Supplementary Information

Design, Synthesis, and Biological Evaluation of a New Class of MT_2-Selective Agonists

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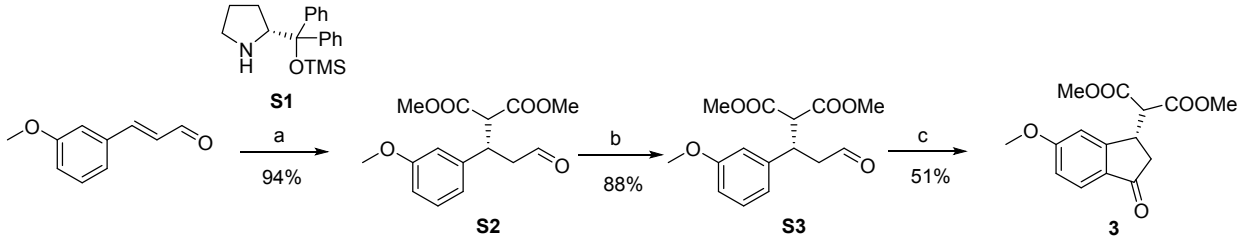
General

Melting points were taken on a Fisher-Johns melting point apparatus, uncorrected and reported in degrees Centigrade. ^{1}H NMR spectra and ^{13}C NMR were recorded in $CDCl_3$ or CD_3OD on a Bruker DRX-500 (500 MHz) or a Bruker DRX–400 (400 MHz) using TMS as an internal standard. Chemical shifts were reported in a δ (ppm) and spin-spin coupling constants as *J* (Hz) values. Mass spectra (MS) were recorded on a Finnigan MAT-95 mass spectrometer. The purities of all tested compounds were investigated by HPLC and found to be >95.0%. HPLC analyses were performed on an Agilent 1200 series instrument using an Agilent Eclipse XDB-C18 (250 mm × 4.6 mm) column.

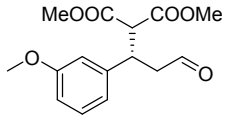
Functional assay

Myo-Inositol-1-phosphate (IP-One) levels were measured in GPCR-expressing cells using HTRF assay. HTRF assays were performed using reagents supplied by Cisbio (IP-One Tb kit, cat. no. 62IPAPEJ). CHO cells expressing MT_1 or MT_2 and Gα16 were seeded onto 384-well plate 24 h prior to the assay. After removal of the culture medium, 7 μL of this suspension was stimulated with 7μL of stimulation buffer containing the test compounds. After 30 min of incubation, a lysis buffer containing IP1-d2 and anti-IP1 Cryptate Tb was added to the cells. After 1 h of incubation at room temperature, plates were read on an Envision microplate reader (PerkinElmer, Waltham,MA), (excitation 340 nm, emission A: 615 nm and emission B: 665 nm).[1]

Preparation and analytical data

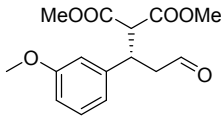


Reagents and condition: a) (*E*)-3-(3-methoxyphenyl)acrylaldehyde, catalyst **S1**, EtOH; b) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O; c) $SOCl_2$, toluene, $SnCl_4$, DCM.



(S)-Dimethyl 2-(1-(3-methoxyphenyl)-3-oxopropyl)malonate **(S2).**

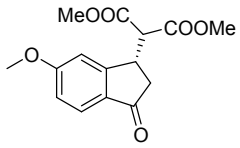
(*E*)-3-(3-methoxyphenyl)acrylaldehyde (3.7 g, 23 mmol) and amino catalyst **S1** (760 mg, 2.3 mmol) were stirred in EtOH (50 mL) at 0 ºC for 30 min, then dimethyl malonate (1.55 g, 11.7 mmol) was added dropwise. The mixture was stirred at 0 ºC for 48 h. The reaction mixture was extracted with EtOAc, washed with 1N HCl and brine. Concentration in vacuo gave crude product, which was purified by column chromatography (EtOAc : petroleum ether = 1:5) to give pure **S2** as a pale yellow liquid (3.2 g, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.22 (t, J = 7.8 Hz, 1H), 6.83 - 6.76 (m, 3H), 4.03 – 3.97 (m, 1H), 3.79 (s, 3H), 3.76 - 3.74 (m, 4H), 3.54 (s, 3H), 2.94 - 2.89 (m, 2H).



(S)-5-Methoxy-4-(methoxycarbonyl)-3-(3-methoxyphenyl)-5-oxopentanoic acid **(S3).**

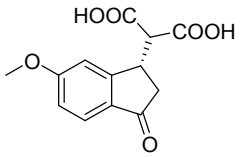
A solution of compound **S2** (2.2 g, 7.6 mmol), sodium chlorite (2.4 g, 26 mmol) and sodium hydrogen phosphate (2.4 g, 20 mmol) in 2-methyl-2-butene (14 mL), *t*-BuOH (60 mL) and water (24 mL) was stirred at room temperature for 90 min. The mixture was extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness to give a white solid, which was crystallized from EtOAc-petroleum ether to afford 2.1 g (88%) of **S3** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (t, J = 7.8 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 6.77 -

6.75 (m, 2H), 3.89 - 3.85 (m, 1H), 3.77 - 3.74 (m, 4H), 3.72 (s, 3H), 3.52 (s, 3H), 2.89 (dd, *J* = 16.4, 4.8 Hz, 1H), 2.79 (dd, *J* = 16.4, 9.4 Hz, 1H).



