=2.1 Hz,
1H), 6.41 (d, J=16.1 Hz, 1H), 5.10 (s, 2H), 4.24 (q, J=7.1Hz, 2H), 3.80 (s, 3H),
1.32 ppm (t, J=7.1 Hz, 3H); MS (EI, 70 ev) m/z: 346.0 [M]+.

(E)-Ethyl 2-(4-bromobenzyloxy)-4-methoxycinnamate (11c): To a mixture
of 10 (3.22 g, 14.50 mmol) and K₂CO₃ (5.00 g, 36.26 mmol) in acetone (80 mL)
was added 4-bromobenzyl chloride (5.97 g, 29.10 mmol). Following the
procedure described for **11a** gave **11c** (4.30 g, 76%) as a white solid: mp: 101-106 °C; ¹H NMR (500 MHz, CDCl₃): δ = 7.97 (d, J=16.1 Hz, 1H), 7.51 (d, J=8.4 Hz, 2H), 7.48 (d, J=8.6 Hz, 1H), 7.31 (d, J=8.4 Hz, 2H), 6.52 (dd, J=8.6, 2.2 Hz, 1H), 6.44 (d, J=2.2 Hz, 1H), 6.41 (d, J=16.1 Hz, 1H), 5.09 (s, 2H), 4.24 (q, J=7.0 Hz, 2H), 3.80 (s, 3H), 1.32 ppm (t, J=7.0 Hz, 3H). MS (EI, 70 ev) m/z: 390.0 [M]+.

**(E)-Ethyl 2-(4-methoxybenzyloxy)-4-methoxycinnamate (11d):** To a mixture of **10** (2.22 g, 10.00 mmol) and K₂CO₃ (3.45 g, 25.00 mmol) in acetone (80 mL) was added 4-methoxybenzyl chloride (2.72 mL, 20.00 mmol). Following the procedure described for **11a** gave **11d** (2.63 g, 77%) as a light yellow solid: mp: 89-95 °C; ¹H NMR (500 MHz, CDCl₃): δ = 7.97 (d, J=16.0 Hz, 1H), 7.46 (d, J=9.2 Hz, 1H), 7.36 (d, J=8.6 Hz, 2H), 6.92 (d, J=8.6 Hz, 2H), 6.51 (d, J=2.3 Hz, 1H), 6.50 (dd, J=9.2, 2.3 Hz, 1H), 6.42 (d, J=16.0 Hz, 1H), 5.07 (s, 2H), 4.22 (q, J=7.2 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 1.31 ppm (t, J=7.2 Hz, 3H); MS (EI, 70 ev) m/z: 342.0 [M]+.

**(E)-Ethyl 2-[(naphthalen-4-yl)methoxy]-4-methoxycinnamate (11e):** To a mixture of **10** (3.00 g, 13.51 mmol) and K₂CO₃ (4.66 g, 33.78 mmol) in acetone (100 mL) was added 1-(chloromethyl)naphthalene (4.08 mL, 27.02 mmol). Following the procedure described for **11a** gave **11e** (3.65 g, 74%) as a white
solid: mp: 115-120 °C; ¹H NMR (500 MHz, [D₆]Acetone): δ= 8.31 (d, J=9.1 Hz, 1H), 8.08 (m, 2H), 8.04 (d, J=16.1 Hz, 1H), 7.86 (d, J=7.1 Hz, 1H), 7.75 (d, J=8.6 Hz, 1H), 7.65 (m, 3H), 7.05 (d, J=2.3 Hz, 1H), 6.74 (dd, J=8.6, 2.3 Hz, 1H), 6.48 (d, J=16.1 Hz, 1H), 5.83 (s, 2H), 4.20 (q, J=6.9 Hz, 2H), 3.98 (s, 3H), 1.30 ppm (t, J=6.9 Hz, 3H); MS (EI, 70 ev) m/z: 362.1 [M]+.

(E)-2-Benzyl-oxy-4-methoxycinnamate (12a): To a solution of 11a (4.10 g, 13.14 mmol) in MeOH (60 mL) was added LiOH (3.20 g, 131.40 mmol). The resulting mixture was heated to 63 °C under N₂ overnight. Following the procedure described for 7a gave 12a (3.58 g, 96%) as a white solid: mp: 152-160 °C; ¹H NMR (500 MHz, [D₆]Acetone): δ= 8.09 (d, J=16.2 Hz, 1H), 7.74 (d, J=8.6 Hz, 1H), 7.64 (d, J=7.4 Hz, 2H), 7.53 (t, J=7.4 Hz, 2H), 7.46 (t, J=7.4 Hz, 1H), 6.84 (d, J=2.3 Hz, 1H), 6.72 (dd, J=8.6, 2.3 Hz, 1H), 6.56 (d, J=16.2 Hz, 1H), 5.37 (s, 2H), 3.95 ppm (s, 3H); MS (ESI-) m/z: 283.3 [M-H]-.

(E)-2-(4-Chlorobenzyloxy)-4-methoxycinnamate (12b): To a solution of 11b (3.25 g, 9.39 mmol) in MeOH (60 mL) was added LiOH (2.25 g, 93.93 mmol). Following the procedure described for 12a gave 12b (2.90 g, 97%) as a white solid: mp: 155-160 °C; ¹H NMR (500 MHz, [D₄]MeOH): δ= 8.56 (d, J=16.1 Hz, 1H), 8.43 (d, J=8.7 Hz, 1H), 8.28 (brs, 4H), 7.49 (d, J=1.8 Hz, 1H), 7.38 (dd, J=8.7, 1.8 Hz, 1H), 7.17 (d, J=16.1 Hz, 1H), 6.00 (s, 2H), 4.58 ppm (s, 3H). MS
(ESI-) \textit{m/z}: 317.4 [M-H].

\textbf{\((E)\)-2-(4-Bromobenzyloxy)-4-methoxycinnamate (12c):} To a solution of 11c (4.23 g, 10.85 mmol) in MeOH (80 mL) was added LiOH (2.68 g, 93.93 mmol). Following the procedure described for 12a gave 12c (3.73 g, 95%) as a yellow solid: mp: 165-170 °C; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$= 7.74 (d, $J$=16.3 Hz, 1H), 7.60 (d, $J$=7.8 Hz, 2H), 7.59 (d, $J$=8.6 Hz, 1H), 7.40 (d, $J$=7.8 Hz, 2H), 6.66 (s, 1H), 6.50 (d, $J$=8.6 Hz, 1H), 6.35 (d, $J$=16.3 Hz, 1H), 5.17 (s, 2H), 3.76 ppm (s, 3H); MS (ESI-) $m/z$: 361.2 [M-H].

\textbf{\((E)\)-2-(4-Methoxybenzyloxy)-4-methoxycinnamate (12d):} To a solution of 11d (2.58 g, 7.54 mmol) in MeOH (50 mL) was added LiOH (1.87 g, 75.44 mmol). Following the procedure described for 12a gave 12d (2.27 g, 96%) as a white solid: mp: 152-155 °C; $^1$H NMR (500 MHz, [D$_6$]acetone): $\delta$= 8.05 (d, $J$=16.1 Hz, 1H), 7.72 (d, $J$=8.7 Hz, 1H), 7.56 (d, $J$=8.6 Hz, 2H), 7.08 (d, $J$=8.6 Hz, 2H), 6.84 (d, $J$=2.3 Hz, 1H), 6.71 (dd, $J$=8.7, 2.3 Hz, 1H), 6.54 (d, $J$=16.1 Hz, 1H), 5.28 (s, 2H), 3.96 (s, 3H), 3.92 ppm (s, 3H); MS (ESI-) $m/z$: 313.3 [M-H].