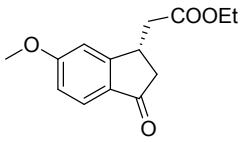
(S)-Dimethyl 2-(6-methoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)malonate **(3).**

Thionyl chloride (1.86 g, 15.6 mmol) was dropped into a solution of compound **S3** (1.62 g, 5.2 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred at room temperature for 6 h. Solvent and thionyl chloride were removed under reduced pressure. Another CH_2Cl_2 (45 mL) was added into the flask. It was cooled to -25 ºC, then $SnCl_4$ (2.1 mL, 18.3 mmol) was slowly dropped in. After stirred at this temperature for 12 h, it was poured into saturated aqueous NH_4Cl. The solution was extracted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4. Concentration in vacuo gave crude product, which was further purified by column chromatography (EtOAc : petroleum ether = 1:5) to give pure **3** as a colorless oil (0.78 g, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.5 Hz, 1H), 6.94 (d, *J* = 9.8 Hz, 1H), 6.91 (s, 1H), 4.08 - 4.05 (m, 1H), 3.87 (s, 3H), 3.82 (d, *J* = 6.7 Hz, 1H), 3.77 (s, 3H), 3.65 (s, 3H), 2.93 (dd, *J* = 18.9, 8.0 Hz, 1H), 2.72 (dd, *J* = 18.9, 3.0 Hz, 1H).



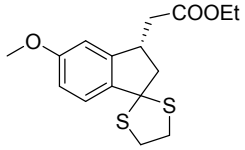
(S)-2-(6-methoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)malonic acid **(4)**

NaOH (20.0 g, 0.50 mol) and compound **3** (30.0 g, 0.10 mol) were refluxed in a mixture of EtOH (200 mL) and water (100 mL) for 2 h. After cooling to room temperature, the mixture was acidized with 100 mL 6 M HCl (aq). Then it was extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was used directly in the next step. mp 67–69 ^{o}C, ^{1}H NMR (400 MHz, CD_3OD) δ 7.62 (d, *J* = 8.5 Hz, 1H), 7.15 (s, 1H), 6.98 (dd, *J* = 8.4, 1.7 Hz, 1H), 4.07–3.99 (m, 1H), 3.95 (d, *J* = 5.8 Hz, 1H), 3.88 (s, 3H), 2.96–2.74 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 206.62, 172.01, 171.35, 167.40, 159.87, 131.65, 126.24, 117.34, 110.75, 56.47, 56.23, 42.36, 38.96; HRMS (ESI): m/z calcd for $C_{13}H_{13}O_6$ ($M + H^+$): 265.0712, found: 265.0699.



Ethyl (S)-2-(6-methoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)acetate **(5)**

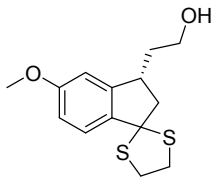
Compound **4** (0.10 mol) was refluxed in a mixture of dioxane (50 mL) and dimethylbenzene (150 mL) for 6 h. After cooling to room temperature, the mixture was treated with NaOH (10 g, 0.25 mmol) and extracted with EtOAc. The aqueous phase was acidized with 6 M HCl (aq) and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Subsequently, it was dissolved in 100 mL EtOH and 20 mL $SOCl_2$ was added dropwise into the flask. After stirring at 0 °C for 2 h, the mixture was evaporated to dryness. The crude product was recrystallized in a mixture of EtOAc and petroleum ether to afford the title compound as a pale yellow solid (11.6 g, 47.8%, two steps). mp 77–79 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 9.0 Hz, 1H), 6.95–6.90 (m, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 3.78–3.74 (m, 1H), 2.96 (dd, *J* = 19.0, 7.7 Hz, 1H), 2.85 (dd, *J* = 16.0, 5.3 Hz, 1H), 2.54 (dd, *J* = 15.9, 9.2 Hz, 1H), 2.43 (dd, *J* = 19.0, 3.3 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.41, 171.72, 165.44, 159.64, 130.11, 125.41, 115.66, 108.90, 60.77, 55.66, 43.53, 40.49, 34.49, 14.19; HRMS (ESI): m/z calcd for $C_{14}H_{16}O_4$ Na (M + Na^+): 271.0941, found: 271.0938.