\textbf{\((E)\)-2-[(Naphthalen-4-yl)methoxy]-4-methoxycinnamate (12e):} To a solution of 11e (3.50 g, 9.67 mmol) in MeOH (50 mL) was added LiOH (2.39 g, 96.69 mmol). Following the procedure described for 12a gave 12e (3.00 g, 93%) as a
white solid: mp: 165-168 °C; ¹H NMR (500 MHz, [D₆]acetone): δ = 8.31 (d, J=8.1 Hz, 1H), 8.08 (m, 2H), 8.05 (d, J=16.2 Hz, 1H), 7.85 (d, J=6.8 Hz, 1H), 7.76 (d, J=8.7 Hz, 1H), 7.68 (m, 3H), 7.05 (d, J=2.3 Hz, 1H), 6.75 (dd, J=8.7, 2.3 Hz, 1H), 6.48 (d, J=16.2 Hz, 1H), 5.83 (s, 2H), 3.98 ppm (s, 3H); MS (ESI-) m/z: 333.4 [M-H]⁻.

1-(2-Chloroethoxy)-4-methoxybenzene (15a): To a mixture of 14 (6.21 g, 50.00 mmol) and K₂CO₃ (17.25 g, 125.00 mmol) in MeCN (200 mL) was added 1-bromo-2-chloroethane (12.40 ml, 150.00 mmol) dropwise. The resulting mixture was heated to 82 °C under N₂ overnight and then concentrated in vacuo. The residue was diluted with distd H₂O (100 mL) and extracted with EtOAc (50 mL x 3). The organic layer was dried (Na₂SO₄), filtered and the solvent removed in vacuo. The residue was purified by silica gel chromatography (EtOAc: n-Hexane= 1: 6) to give 15a (7.63 g, 82%) as a white solid: mp: 90-95 °C; ¹H NMR (500 MHz, CDCl₃): δ = 6.87 (d, J=9.1 Hz, 2H), 6.84 (d, J=9.1 Hz, 2H), 4.18 (t, J=5.9 Hz, 2H), 3.79 (t, J=5.9 Hz, 2H), 3.78 ppm (s, 3H); MS (EI, 70 ev) m/z: 186 [M]⁺.

1-(3-Chloropropoxy)-4-methoxybenzene (15b): To a mixture of 14 (5.00 g, 40.32 mmol) and K₂CO₃ (13.91 g, 100.80 mmol) in MeCN (120 mL) was added 1-bromo-3-chloropropane (11.98 ml, 120.96 mmol) dropwise. Following the
procedure described for 15a gave 15b (7.34 g, 91%) as a light yellow liquid: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 6.84 (m, 4H), 4.07 (t, $J$=6.1 Hz, 2H), 3.77 (s, 3H), 3.74 (t, $J$=6.1 Hz, 2H), 2.21 ppm (q, $J$=6.1 Hz, 2H); MS (ESI-) m/z: 199.2 [M-H]$^-$. 

1-(4-Chlorobutoxy)-4-methoxybenzene (15c): To a mixture of 14 (5.00 g, 40.32 mmol) and K$_2$CO$_3$ (13.91 g, 100.80 mmol) in MeCN (120 mL) was added 1-bromo-4-chlorobutane (14.01 ml, 120.96 mmol) dropwise. Following the procedure described for 15a gave 15c (7.33 g, 85%) as a yellow liquid: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 6.81 (m, 4H), 3.93 (t, $J$=6.0 Hz, 2H), 3.75 (s, 3H), 3.60 (t, $J$=6.3 Hz, 2H), 1.93 ppm (m, 4H); MS (EI, 70 ev) m/z: 214 [M]$^+$. 

1-(5-Chloropentyloxy)-4-methoxybenzene (15d): To a mixture of 14 (5.00 g, 40.32 mmol) and K$_2$CO$_3$ (13.91 g, 100.80 mmol) in MeCN (120 mL) was added 1-bromo-5-chloropentane (15.98 ml, 120.96 mmol) dropwise. Following the procedure described for 15a gave 15d (8.09 g, 88%) as a yellow liquid: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 6.82 (s, 4H), 3.91 (t, $J$=6.5 Hz, 2H), 3.76 (s, 3H), 3.20 (q, $J$=7.0 Hz, 2H), 1.89 (m, 2H), 1.84 (m, 2H), 1.78 ppm (m, 2H); MS (EI, 70 ev) m/z: 228 [M]$^+$. 

(E)-Ethyl 2-(2-(4-methoxyphenoxyoxy)ethoxy)-4-methoxycinnamate (16a): To a mixture of 15a (3.72 g, 20.00 mmol) and K$_2$CO$_3$ (6.90 g, 50.00 mmol) in
DMF (20 mL) was added 10 (3.55 g, 16.00 mmol). The resulting solution was stirred at RT under N₂ overnight. After filtration to remove K₂CO₃, the filtrate was concentrated in vacuo. The residue was diluted with distd H₂O (100 mL) and extracted with EtOAc (50 mL x 3). The organic layer was dried (Na₂SO₄), filtered and the solvent removed in vacuo. The residue was purified by silica gel chromatography (EtOAc:n-Hexane= 1: 6-1: 4) to give 16a (3.21 g, 54%) as a white solid: mp: 92-97 °C; ¹H NMR (500 MHz, CDCl₃): δ= 7.89 (d, J=16.2 Hz, 1H), 7.43 (d, J=8.1 Hz, 1H), 6.90 (d, J=9.0 Hz, 2H), 6.82 (d, J=9.0 Hz, 2H), 6.51 (d, J=8.1 Hz, 1H), 6.50 (s, 1H), 6.45 (d, J=16.2 Hz, 1H), 4.32 (m, 4H), 4.20 (q, J=7.1 Hz, 2H), 3.81 (s, 3H), 3.75 (s, 3H), 1.27 (t, J=7.1 Hz, 3H); MS (EI, 70 ev) m/z: 372.2 [M]⁺.

(E)-Ethyl 2-(2-(4-methoxyphenoxyoxy)propoxy)-4-methoxycinnamate (16b): To a mixture of 15b (4.00 g, 20.00 mmol) and K₂CO₃ (6.90 g, 50.00 mmol) in DMF (20 mL) was added 10 (3.55 g, 16.00 mmol). Following the procedure described for 16a gave 16b (2.66 g, 43%) as a colorless liquid: ¹H NMR (500 MHz, CDCl₃): δ= 7.92 (d, J=16.1 Hz, 1H), 7.44 (d, J=8.4 Hz, 1H), 6.86 (d, J=9.3 Hz, 2H), 6.82 (d, J=9.3 Hz, 2H), 6.51 (d, J=2.1 Hz, 1H), 6.48 (dd, J=2.1, 8.4 Hz, 1H), 6.41 (d, J=16.1 Hz, 1H), 4.23 (m, 4H), 4.14 (t, J=6.0 Hz, 2H), 3.82 (s, 3H), 3.76 (s, 3H), 2.31 (q, J=6.0 Hz, 2H), 1.31 ppm (t, J=7.2 Hz,
(E)-Ethyl 2-(2-(4-methoxyphenoxyoxy)butoxy)-4-methoxycinnamate (16c):

To a mixture of 15c (4.28 g, 20.00 mmol) and K$_2$CO$_3$ (6.90 g, 50.00 mmol) in DMF (20 mL) was added 10 (3.55 g, 16.00 mmol). Following the procedure described for 16a gave 16c (3.10 g, 47%) as a colorless liquid: $^1$H NMR (500 MHz, CDCl$_3$): δ= 7.91 (d, $J$=16.1 Hz, 1H), 7.43 (d, $J$=8.6 Hz, 1H), 6.81 (m, 4H), 6.48 (dd, $J$=2.3, 8.6 Hz, 1H), 6.42 (s, 1H), 6.41 (d, $J$=16.1 Hz, 1H), 4.22 (q, $J$=7.2 Hz, 2H), 4.06 (t, $J$=6.1 Hz, 2H), 3.98 (t, $J$=6.1 Hz, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 2.02 (m, 2H), 1.96 (m, 2H), 1.30 ppm (t, $J$=7.2 Hz, 3H); MS (ESI+) m/z: 409.2 [M+Na]$^+$. MS (EI, 70 ev) m/z: 400 [M]$^+$. 

(E)-Ethyl 2-(2-(4-methoxyphenoxyoxy)pentyloxy)-4-methoxycinnamate (16d): To a mixture of 15d (3.42 g, 15.00 mmol) and K$_2$CO$_3$ (3.45 g, 25.00 mmol) in DMF (16 mL) was added 10 (2.22 g, 10.00 mmol). Following the procedure described for 16a gave 16d (3.04 g, 49%) as a yellow liquid: $^1$H NMR (500 MHz, CDCl$_3$): δ= 7.92 (d, $J$=16.1 Hz, 1H), 7.43 (d, $J$=8.6 Hz, 1H), 6.83 (d, $J$=9.3 Hz, 2H), 6.81 (d, $J$=9.3 Hz, 2H), 6.48 (dd, $J$=2.3, 8.6 Hz, 1H), 6.43 (d, $J$=16.1 Hz, 1H), 6.42 (d, $J$=2.3 Hz, 1H), 4.23 (q, $J$=7.0 Hz, 2H), 4.02 (t, $J$=6.4 Hz, 2H), 3.94 (t, $J$=6.4 Hz, 2H), 3.81 (s, 3H), 3.75 (s, 3H), 1.93 (q, $J$=7.2 Hz, 2H), 1.85 (q, $J$=7.0 Hz, 2H), 1.68 (q, $J$=9.0 Hz, 2H), 1.31 ppm (t, $J$=7.0 Hz, 2H).
(E)-2-(2-(4-Methoxyphenoxyoxy)ethoxy)-4-methoxycinnamate (17a): To a mixture of 16a (1.12 g, 3.00 mmol) in MeOH (30 mL) was added LiOH (720 mg, 30.00 mmol). The resulting solution was heated to 63 °C under N₂ overnight. The reaction mixture was diluted with distd H₂O (50 mL), acidified with 2N HCl to pH 5~6 and extracted with EtOAc (50 mL x 3). The organic layer was dried (Na₂SO₄), filtered and the solvent removed in vacuo to give 17a (992 mg, 96%) as a white solid: mp: 120-125 °C; ¹H NMR (500 MHz, [D₆]acetone): δ= 7.93 (d, J=16.1 Hz, 1H), 7.58 (d, J=8.6 Hz, 1H), 6.94 (d, J=9.5 Hz, 2H), 6.85 (d, J=9.5 Hz, 2H), 6.69 (d, J=2.4 Hz, 1H), 6.59 (dd, J=2.4, 8.6 Hz, 1H), 6.47 (d, J=16.1 Hz, 1H), 4.42 (m, 2H), 4.36 (m, 2H), 3.83 (s, 3H), 3.71 ppm (s, 3H); MS (EI, 70 ev) m/z: 344.1 [M]+.

(E)-2-(2-(4-Methoxyphenoxyoxy)propoxy)-4-methoxycinnamate (17b): To a solution of 16b (500 mg, 1.29 mmol) in MeOH (15 mL) was added LiOH (310 mg, 12.90 mmol). Following the procedure described for 17a gave 17b (435 mg, 94%) as a white solid: mp: 127-130 °C; ¹H NMR (500 MHz, [D₆]acetone): δ= 7.94 (d, J=16.2 Hz, 1H), 7.58 (d, J=8.6 Hz, 1H), 6.90 (d, J=9.1 Hz, 2H), 6.83 (d, J=9.1 Hz, 2H), 6.65 (d, J=2.4 Hz, 1H), 6.58 (dd, J=2.4, 8.6 Hz, 1H), 6.44 (d, J=16.2 Hz, 1H), 4.29 (t, J=6.2 Hz, 2H), 4.18 (t, J=6.2 Hz, 2H), 3.84 (s, 3H),
3.71 (s, 3H), 2.29 ppm (q, J=6.2 Hz, 2H); MS (ESI+) m/z: 381.1 [M+Na]⁺.

**(E)-2-(2-(4-Methoxyphenoxyoxy)butoxy)-4-methoxycinnamate (17c):** To a solution of 16c (400 mg, 1.00 mmol) in MeOH (15 mL) was added LiOH (240 mg, 10.00 mmol). Following the procedure described for 17a gave 17c (338 mg, 91%) as a white solid: mp: 108-112 °C; ¹H NMR (500 MHz, [D₆]DMSO): δ = 7.92 (d, J=16.1 Hz, 1H), 7.57 (d, J=8.6 Hz, 1H), 6.85 (d, J=9.3 Hz, 2H), 6.80 (d, J=9.3 Hz, 2H), 6.61 (d, J=2.2 Hz, 1H), 6.56 (dd, J=2.2, 8.6 Hz, 1H), 6.44 (d, J=16.1 Hz, 1H), 4.17 (t, J=6.3 Hz, 2H), 4.01 (t, J=6.3 Hz, 2H), 3.82 (s, 3H), 3.69 (s, 3H), 1.96 ppm (m, 4H); MS (EI, 70 ev) m/z: 372 [M]⁺.

**(E)-2-(2-(4-Methoxyphenoxyoxy)pentyloxy)-4-methoxycinnamate (17d):** To a solution of 16d (500 mg, 1.21 mmol) in MeOH (20 mL) was added LiOH (290 mg, 12.10 mmol). Following the procedure described for 17a gave 17d (443 mg, 95%) as a white solid: mp: 100-102 °C; ¹H NMR (500 MHz, [D₆]acetone): δ = 7.93 (d, J=16.1 Hz, 1H), 7.58 (d, J=8.6 Hz, 1H), 6.86 (d, J=9.2 Hz, 2H), 6.82 (d, J=9.2 Hz, 2H), 6.62 (d, J=2.3 Hz, 1H), 6.57 (dd, J=2.3, 8.6 Hz, 1H), 6.46 (d, J=16.1 Hz, 1H), 4.14 (t, J=6.4 Hz, 2H), 3.97 (t, J=6.4 Hz, 2H), 3.84 (s, 3H), 3.72 (s, 3H), 1.94 (q, J=6.4 Hz, 2H), 1.85 (q, J=8.0 Hz, 2H), 1.70 ppm (q, J=6.4 Hz, 2H); MS (EI, 70 ev) m/z: 386 [M]⁺.