Ethyl (R)-2-(5-methoxy-2,3-dihydrospiro[indene-1,2'-[1,3]dithiolan]-3-yl)acetate **(6)**

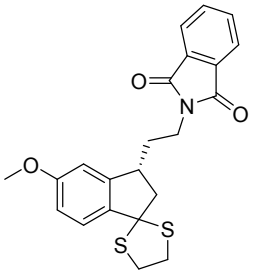
Compound **5** (10.3 g, 41.5 mmol), ethane-1,2-dithiol (7.3 mL, 85.8 mmol) and $SnCl_4$ (250 μL, 2.1 mmol) were stirred in 100 mL DCM overnight at room temperature. The reaction was quenched with saturated $NaHCO_3$ (aq), extracted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether : EtOAc = 10:1) to give pure **6** as a colourless oil (12.7 g, 94.5%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.5 Hz, 1H), 6.82 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.67 (d, *J* = 1.9 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 3.55–3.35 (m, 5H), 3.02 (dd, *J* = 13.4, 7.2 Hz, 1H), 2.84 (dd, *J* = 15.8, 5.7 Hz, 1H), 2.54 (dd, *J* = 15.8, 9.0 Hz, 1H), 2.46 (dd, *J* = 12.4, 7.3 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.30,

160.35, 145.80, 136.91, 125.76, 114.25, 108.35, 70.94, 60.57, 55.47, 54.87, 41.21, 40.64, 39.28, 39.20, 14.29; HRMS (ESI): m/z calcd for $C_{16}H_{21}O_3S_2$ ($M + H^+$): 325.0927, found: 325.0921.



(R)-2-(5-methoxy-2,3-dihydrospiro[indene-1,2'-[1,3]dithiolan]-3-yl)ethan-1-ol **(7)**

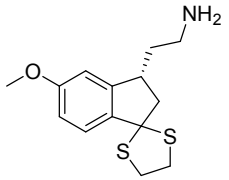
Compound **6** (12.3 g, 38.0 mmol) was dissolved in 100 mL THF and cooled to 0 °C. Then $LiAlH_4$ (1.44 g, 38.0 mmol) was added into the flask. After 1 h, the mixture was treated with saturated NH_4Cl (aq) and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration in vacuo afforded the crude product as a colourless oil (10.7 g, 99.9%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.5 Hz, 1H), 6.81 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.69 (d, *J* = 1.9 Hz, 1H), 3.81–3.70 (m, 5H), 3.54–3.31 (m, 5H), 2.94 (dd, *J* = 13.1, 6.9 Hz, 1H), 2.38 (dd, *J* = 13.1, 7.8 Hz, 1H), 2.40–2.35 (m, 1H), 2.09 (s, 1H), 1.75–1.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.26, 147.19, 137.00, 125.59, 113.79, 108.47, 71.27, 61.09, 55.54, 54.79, 41.18, 40.54, 39.70, 37.02; HRMS (ESI): m/z calcd for $C_{14}H_{19}O_2S_2$ ($M + H^+$): 283.0821, found: 283.0829.



(R)-2-(2-(5-methoxy-2,3-dihydrospiro[indene-1,2'-[1,3]dithiolan]-3-yl)ethyl)isoindoline-1,3-dione **(8)**

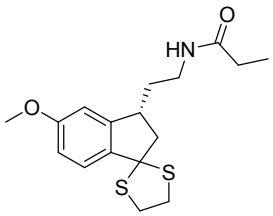
Compound **7** (10.7 g, 37.9 mmol) and triethylamine (7.93 mL, 57.0 mmol) were stirred in 100 mL DCM. Then MsCl was added dropwise into the flask and the mixture was reacted at room temperature for 12 h. The mixture was extracted with DCM and washed with 1M HCl (aq). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Subsequently, isoindoline-1,3-dione (6.53 g, 44.4 mmol) and K_2CO_3 (7.15 g, 51.8 mmol) were added into the flask, the mixture

was refluxed in 150 mL CH_3CN for 24 h. After cooling to room temperature, it was extracted with DCM and the organic layer was evaporated to dryness. The crude product was recrystallized in 100 mL EtOH to give the title compound as a white solid (12.1 g, 77.9%). mp 145–148 ^oC, ^1H NMR (500 MHz, $CDCl_3$) δ 7.82–7.78 (m, 2H), 7.69–7.65 (m, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 6.76 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.70 (d, *J* = 1.0 Hz, 1H), 3.80–3.76 (m, 2H), 3.75 (s, 3H), 3.52–3.30 (m, 5H), 3.03 (dd, *J* = 13.1, 6.9 Hz, 1H), 2.47 (dd, *J* = 13.1, 8.0 Hz, 1H), 2.40–2.25 (m, 1H), 1.90–1.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.25 (2 x *C*=O), 160.30, 146.24, 136.83, 133.94 (2 x Ar*C*H), 132.11 (2 x Ar*C*), 125.64, 123.21 (2 x Ar*C*H), 114.35, 107.97, 71.16, 55.48, 54.42, 41.23, 40.60, 40.40, 36.24, 32.58; HRMS (ESI): m/z calcd for $C_{22}H_{22}NO_3S_2$ ($M + H^+$): 412.1036, found: 412.1037.



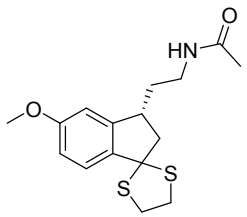
(R)-2-(5-methoxy-2,3-dihydrospiro[indene-1,2'-[1,3]dithiolan]-3-yl)ethan-1-amine **(9)**

Compound **8** (11.9 g, 29.0 mmol) and 85% hydrazine hydrate (14 mL, 290 mmol) were refluxed in 300 mL EtOH for 1 h. After cooling to room temperature, the mixture was filtered and the filtrate was extracted with EtOAc. The organic layer was washed with water followed by brine and dried over Na_2SO_4. The crude product was obtained as a yellow oil after concentration in vacuo (7.61 g, 93.5%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.5 Hz, 1H), 6.80 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.68 (d, *J* = 1.9 Hz, 1H), 3.78 (s, 3H), 3.60–3.45 (m, 3H), 3.40–3.25 (m, 2H), 2.95–2.73 (m, 3H), 3.34 (dd, *J* = 13.1, 8.0 Hz, 1H), 2.15–2.03 (m, 1H), 1.65–1.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.27, 147.14, 136.96, 125.56, 113.78, 108.36, 71.20, 55.49, 54.79, 41.19, 40.55, 40.54, 40.34, 37.81; HRMS (ESI): m/z calcd for $C_{14}H_{20}NOS_2$ ($M + H^+$): 282.0981, found: 282.0982.



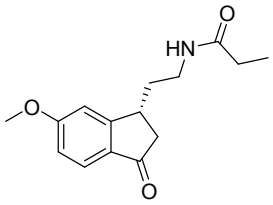
(R)-N-(2-(5-methoxy-2,3-dihydrospiro[indene-1,2'-[1,3]dithiolan]-3-yl)ethyl)propionamide **(10a)**

Compound **9** (2.55 g, 9.1 mmol), propionic anhydride (1.30 g, 10.0 mmol) and triethylamine (2.5 mL, 18.1 mmol) were stirred in 60 mL DCM at room temperature for 12 h. The mixture was extracted with EtOAc, washed with 1M HCl (aq). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (DCM : MeOH = 30 :1) to give pure **10a** as a colourless oil (3.0 g, 98.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 1H), 6.86–6.77 (m, 1H), 6.69 (s, 1H), 5.60 (br s, 1H), 3.79 (s, 3H), 3.60–3.25 (m, 6H), 3.24–3.15 (m, 1H), 2.94 (dd, *J* = 13.1, 7.0 Hz, 1H), 2.50–2.10 (m, 4H), 1.75–1.61 (m, 1H), 1.20-1.10 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.02, 160.30, 146.64, 136.80, 125.69, 114.11, 108.21, 71.12, 55.54, 54.62, 41.24, 40.61, 40.53, 37.96, 34.03, 29.79, 9.94; HPLC: room temperature; eluent, CH_3OH–H_2O (70:30); flow rate, 1.0 mL/min; t_R = 10.17 min, UV_{254} = 95.0%; HRMS (ESI): m/z calcd for $C_{17}H_{24}NO_2S_2$ (M + H^+): 338.1243, found: 338.1242.



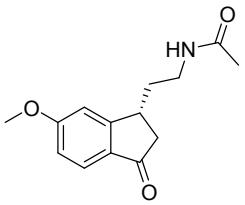
(R)-N-(2-(5-methoxy-2,3-dihydrospiro[indene-1,2'-[1,3]dithiolan]-3-yl)ethyl)acetamide **(10b)**

Compound **9** (2.95 g, 10.5 mmol), acetic anhydride (1.18 g, 11.6 mmol) and triethylamine (2.9 mL, 21.0 mmol) were stirred in 60 mL DCM at room temperature for 12 h. The mixture was extracted with EtOAc, washed with 1M HCl (aq). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (DCM : MeOH = 30 :1) to give pure **10b** as a colourless oil (3.4 g, 99.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 1H), 6.86–6.77 (m, 1H), 6.69 (s, 1H), 5.56 (br s, 1H), 3.79 (s, 3H), 3.60–3.43 (m, 3H), 3.44–3.31 (m, 3H), 3.28–3.13 (m, 1H), 2.94 (dd, *J* = 13.1, 7.0 Hz, 1H), 2.39 (dd, *J* = 13.1, 7.6 Hz, 1H), 2.24–2.10 (m, 1H), 1.99 (s, 3H), 1.75–1.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.19, 160.31, 146.60, 136.79, 125.70, 114.12, 108.20, 71.11, 55.53, 54.64, 41.24, 40.62, 40.50, 38.10, 34.00, 23.42; HPLC: room temperature; eluent, CH_3OH–H_2O (70:30); flow rate, 1.0 mL/min; t_R = 8.04 min, UV_{254} = 97.1%; HRMS (ESI): m/z calcd for $C_{16}H_{22}NO_2S_2$ (M + H^+): 324.1087, found: 324.1089.