**(E)-Ethyl 4-methoxy-2-(trifluoromethanesulfonyl)cinnamate (19):** To a
mixture of 10 (10.00 g, 45.05 mmol) and pyridine (14.57 mL, 180.18 mmol) in CH₂Cl₂ (100 mL) was added trifluoromethanesulfonic anhydride (15.12 mL, 91.10 mmol) dropwise at ice-bath under N₂. The resulting solution was then warmed to RT and stirred for additional 2 h. The reaction was diluted with CH₂Cl₂ (50 mL) and washed with distd H₂O (25 mL x 3). The organic layer was dried (Na₂SO₄), filtered and the solvent removed in vacuo. The residue was purified by silica gel chromatography (EtOAc/n-Hexane: 1/10) to give 19 (9.89 g, 62%) as a white solid: mp: 38-40 °C; ¹H NMR (500 MHz, CDCl₃): δ= 7.80 (d, J=16.0 Hz, 1H), 7.63 (d, J=8.8 Hz, 1H), 6.94 (dd, J=2.2, 8.8 Hz), 6.87 (d, J=2.2 Hz, 1H), 6.38 (d, J=16.0 Hz), 4.27 (q, J=7.0 Hz, 2H), 3.86 (s, 3H), 1.32 ppm (t, J=7.0 Hz, 3H). MS (ESI+) m/z: 377.0 [M+Na]⁺.

(E)-Ethyl 4-methoxy-2-phenylcinnamate (20a): To a mixture of 19 (2.00 g, 5.65 mmol), phenylboronic acid (1.03 g, 8.48 mmol) and K₂CO₃ (1.56 g, 11.30 mmol) in DMF (30 mL) was added Pd(PPh₃)₄ (659 mg, 0.57 mmol). The resulting solution was heated to 90 °C under N₂ overnight. The reaction mixture was concentrated in vacuo. The residue was diluted with EtOAc (50 mL) and then washed with distd H₂O (25 mL x 2). The organic layer was dried (Na₂SO₄), filtered and the solvent removed in vacuo. The residue was purified by silica gel chromatography (EtOAc: n-Hexane= 1: 8) to give 20a (1.08 g,
68%) as a light yellow liquid: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.66 (d, $J$=15.4 Hz, 1H), 7.42 (t, $J$=7.5 Hz, 2H), 7.40 (d, $J$=7.2 Hz, 1H), 7.32 (m, 2H), 6.93 (dd, $J$=2.7, 8.7 Hz, 1H), 6.87 (d, $J$=2.7 Hz, 1H), 6.78 (d, $J$=15.4 Hz, 1H), 4.18 (q, $J$=7.1 Hz, 2H), 3.86 (s, 3H), 1.27 ppm (t, $J$=7.1 Hz, 3H); MS (ESI+) $m/z$: 305.9 [M+Na]$^+$. 

$(E)$-Ethyl 4-methoxy-2-(4-bromophenyl)cinnamate (20b): To a mixture of 19 (2.20 g, 6.22 mmol), 4-bromophenylboronic acid (1.87 g, 9.33 mmol) and K$_2$CO$_3$ (1.72 g, 12.44 mmol) in DMF (30 mL) was added Pd(PPh$_3$)$_4$ (719 mg, 0.62 mmol). Following the procedure as described for 20a gave 20b (850 mg, 38%) as a white solid: mp: 80-82 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.65 (d, $J$=8.7 Hz, 1H), 7.59 (d, $J$=15.9 Hz, 1H), 7.56 (t, $J$=8.4 Hz, 2H), 7.16 (d, $J$=8.4 Hz, 2H), 6.93 (dd, $J$=2.7, 8.7 Hz, 1H), 6.82 (d, $J$=2.7 Hz, 1H), 6.28 (d, $J$=15.9 Hz, 1H), 4.19 (q, $J$=7.2 Hz, 2H), 3.86 (s, 3H), 1.28 ppm (t, $J$=7.2 Hz, 3H); MS (EI) $m/z$: 360.0 [M]$^+$. 

$(E)$-Ethyl 4-methoxy-2-(naphthalen-1-yl)cinnamate (20c): To a mixture of 19 (1.50 g, 4.24 mmol), 1-naphthaleneboronic acid (1.09 g, 6.36 mmol) and K$_2$CO$_3$ (1.17 g, 8.48 mmol) in DMF (22 mL) was added Pd(PPh$_3$)$_4$ (486 mg, 0.42 mmol). Following the procedure as described for 20a gave 20c (1.39 g, 99%) as a white solid: mp: 62-64 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.90 (dd,
$J=4.0, 8.1$ Hz, 2H), 7.76 (d, $J=8.7$ Hz, 1H), 7.53 (dd, $J=6.8, 8.2$ Hz, 1H), 7.48 (dd, $J=1.1, 7.9$ Hz, 1H), 7.46 (s, 1H), 7.38 (1H, m), 7.32 (dd, $J=1.1, 6.8$ Hz, 1H), 7.28 (d, $J=15.9$ Hz, 1H), 7.01 (dd, $J=2.8, 8.7$ Hz, 1H), 6.87 (d, $J=2.8$ Hz, 1H), 6.22 (d, $J=15.9$ Hz, 1H), 4.06 (q, $J=7.4$ Hz, 2H), 3.83 (s, 3H), 1.15 ppm (t, $J=7.4$ Hz, 3H); MS (ESI+) $m/z$: 355.1 [M+Na]$^+$. 

(E)-Ethyl 4-methoxy-2-(biphenyl-4-yl)cinnamate (20d): To a mixture of 19 (1.80 g, 5.08 mmol), 4-Biphenylboronic acid (1.51 g, 7.63 mmol) and $K_2CO_3$ (1.40 g, 10.16 mmol) in DMF (30 mL) was added Pd(PPh$_3$)$_4$ (590 mg, 0.51 mmol). Following the procedure as described for 20a gave 20d (1.27 g, 70%) as a white solid: mp: 130-132 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta= 7.73$ (d, $J=15.9$ Hz, 1H), 7.67 (m, 5H), 7.47 (t, $J=7.5$ Hz, 2H), 7.39 (d, $J=8.2$ Hz, 2H), 7.37 (d, $J=7.4$ Hz, 1H), 6.95 (dd, $J=2.7, 8.7$ Hz, 1H), 6.92 (d, $J=2.7$ Hz, 1H), 6.32 (d, $J=15.9$ Hz, 1H), 4.23 (q, $J=7.2$ Hz, 2H), 3.73 (s, 3H), 1.24 ppm (t, $J=7.2$ Hz, 3H); MS (ESI+) $m/z$: 381.9 [M+Na]$^+$. 

(E)-Ethyl 4-methoxy-2-(4-phenoxyphenyl)cinnamate (20e): To a mixture of 19 (2.00 g, 5.65 mmol), 4-Phenoxyphenylboronic acid (1.81 g, 8.47 mmol) and $K_2CO_3$ (1.56 g, 11.30 mmol) in DMF (30 mL) was added Pd(PPh$_3$)$_4$ (659 mg, 0.57 mmol). Following the procedure as described for 20a gave 20e (1.10 g, 52%) as a white solid: mp: 90-92 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta= 7.70$ (d,
\( J=15.9 \text{ Hz, 1H}) \), 7.66 (d, \( J=8.7 \text{ Hz, 1H}) \), 7.38 (dd, \( J=7.5 \), 8.4 Hz, 2H), 7.27 (d, \( J=8.6 \text{ Hz, 2H}) \), 7.14 (t, \( J=7.4 \text{ Hz, 1H}) \), 7.11 (d, \( J=0.9 \text{ Hz, 1H}) \), 7.09 (s, 1H), 7.06 (d, \( J=8.6 \text{ Hz, 2H}) \), 6.92 (dd, \( J=2.6 \), 8.7 Hz, 1H), 6.86 (d, \( J=2.6 \text{ Hz, 1H}) \), 6.29 (d, \( J=15.9 \text{ Hz, 1H}) \), 4.20 (q, \( J=7.2 \text{ Hz, 2H}) \), 3.87 (s, 3H), 1.29 ppm (t, \( J=7.2 \text{ Hz, 3H}) \); MS (ESI+) \( m/z \): 397.2 [M+Na]^+.