(R)-N-(2-(6-methoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)ethyl)propionamide **(11a)**

Compound **10a** (3.0, 9.1 mmol) and $AgNO_3$ (3.1 g, 18.2 mmol) were stirred in 100 mL EtOH at room temperature for 12 h. Then the mixture was filtrated and the filtration was extracted with EtOAc. The organic layer was concentrated in vacuo to give 1.50 g crude product. Recrystallization of the crude product in a mixture of DCM and petroleum ether gave the pure **11a** as a white solid (1.15g, 48.4%, 99.9% *ee*). mp 118–119 ^{o}C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.5 Hz, 1H), 6.95 (s, 1H), 6.91 (dd, J = 8.5, 1.9 Hz, 1H), 5.62 (br s, 1H), 3.89 (s, 3H), 3.42–3.30 (m, 3H), 2.87 (dd, J = 18.8, 7.6 Hz, 1H), 2.37 (dd, J = 18.7, 3.2 Hz, 1H), 2.23–2.14 (m, 3H), 1.68–1.65 (m, 1H), 1.15 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.90, 173.98, 165.49, 160.94, 129.87, 125.35, 115.68, 108.91, 55.75, 43.18, 37.94, 36.03, 35.92, 29.71, 9.85; HPLC: room temperature; eluent, CH_3OH–H_2O (70:30); flow rate, 1.0 mL/min; t_R = 3.33 min, UV_{254} = 100.0%; HRMS (ESI): m/z calcd for $C_{15}H_{20}NO_3$ ($M + H^+$): 262.1438, found: 262.1438. The enantiomeric excess of **11a** was determined by HPLC as > 99.9% after conversion to compound **2**. [column, CHIRALPAK AS-H (4.6mm×250mm), room temperature; eluent, hexane:i-propanol:trifluoroacetic acid (90:10:0.1); flow rate, 1.0 mL/min; detect, 290 nm, t_R (*S*)-**2** = 34.7 min; t_R (*R*)-**2** = 41.3 min].



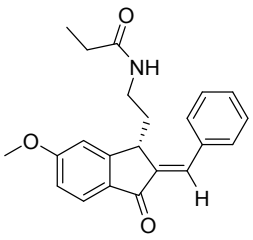
(R)-N-(2-(6-methoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)ethyl)acetamide **(11b)**

Compound **10b** (3.4 g, 10.5 mmol) and $AgNO_3$ (3.6 g, 21.0 mmol) were stirred in 100 mL EtOH at room temperature for 12 h. Then the mixture was filtrated and the filtration was extracted with EtOAc. The organic layer was concentrated in vacuo and the title compound was obtained as a white solid after recrystallization in a mixture of DCM and petroleum ether (1.52 g, 40.9%). mp 127–128 ^{o}C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 8.5 Hz, 1H), 6.91 (s, 1H), 6.85 (dd, J =

8.5, 1.9 Hz, 1H), 6.25 (br s, 1H), 3.84 (s, 3H), 3.35–3.28 (m, 3H), 2.82 (dd, *J* = 18.7, 7.6 Hz, 1H), 2.32 (dd, *J* = 18.7, 3.2 Hz, 1H), 2.15–2.10 (m, 1H), 1.95 (s, 3H), 1.65–1.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.96, 170.40, 165.51, 161.00, 129.79, 125.24, 115.63, 108.96, 55.72, 43.18, 38.00, 35.89(2 x *C*H_2), 23.21; HPLC: room temperature; eluent, CH_3OH–H_2O (70:30); flow rate, 1.0 mL/min; t_R = 3.06 min, UV_{254} = 99.8%; HRMS (ESI): m/z calcd for $C_{14}H_{18}NO_3$ (M + H^+): 248.1281, found: 248.1283.

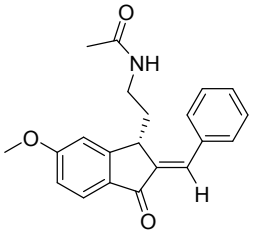
Representative Procedure for **12-20**

Compound **11a/b** (1.0 equiv), corresponding aldehyde (1.1 equiv) and MeONa (2.1 equiv) was refluxed in MeOH for 10 h. The mixture was acidized with 1 M HCl (aq) and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was crystallized in a mixture of EtOAc and petroleum ether to afford the pure compound.



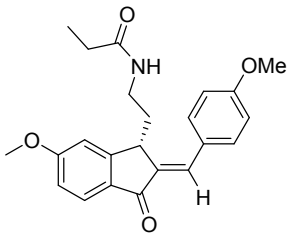
(S,E)-N-(2-(2-benzylidene-6-methoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)ethyl)propionamide **(12a)**

Starting from **11a** and benzaldehyde, 42.5% of **12a** was obtained as a pale yellow needle-like crystal according to above-mentioned general procedure. mp 120–121 ºC, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.5 Hz, 1H), 7.66–7.60 (m, 3H), 7.49–7.39 (m, 3H), 7.16 (s, 1H), 6.98 (d, *J* = 7.1 Hz, 1H), 5.10 (br s, 1H), 4.51 (s, 1H), 3.94 (s, 3H), 3.25–3.18 (m, 1H), 2.97–2.87 (m, 1H), 2.22–2.15 (m, 1H), 2.05–1.95 (m, 3H), 1.02 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.13, 173.49, 165.67, 156.41, 139.54, 134.93, 132.81, 130.70, 130.41 (2 x Ar*C*H), 129.37, 128.87 (2 x Ar*C*H), 126.28, 115.89, 109.12, 55.84, 39.56, 36.19, 31.50, 29.53, 9.60; HPLC: room temperature; eluent, CH_3OH–H_2O (70:30); flow rate, 1.0 mL/min; t_R = 7.25 min, UV_{254} = 100.0%; HRMS (ESI): m/z calcd for $C_{22}H_{24}NO_3$ (M + H^+): 350.1751, found: 350.1751.



(S,E)-N-(2-(2-benzylidene-6-methoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)ethyl)acetamide **(12b)**

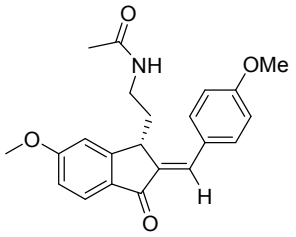
Starting from **11b** and benzaldehyde, 74.6% of **12b** was obtained as a pale yellow solid according to above-mentioned general procedure. mp 88–89 ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.5 Hz, 1H), 7.66 (d, *J* = 1.6 Hz, 1H), 7.61 (d, *J* = 7.4 Hz, 2H), 7.49–7.36 (m, 3H), 7.14 (d, *J* = 2.0 Hz, 1H), 6.99 (dd, *J* = 8.5, 2.1 Hz, 1H), 5.08 (br s, 1H), 4.51 (s, 1H), 3.94 (s, 3H), 3.28–3.12 (m, 1H), 3.01–2.81 (m, 1H), 2.23–2.11 (m, 1H), 2.05–1.94 (m, 1H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.17, 169.88, 165.67, 156.38, 139.45, 134.92, 132.89, 130.70, 130.41 (2 x Ar*C*H), 129.40, 128.88 (2 x Ar*C*H), 126.31, 115.95, 109.02, 55.86, 39.54, 36.34, 31.33, 23.08; HPLC: room temperature; eluent, CH_3CN–H_2O (45:55); flow rate, 1.0 mL/min; t_R = 6.10 min, UV_{254} = 95.4%; HRMS (ESI): m/z calcd for $C_{21}H_{22}NO_3$ ($M + H^+$): 336.1594, found: 336.1600.



(S,E)-N-(2-(6-methoxy-2-(4-methoxybenzylidene)-3-oxo-2,3-dihydro-1H-inden-1-yl)ethyl)propionamide **(13a)**

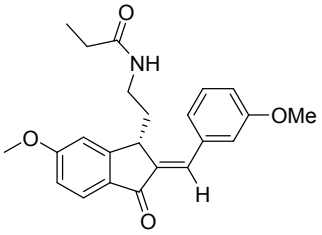
Starting from **11a** and 4-methoxybenzaldehyde, 52.8% of **13a** was obtained as a pale yellow solid according to above-mentioned general procedure. mp 132–133 ºC, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 1H), 7.63–7.55 (m, 3H), 7.14 (s, 1H), 6.98 (m, 3H), 5.06 (br s, 1H), 4.47 (s, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 3.25–3.18 (m, 1H), 2.95–2.87 (m, 1H), 2.25–2.18 (m, 1H), 2.10–1.95 (m, 3H), 1.02 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.43, 173.44, 165.43, 160.65, 156.21, 137.07, 132.72, 132.40 (2 x Ar*C*H), 130.89, 127.31, 126.13, 115.69 (2 x Ar*C*H), 114.41, 109.08, 55.79, 55.37, 39.71, 36.18, 31.19, 29.50, 9.55; HPLC: room temperature;

eluent, $CH_3OH–H_2O$ (70:30); flow rate, 1.0 mL/min; t_R = 7.58 min, UV_{254} = 100.0%; HRMS (ESI): m/z calcd for $C_{23}H_{26}NO_4$ ($M + H^+$): 380.1856, found: 380.1858.



(S,E)-N-(2-(6-methoxy-2-(4-methoxybenzylidene)-3-oxo-2,3-dihydro-1H-inden-1-yl)ethyl)acetamide **(13b)**