\((E)\)-Ethyl 4-methoxy-2-(4-benzoylephenyl)cinnamate \(20f\): To a mixture of 19 (1.70 g, 4.80 mmol), 4-Benzoylphenylboronic acid (1.63 g, 7.20 mmol) and \( K_2CO_3 \) (1.32 g, 9.60 mmol) in DMF (30 mL) was added Pd(PPh\( _3 \))\( _4 \) (555 mg, 0.48 mmol). Following the procedure as described for \(20a\) gave \(20f\) (1.37 g, 74%) as a white solid: mp: 65-67 \(^\circ\)C; \(^1\)H NMR (500 MHz, CDCl\( _3 \)): \( \delta = 7.87 \) (m, 4H), 7.69 (d, \( J=8.7 \text{ Hz, 1H}) \), 7.65 (d, \( J=15.9 \text{ Hz Hz, 1H}) \), 7.61 (t, \( J=7.4 \text{ Hz, 1H}) \), 7.51 (t, \( J=7.7 \text{ Hz, 2H}) \), 7.44 (d, \( J=8.1 \text{ Hz, 1H}) \), 6.97 (dd, \( J=2.6 \), 8.7 Hz, 1H), 6.88 (d, \( J=2.6 \text{ Hz, 1H}) \), 6.31 (d, \( J=15.9 \text{ Hz, 1H}) \), 4.19 (q, \( J=7.1 \text{ Hz, 2H}) \), 3.87 (s, 3H), 1.28 ppm (t, \( J=7.1 \text{ Hz, 3H}) \); MS (EI+) \( m/z \): 386 [M]^+.

\((E)\)-Ethyl 4-methoxy-2-(dibenzofuran-4-yl)cinnamate \(20g\): To a mixture of 19 (1.50 g, 4.24 mmol), 4-(dibenzofuranyl)boronic acid (1.35 g, 6.36 mmol) and \( K_2CO_3 \) (1.17 g, 8.48 mmol) in DMF (30 mL) was added Pd(PPh\( _3 \))\( _4 \) (486 mg, 0.42 mmol). Following the procedure as described for \(20a\) gave \(20g\) (1.24 g, 79%) as a white solid: mp: 98-99 \(^\circ\)C; \(^1\)H NMR (500 MHz, CDCl\( _3 \)): \( \delta = 8.00 \) (m,
(E)-4-methoxy-2-phenylcinnamate (21a): To a solution of 20a (1.00 g, 3.55 mmol) in MeOH (20 mL) was added LiOH (868 mg, 35.50 mmol). The resulting solution was heated to 63 °C under N₂ overnight. The reaction mixture was diluted with distd H₂O (50 mL), acidified with 2N HCl to pH 5~6 and extracted with EtOAc (50 mL x 3). The organic layer was dried (Na₂SO₄), filtered and the solvent removed in vacuo to give 21a (857 mg, 95%) as a white solid: mp: 105-106 °C; ¹H NMR (500 MHz, [D₆]Acetone): δ= 7.85 (d, J=8.7 Hz, 1H), 7.62 (d, J=15.9 Hz, 1H), 7.47 (m, 3H), 7.37 (m, 2H), 7.03 (dd, J=2.7, 8.7 Hz, 1H), 6.91 (d, J=2.7 Hz, 1H), 6.35 (d, J=15.9 Hz, 1H), 3.89 ppm (s, 3H); MS (ESI-) m/z: 253.6 [M-H].

(E)-4-methoxy-2-(4-bromophenyl)cinnamate (21b): To a solution of 20b (800 mg, 2.22 mmol) in MeOH (15 mL) was added LiOH (543 mg, 22.22 mmol). Following the procedure as described for 21a gave 21b (730 mg, 99%) as a white solid: mp: 174-177 °C; ¹H NMR (500 MHz, [D₆]DMSO): δ= 7.84 (d, J=8.9 Hz, 1H), 7.66 (d, J=8.4 Hz, 2H), 7.36 (d, J=15.9 Hz, 1H), 7.26 (d, J=8.4 Hz, 2H),
7.01 (dd, J=2.5, 8.8 Hz, 1H), 6.86 (d, J=2.5 Hz, 1H), 6.34 (d, J=15.9 Hz, 1H), 3.81 ppm (s, 3H); MS (ESI-) m/z: 332.6 [M-H].

**(E)-4-methoxy-2-(naphthalen-1-yl)cinnamate (21c):** To a solution of 20c (1.20 g, 3.61 mmol) in MeOH (20 mL) was added LiOH (883 mg, 36.14 mmol). Following the procedure as described for 21a gave 21c (1.05 g, 96%) as a white solid: mp: 214-216 °C; $^1$H NMR (500 MHz, [D$_6$]DMSO): δ= 8.00 (d, J=8.2 Hz, 2H), 7.96 (d, J=8.8 Hz, 1H), 7.59 (t, J=7.8 Hz, 1H), 7.52 (t, J=7.8 Hz, 1H), 7.43 (t, J=7.8 Hz, 1H), 7.35 (d, J=6.8 Hz, 1H), 7.30 (d, J=8.4 Hz, 1H), 7.10 (dd, J=2.6, 8.8 Hz, 1H), 6.96 (d, J=15.9 Hz, 1H), 6.84 (d, J=2.6 Hz, 1H), 6.28 (d, J=15.9 Hz, 1H), 3.80 ppm (s, 3H); MS (ESI-) m/z: 303.7 [M-H].

**(E)-4-methoxy-2-(biphenyl-4-yl)cinnamate (21d):** To a solution of 20d (1.10 g, 3.07 mmol) in MeOH (20 mL) was added LiOH (751 mg, 30.73 mmol). Following the procedure as described for 21a gave 21d (1.00 g, 99%) as a white solid: mp: 244-246 °C; $^1$H NMR (500 MHz, [D$_6$]DMSO): δ= 7.80 (d, J=8.8 Hz, 1H), 7.72 (d, J=8.3 Hz, 1H), 7.67 (d, J=7.5 Hz, 1H), 7.45 (d, J=15.7 Hz, 1H), 7.44 (s, 1H), 7.35 (m, 3H), 7.00 (dd, J=2.7, 8.8 Hz, 1H), 6.85 (d, J=2.7 Hz, 1H), 6.30 (d, J=15.7 Hz, 1H), 3.73 ppm (s, 3H); MS (ESI-) m/z: 329.7 [M-H].

**(E)-4-methoxy-2-(4-phenoxyphenyl)cinnamate (21e):** To a solution of 20e (1.00 g, 2.67 mmol) in MeOH (20 mL) was added LiOH (653 mg, 26.74 mmol).
Following the procedure as described for **21a** gave **21e** (914 mg, 99%) as a white solid: mp: 169-171 °C; \(^1\)H NMR (500 MHz, [D\(_6\)]DMSO): \(\delta = 7.82\ (d, J=8.8\ Hz, 1H), 7.44\ (d, J=16.2\ Hz, 1H), 7.42\ (t, J=7.8\ Hz, 2H), 7.31\ (d, J=8.4\ Hz, 2H), 7.18\ (t, J=7.5\ Hz, 1H), 7.10\ (d, J=8.2\ Hz, 1H), 7.06\ (d, J=8.2\ Hz, 2H), 6.98\ (dd, J=2.4, 8.8\ Hz, 1H), 6.86\ (d, J=2.4\ Hz, 1H), 6.33\ (d, J=16.2\ Hz, 1H), 3.81\ (s, 3H); MS (ES-I) \(m/z\): 345.0 [M-H].

**(E)-4-methoxy-2-(4-benzoylphenyl)cinnamate (21f):** To a solution of **20f** (1.20 g, 3.11 mmol) in MeOH (20 mL) was added LiOH (760 mg, 31.09 mmol). Following the procedure as described for **21a** gave **21f** (990 mg, 89%) as a white solid: mp: 174-176 °C; \(^1\)H NMR (500 MHz, [D\(_6\)]Acetone): \(\delta = 7.91\ (t, J=8.3\ Hz, 3H), 7.84\ (d, J=8.5\ Hz, 2H), 7.67\ (m, 1H), 7.62\ (d, J=15.9\ Hz, 1H), 7.56\ (m, 4H), 7.08\ (dd, J=2.6, 8.7\ Hz, 1H), 6.99\ (d, J=2.6\ Hz, 1H), 6.38\ (d, J=15.9\ Hz, 1H), 3.91\ ppm\ (s, 3H); MS (EI, 70 ev) \(m/z\): 358 [M]⁺.

**(E)-4-methoxy-2-(dibenzofuran-4-yl)cinnamate (21g):** To a solution of **20g** (1.20 g, 3.23 mmol) in MeOH (20 mL) was added LiOH (813 mg, 32.26 mmol). Following the procedure as described for **21a** gave **21g** (1.10 g, 99%) as a white solid: mp: 247-249 °C; \(^1\)H NMR (500 MHz, [D\(_6\)]DMSO): \(\delta = 8.22\ (d, J=7.6\ Hz, 1H), 8.19\ (d, J=7.6\ Hz, 1H), 7.96\ (d, J=8.8\ Hz, 1H), 7.62\ (d, J=8.2\ Hz, 1H), 7.50\ (m, 2H), 7.41\ (t, J=7.2\ Hz, 2H), 7.23\ (d, J=15.8\ Hz, 1H), 7.10\ (dd, J=2.5,
8.8 Hz, 1H), 7.02 (d, J=2.5 Hz, 1H), 6.35 (d, J=15.8 Hz, 1H), 3.87 ppm (s, 3H);
MS (ESI-) m/z: 343.7 [M-H].

**7-Propoxycoumarin (23a):** To a mixture of 3 (1.20 g, 7.41 mmol) and K₂CO₃ (2.56 g, 18.52 mmol) in acetone (30 mL) was added 1-bromopropane (1.35 mL, 14.82 mmol). The resulting solution was heated to 56 °C overnight. The reaction was concentrated in vacuo. The residue was diluted with EtOAc (50 mL) and then washed with disted H₂O (25 mL x 3). The organic layer was dried (Na₂SO₄), filtered and the solvent removed in vacuo. The residue was purified by silica gel chromatography (EtOAc: n-Hexane= 1: 4) to give 23a (1.35 g, 89%) as a white solid: mp: 77-79 °C; ¹H NMR (500 MHz, CDCl₃): δ= 7.61 (d, J=9.5 Hz, 1H), 7.34 (d, J=8.6 Hz, 1H), 6.82 (dd, J=2.4, 8.6 Hz, 1H), 6.79 (d, J=2.4 Hz, 1H), 6.22 (d, J=9.5 Hz, 1H), 3.96 (t, J=6.5 Hz, 2H), 1.83 (m, 2H), 1.05 ppm (t, J=7.5 Hz, 3H); MS (ESI+) m/z: 227.1 [M+Na].

**7-Butoxycoumarin (23b):** To a mixture of 3 (1.50 g, 9.26 mmol) and K₂CO₃ (3.19 g, 23.15 mmol) in acetone (30 mL) was added 1-bromobutane (2.00 mL, 18.52 mmol). Following the procedure as described for 23a gave 23b (1.86 g, 92%) as a white solid: mp: 65-67 °C; ¹H NMR (500 MHz, CDCl₃): δ= 7.61 (d, J=9.5 Hz, 1H), 7.35 (d, J=8.8 Hz, 1H), 6.81 (dd, J=2.4, 8.8 Hz, 1H), 6.78 (d, J=2.4 Hz, 1H), 6.22 (d, J=9.5 Hz, 1H), 4.00 (t, J=6.5 Hz, 2H), 1.79 (m, 2H),
1.49 (m, 2H), 0.97 (t, J=7.4 Hz, 3H); MS (ESI+) m/z: 241.8 [M+Na]+.

7-Pentoxycoumarin (23c): To a mixture of 3 (1.30 g, 8.02 mmol) and K$_2$CO$_3$ (2.77 g, 20.06 mmol) in acetone (30 mL) was added 1-bromopentane (2.00 mL, 16.04 mmol). Following the procedure as described for 23a gave 23c (1.73 g, 93%) as a white solid: mp: 58-61 °C; $^1$H NMR (500 MHz, CDCl$_3$): δ= 7.62 (d, J=9.5 Hz, 1H), 7.34 (d, J=8.6 Hz, 1H), 6.82 (dd, J=2.4, 8.6 Hz, 1H), 6.79 (d, J=2.4 Hz, 1H), 6.22 (d, J=9.5 Hz, 1H), 4.00 (t, J=6.3 Hz, 2H), 1.81 (m, 2H), 1.42 (m, 4H), 0.93 ppm (t, J=7.2 Hz, 3H); MS (ESI+) m/z: 255.9 [M+Na]+.

(E)-Ethyl 2-hydroxy-4-propoxycinnamate (24a): To a solution of 23a (1.30 g, 6.37 mmol) in anhydrous EtOH (20 mL) was added NaOEt (901 mg, 12.75 mmol) in anhydrous EtOH (10 mL) dropwise at RT under N$_2$. The reaction mixture was heated to 78 °C for 6 h. The reaction was diluted with distd H$_2$O (50 mL) at ice bath, acidified with 1N HCl(aq) to pH 4-5 and extracted with EtOAc (25 mL x 3). The organic layer was dried (Na$_2$SO$_4$), filtered and the solvent removed in vacuo. The residue was purified by silica gel chromatography (MeOH: CH$_2$Cl$_2$ = 2: 98) to give 24a (668 mg, 42%) as a white solid: mp: 110-113 °C; $^1$H NMR (500 MHz, CDCl$_3$): δ= 9.15 (s, 1H), 7.91 (d, J=16.2 Hz, 1H), 7.50 (d, J=8.7 Hz, 1H), 6.51 (d, J=2.4 Hz, 1H), 6.49 (dd, J=2.4, 8.7 Hz, 1H), 6.45 (d, J=16.2 Hz, 1H), 4.17 (q, J=6.8 Hz, 2H), 3.93 (t, J=6.6 Hz,
2H), 1.76 (m, 2H), 1.26 (t, $J=6.8$ Hz, 3H), 1.01 ppm (t, $J=7.4$ Hz, 3H); MS (ESI-) $m/z$: 249.7 [M-H].