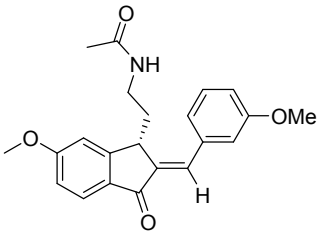
Starting from **11b** and 4-methoxybenzaldehyde, 53.4% of **13b** was obtained as a pale yellow solid according to above-mentioned general procedure. mp 132–133 ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.5 Hz, 1H), 7.63–7.54 (m, 3H), 7.12 (d, *J* = 1.3 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 3H), 5.15 (br s, 1H), 4.46 (s, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 3.26–3.10 (m, 1H), 3.02–2.82 (m, 1H), 2.29–2.16 (m, 1H), 2.11–1.98 (m, 1H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.33, 169.88, 165.45, 160.66, 156.21, 137.03, 132.78, 132.44 (2 x Ar*C*H), 130.90, 127.29, 126.16, 115.75, 114.43 (2 x Ar*C*H), 109.03, 55.83, 55.41, 39.70, 36.35, 31.09, 23.08; HPLC: room temperature; eluent, $CH_3CN–H_2O$ (45:55); flow rate, 1.0 mL/min; t_R = 4.55 min, UV_{254} = 95.5%; HRMS (ESI): m/z calcd for $C_{22}H_{24}NO_4$ ($M + H^+$): 366.1700, found: 366.1706.



(S,E)-N-(2-(6-methoxy-2-(3-methoxybenzylidene)-3-oxo-2,3-dihydro-1H-inden-1-yl)ethyl)propionamide **(14a)**

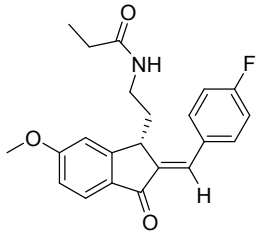
Starting from **11a** and 3-methoxybenzaldehyde, 35.6% of **14a** was obtained as a pale yellow solid according to above-mentioned general procedure. mp 91–93 ºC, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 1H), 7.61 (s, 1H), 7.39–7.35 (m, 1H), 7.22–7.13 (m, 3H), 7.00–6.92 (m, 2H), 5.14 (br s, 1H), 4.47 (s, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.40–3.34 (m, 1H), 2.94–2.86 (m, 1H), 2.20–1.93 (m, 4H), 1.06 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ

192.15, 173.67, 165.71, 159.80, 156.52, 139.96, 136.26, 132.53, 130.61, 129.86, 126.27, 123.02, 116.16, 116.02, 114.47, 109.13, 55.86, 55.37, 39.38, 36.18, 31.64, 29.54, 9.63; HPLC: room temperature; eluent, $CH_3OH–H_2O$ (70:30); flow rate, 1.0 mL/min; t_R = 8.17 min, UV_{254} = 99.4%; HRMS (ESI): m/z calcd for $C_{23}H_{26}NO_4$ ($M + H^+$): 380.1856, found: 380.1858.



(S,E)-N-(2-(6-methoxy-2-(3-methoxybenzylidene)-3-oxo-2,3-dihydro-1H-inden-1-yl)ethyl)acetamide **(14b)**

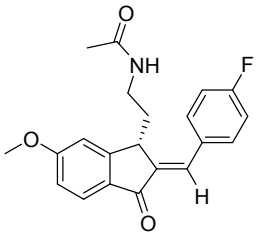
Starting from **11b** and 3-methoxybenzaldehyde, 46.6% of **14b** was obtained as a pale yellow solid according to above-mentioned general procedure. mp 103–105 ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.5 Hz, 1H), 7.59 (s, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.24–7.13 (m, 3H), 7.00–6.90 (m, 2H), 5.29 (br s, 1H), 4.50–4.42 (m, 1H), 3.94 (s, 3H), 3.86 (s, 3H), 3.40–3.29 (m, 1H), 2.95–2.84 (m, 1H), 2.22–2.11 (m, 1H), 1.98–1.87 (m, 1H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.16, 170.09, 165.70, 159.76, 156.53, 139.97, 136.23, 132.49, 130.58, 129.87, 126.26, 123.09, 116.15, 116.06, 114.42, 109.08, 55.86, 55.37, 39.31, 36.33, 31.63, 23.06; HPLC: room temperature; eluent, $CH_3CN–H_2O$ (45:55); flow rate, 1.0 mL/min; t_R = 4.71 min, UV_{254} = 97.3%; HRMS (ESI): m/z calcd for $C_{22}H_{24}NO_4$ ($M + H^+$): 366.1700, found: 366.1707.



(S,E)-N-(2-(2-(4-fluorobenzylidene)-6-methoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)ethyl)propionamide **(15a)**

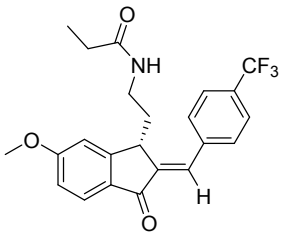
Starting from **11a** and 4-fluorobenzaldehyde, 17.7% of **15a** was obtained as a pale yellow solid according to above-mentioned general procedure. mp 104–107 ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.5 Hz, 1H), 7.63–7.55 (m, 3H), 7.16–7.10 (m, 3H), 6.98 (m, 1H), 5.15 (br s, 1H),