(E)-Ethyl 4-butoxy-2-hydroxycinnamate (24b): To a solution of 23b (1.80 g, 8.26 mmol) in anhydrous EtOH (20 mL) was added NaOEt (1.17 g, 16.51 mmol) in anhydrous EtOH (20 mL) dropwise at RT under N$_2$. Following the procedure as described for 24a gave 24b (676 mg, 31%) as a white solid: mp: 130-133 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$= 9.16 (s, 1H), 7.91 (d, $J=16.1$ Hz, 1H), 7.50 (d, $J=8.5$ Hz, 1H), 6.51 (d, $J=2.3$ Hz, 1H), 6.49 (dd, $J=2.3$, 8.6 Hz, 1H), 6.46 (d, $J=16.1$ Hz, 1H), 4.17 (q, $J=6.8$ Hz, 2H), 3.98 (t, $J=6.5$ Hz, 2H), 1.72 (m, 2H), 1.46 (m, 2H), 1.26 (t, $J=6.8$ Hz, 3H), 0.94 ppm (t, $J=7.9$ Hz, 3H); MS (ESI-) $m/z$: 263.8 [M-H].

(E)-Ethyl 2-hydroxy-4-pentoxycinnamate (24c): To a solution of 23c (1.70 g, 7.33 mmol) in anhydrous EtOH (20 mL) was added NaOEt (1.04 g, 14.66 mmol) in anhydrous EtOH (15 mL) dropwise at RT under N$_2$. Following the procedure as described for 24a gave 24c (672 mg, 33%) as a white solid: mp: 102-105 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$= 9.13 (s, 1H), 7.90 (d, $J=16.0$ Hz, 1H), 7.50 (d, $J=8.5$ Hz, 1H), 6.51 (d, $J=2.3$ Hz, 1H), 6.49 (dd, $J=2.3$, 8.5 Hz, 1H), 6.45 (d, $J=16.0$ Hz, 1H), 4.17 (q, $J=6.9$ Hz, 2H), 3.97 (t, $J=6.5$ Hz, 2H), 1.75 (m, 2H), 1.39 (m, 4H), 1.26 (t, $J=6.8$ Hz, 3H), 0.91 ppm (t, $J=7.0$ Hz, 3H);
(E)-Ethyl 4-propoxy-2-trifluoromethanesulfonoylcinnamate (25a): To a mixture of 24a (600 mg, 2.40 mmol) and pyridine (0.78 mL, 9.60 mmol) in CH₂Cl₂ (15 mL) was added trifluoromethanesulfonic anhydride (0.15 mL, 4.80 mmol) dropwise at ice-bath under N₂. The resulting solution was then warmed to RT and stirred for additional 2 h. The reaction was diluted with CH₂Cl₂ (50 mL) and washed with distd H₂O (25 mL x 3). The organic layer was dried (Na₂SO₄), filtered and the solvent removed in vacuo. The residue was purified by silica gel chromatography (EtOAc: n-Hexane= 1: 5) to give 25a (568 mg, 62%) as a brown liquid: ¹H NMR (500 MHz, CDCl₃): δ= 7.81 (d, J=16.0 Hz, 1H), 7.62 (d, J=8.9 Hz, 1H), 6.94 (dd, J=2.4, 8.9 Hz, 1H), 6.87 (d, J=2.4 Hz, 1H), 6.38 (d, J=16.0 Hz, 1H), 4.27 (q, J=7.2 Hz, 2H), 3.96 (t, J=7.5 Hz, 2H), 1.84 (m, 2H), 1.34 (t, J=7.2 Hz, 3H), 1.05 ppm (t, J=7.5 Hz, 3H); MS (ESI+) m/z= 405.8 [M+Na]⁺.

(E)-Ethyl 4-butoxy-2-trifluoromethanesulfonoylcinnamate (25b): To a mixture of 24b (650 mg, 2.46 mmol) and pyridine (0.80 mL, 9.85 mmol) in CH₂Cl₂ (15 mL) was added trifluoromethanesulfonic anhydride (0.16 mL, 4.96 mmol) dropwise at ice-bath under N₂. Following the procedure as described for 25a gave 25b (925 mg, 95%) as a colorless liquid: ¹H NMR (500 MHz, CDCl₃):
δ=7.80 (d, J=16.0 Hz, 1H), 7.61 (d, J=8.9 Hz, 1H), 6.93 (dd, J=2.3, 8.9 Hz, 1H), 6.86 (d, J=2.3 Hz, 1H), 6.38 (d, J=16.0 Hz, 1H), 4.27 (q, J=7.2 Hz, 2H), 4.00 (t, J=7.4 Hz, 2H), 1.79 (m, 2H), 1.50 (m, 2H), 1.33 (t, J=7.2 Hz, 3H), 0.98 ppm (t, J=7.4 Hz, 3H); MS (ESI+) m/z: 419.8 [M+Na]+.

(**E**)-Ethyl 4-pentoxy-2-trifluoromethanesulfonoylcinnamate (25c): To a mixture of 24c (650 mg, 2.34 mmol) and pyridine (0.76 mL, 9.35 mmol) in CH2Cl2 (15 mL) was added trifluoromethanesulfonic anhydride (0.15 mL, 4.68 mmol) dropwise at ice-bath under N2. Following the procedure as described for 25a gave 25c (882 mg, 92%) as a colorless liquid: 1H NMR (500 MHz, CDCl3): δ= 7.80 (d, J=16.0 Hz, 1H), 7.61 (d, J=8.9 Hz, 1H), 6.92 (dd, J=2.4, 8.8 Hz, 1H), 6.85 (d, J=2.4 Hz, 1H), 6.37 (d, J=16.0 Hz, 1H), 4.26 (q, J=7.2 Hz, 2H), 3.98 (t, J=6.4 Hz, 2H), 1.80 (m, 2H), 1.41 (m, 2H), 1.33 (t, J=7.2 Hz, 3H), 0.93 ppm (t, J=6.4 Hz, 3H); MS (ESI+) m/z: 433.8 [M+Na]+.

(**E**)-Ethyl 4-propoxy-2-phenylcinnamate (26a): To a mixture of 25a (550 mg, 1.44 mmol), phenylboronic acid (262 mg, 2.16 mmol) and K2CO3 (397 mg, 2.88 mmol) in DMF (10 mL) was added Pd(PPh3)4 (162 mg, 0.14 mmol). The resulting solution was heated to 90 °C under N2 overnight. The reaction mixture was concentrated in vacuo. The residue was diluted with EtOAc (40 mL) and then washed with distd H2O (20 mL x 2). The organic layer was dried
(Na₂SO₄), filtered and the solvent removed in vacuo. The residue was purified by silica gel chromatography (EtOAc: n-Hexane= 1: 7) to give 26a (406 mg, 91%) as a light yellow liquid: ¹H NMR (500 MHz, CDCl₃): δ = 7.66 (d, J=16.0 Hz, 1H), 7.65 (d, J=8.6 Hz, 1H), 7.41 (m, 3H), 7.30 (m, 2H), 6.92 (dd, J=2.6, 8.6 Hz, 1H), 6.86 (d, J=2.6 Hz, 1H), 6.28 (d, J=16.0 Hz, 1H), 4.18 (q, J=7.6 Hz, 2H), 3.97 (t, J=6.6 Hz, 2H), 1.82 (m, 2H), 1.25 (t, J=6.6 Hz, 3H), 1.04 ppm (t, J=7.6 Hz, 3H); MS (ESI+) m/z: 333.9 [M+Na]^+.

(E)-Ethyl 4-butoxy-2-phenylcinnamate (26b): To a mixture of 25b (900 mg, 2.27 mmol), phenylboronic acid (414 mg, 3.41 mmol) and K₂CO₃ (627 mg, 4.54 mmol) in DMF (15 mL) was added Pd(PPh₃)₄ (263 mg, 0.23 mmol). Following the procedure as described for 26a gave 26b (647 mg, 88%) as a yellow liquid: ¹H NMR (500 MHz, CDCl₃): δ = 7.66 (d, J=16.0 Hz, 1H), 7.65 (d, J=8.6 Hz, 1H), 7.40 (m, 3H), 7.31 (d, J=6.9 Hz, 2H), 6.92 (dd, J=2.5, 8.7 Hz, 1H), 6.86 (d, J=2.5 Hz, 1H), 6.28 (d, J=16.0 Hz, 1H), 4.18 (q, J=7.6 Hz, 2H), 4.01 (t, J=6.5 Hz, 2H), 1.78 (m, 2H), 1.49 (m, 2H), 1.25 (t, J=6.6 Hz, 3H), 0.98 ppm (t, J=7.6 Hz, 3H); MS (ESI+) m/z: 347.5 [M+Na]^+.

(E)-Ethyl 4-pentoxy-2-phenylcinnamate (26c): To a mixture of 25c (850 mg, 2.07 mmol), phenylboronic acid (378 mg, 3.11 mmol) and K₂CO₃ (571 mg, 4.14 mmol) in DMF (15 mL) was added Pd(PPh₃)₄ (240 mg, 0.21 mmol). Following
the procedure as described for \textbf{26a} gave \textbf{26c} (588 mg, 84\%) as a yellow liquid:

\begin{align*}
\text{\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3})}: \delta &= 7.67 (d, J=16.0 \text{ Hz}, 1\text{H}), 7.65 (d, J=8.7 \text{ Hz}, 1\text{H}), \\
&7.42 (m, 3\text{H}), 7.31 (m, 2\text{H}), 6.92 (dd, J=2.6, 8.7 \text{ Hz}, 1\text{H}), 6.86 (d, J=2.6 \text{ Hz}, 1\text{H}), \\
&6.28 (d, J=16.0 \text{ Hz}, 1\text{H}), 4.18 (q, J=7.2 \text{ Hz}, 2\text{H}), 4.00 (t, J=6.9 \text{ Hz}, 2\text{H}), 1.80 (m, \\
&2\text{H}), 1.42 (m, 4\text{H}), 1.27 (t, J=6.9 \text{ Hz}, 3\text{H}), 0.93 \text{ ppm (t, J=7.2 Hz, 3H); MS (ESI+) m/z: 361.0 [M+Na]\^\text{+}.}
\end{align*}

\textbf{7-Trifluoromethanesulfonoylcoumarin (28):} To a mixture of \textbf{3} (5.00 g, 30.86 mmol) and pyridine (10.03 mL, 123.43 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (60 mL) was added trifluoromethanesulfonic anhydride (2.00 mL, 61.72 mmol) dropwise at ice-bath under N\textsubscript{2}. Following the procedure as described for \textbf{25a} gave \textbf{28} (7.23 g, 80\%) as a white solid: mp: 82-84 °C; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \delta = 7.71 (d, J=9.6 \text{ Hz}, 1\text{H}), 7.58 (d, J=8.6 \text{ Hz}, 1\text{H}), 7.28 (d, J=2.3 \text{ Hz}, 1\text{H}), 7.22 (dd, J=2.3, 8.6 \text{ Hz}, 1\text{H}), 6.49 (d, J=9.6 \text{ Hz}, 1\text{H}); MS (ESI+) m/z: 316.8 [M+Na]\^\text{+}.

\textbf{7-Phenylcoumarin (29):} To a mixture of \textbf{28} (6.00 g, 20.41 mmol), phenylboronic acid (3.72 g, 30.61 mmol) and K\textsubscript{2}CO\textsubscript{3} (5.63 g, 40.82 mmol) in DMF (40 mL) was added Pd(PPh\textsubscript{3})\textsubscript{4} (2.33 g, 2.04 mmol). Following the procedure as described for \textbf{26a} gave \textbf{29} (3.39 g, 75\%) as a white solid: mp: 152-154 °C; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \delta = 7.73 (d, J=9.1 \text{ Hz}, 1\text{H}), 7.62 (d, J=8.5 \text{ Hz}, 2\text{H}), 7.52 (m, 3\text{H}), 7.48 (m, 2\text{H}), 7.39 (m, 1\text{H}), 6.42 \text{ ppm (d, J=9.1 Hz,}
(E)-Methyl 2-hydroxy-4-phenylcinnamate (30): To a solution of 29 (3.20 g, 14.41 mmol) in anhydrous MeOH (30 mL) was added NaOMe (1.56 g, 28.83 mmol) in anhydrous MeOH (20 mL) dropwise at RT under N₂. Following the procedure as described for 24a gave 30 (1.28 g, 35%) as a white solid: mp: 128-132 °C; ¹H NMR (500 MHz, [D₄]MeOH): δ= 9.27 (d, J=16.1 Hz, 1H), 8.93 (d, J=8.1 Hz, 1H), 8.89 (d, J=7.2 Hz, 2H), 8.71 (t, J=7.8 Hz, 2H), 8.63 (t, J=7.3 Hz, 1H), 8.51 (d, J=1.6 Hz, 1H), 8.46 (dd, J=1.6, 8.1 Hz, 1H), 7.91 (d, J=16.1 Hz, 1H), 3.30 ppm (s, 3H); MS (ESI-) m/z: 253.7 [M-H]-.

(E)-Methyl 4-phenyl-2-trifluoromethanesulfonylcinnamate (31): To a mixture of 30 (1.18 g, 4.65 mmol) and pyridine (1.51 mL, 18.58 mmol) in CH₂Cl₂ (20 mL) was added trifluoromethanesulfonyl anhydride (0.30 mL, 9.30 mmol) dropwise at ice-bath under N₂. Following the procedure as described for 25a gave 31 (1.22 g, 68%) as a white solid: mp: 158-159 °C; ¹H NMR (500 MHz, [D₄]MeOH): δ= 7.99 (d, J=16.1 Hz, 1H), 7.60 (d, J=8.3 Hz, 2H), 7.56 (d, J=7.9 Hz, 1H), 7.43 (t, J=7.9 Hz, 2H), 7.35 (dd, J=1.7, 8.3 Hz, 1H), 7.14 (d, J=1.7 Hz, 1H), 6.60 (d, J=16.1 Hz, 1H), 3.14 ppm (s, 3H); MS (ESI+) m/z: 409.7 [M+Na]+.

(E)-Methyl 2,4-diphenylcinnamate (32): To a mixture of 31 (1.10 g, 2.85
mmol), phenylboronic acid (520 mg, 4.27 mmol) and K$_2$CO$_3$ (787 mg, 5.70 mmol) in DMF (40 mL) was added Pd(PPh$_3$)$_4$ (330 mg, 0.29 mmol). Following the procedure as described for 26a gave 32 (393 mg, 44%) as a colorless liquid: $^1$H NMR (500 MHz, CDCl$_3$): δ = 7.78 (d, $J$=8.3 Hz, 1H), 7.76 (d, $J$=16.0 Hz, 1H), 7.64 (d, $J$=7.5 Hz, 2H), 7.61 (dd, $J$=1.7, 6.9 Hz, 1H), 7.46 (m, 3H), 7.42 (m, 1H), 7.38 (m, 3H), 6.44 (d, $J$=16.0 Hz, 1H), 3.75 ppm (s, 3H); MS (ESI+) m/z: 337.1 [M+Na]$^+$.  

**Table S1.** The antibodies and their reaction conditions used in the present study.

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