4.45 (s, 1H), 3.93 (s, 3H), 3.22–3.15 (m, 1H), 2.96–2.88 (m, 1H), 2.23–2.14 (m, 1H), 2.06–1.93 (m, 3H), 1.02 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.06, 173.58, 165.69, 163.1 (d, $^{1}J_{C–F}$ = 250 Hz, Ar*C*F), 156.25, 139.02, 132.47 (d, $^{3}J_{C–F}$ = 8.5 Hz, 2 x Ar*C*H), 131.62, 131.00 (d, $^{4}J_{C–F}$ = 3.4 Hz, Ar*C*), 130.61, 126.32, 116.10 (d, $^{2}J_{C–F}$ = 21.0 Hz, 2 x Ar*C*H), 115.89, 109.13, 55.87, 39.52, 36.16, 31.30, 29.52, 9.61; HPLC: room temperature; eluent, CH_3OH–H_2O (70:30); flow rate, 1.0 mL/min; t_R = 7.71 min, UV_{254} = 98.0%; HRMS (ESI): m/z calcd for $C_{22}H_{23}FNO_3$ (M + H^+): 368.1657, found: 368.1653.



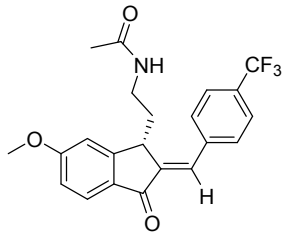
(S,E)-N-(2-(2-(4-fluorobenzylidene)-6-methoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)ethyl)acetamide **(15b)**

Starting from **11b** and 4-fluorobenzaldehyde, 55.2% of **15b** was obtained as a pale yellow solid according to above-mentioned general procedure. mp 95–97 ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.5 Hz, 1H), 7.63–7.55 (m, 3H), 7.19–7.11 (m, 3H), 6.99 (dd, J = 8.5, 1.9 Hz, 1H), 5.15 (br s, 1H), 4.46 (s, 1H), 3.94 (s, 3H), 3.22–3.09 (m, 1H), 2.96–2.85 (m, 1H), 2.25–2.14 (m, 1H), 2.06–1.93 (m, 1H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.05, 169.98, 165.67, 163.08 (d, $^{1}J_{C–F}$ = 250 Hz, Ar*C*F), 156.22, 138.98, 132.37 (d, $^{3}J_{C–F}$ = 8.3 Hz, 2 x Ar*C*H), 131.60, 130.97 (d, $^{4}J_{C–F}$ = 3.5 Hz, Ar*C*), 130.57, 126.28, 116.08 (d, $^{2}J_{C–F}$ = 21.0 Hz, 2 x Ar*C*H), 115.89, 109.10, 55.86, 39.48, 36.29, 31.24, 23.04; HPLC: room temperature; eluent, CH_3CN–H_2O (45:55); flow rate, 1.0 mL/min; t_R = 6.06 min, UV_{254} = 95.5%; HRMS (ESI): m/z calcd for $C_{21}H_{21}FNO_3$ (M + H^+): 354.1500, found: 354.1507.



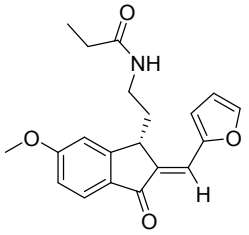
(S,E)-N-(2-(6-methoxy-3-oxo-2-(4-(trifluoromethyl)benzylidene)-2,3-dihydro-1H-inden-1-yl)ethyl)propionamide **(16a)**

Starting from **11a** and 4-(trifluoromethyl)benzaldehyde, 18.0% of **16a** was obtained as a yellow solid according to above-mentioned general procedure. mp 148–151 ºC, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.5 Hz, 1H), 7.73–7.68 (m, 4H), 7.63 (s, 1H), 7.17 (s, 1H), 7.00 (dd, *J* = 8.5,1.8 Hz, 1H), 5.08(br s, 1H), 4.51 (s, 1H), 3.95 (s, 3H), 3.24–3.15 (m, 1H), 2.95–2.89 (m, 1H), 2.20–1.93 (m, 4H), 1.03 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.70, 173.59, 165.95, 156.21, 141.62, 138.49, 130.85, 130.79 (q, $^{2}J_{C–F}$ = 33.0 Hz, Ar*C*), 130.43, 130.36 (2 x Ar*C*H), 126.51, 125.79 (q, $^{3}J_{C–F}$ = 4.0 Hz, 2 x Ar*C*H), 124.08 (q, $^{1}J_{C–F}$ = 251.0 Hz, *C*F_3), 116.14, 109.14, 55.91, 39.52, 36.12, 31.55, 29.52, 9.58; HPLC: room temperature; eluent, $CH_3OH–H_2O$ (70:30); flow rate, 1.0 mL/min; t_R = 13.35 min, UV_{254} = 97.2%; HRMS (ESI): m/z calcd for $C_{23}H_{23}F_3NO_3$ (M + H^+): 418.1625, found: 418.1624.



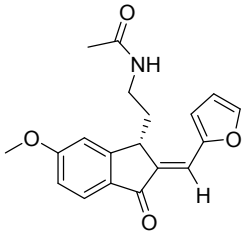
(S,E)-N-(2-(6-methoxy-3-oxo-2-(4-(trifluoromethyl)benzylidene)-2,3-dihydro-1H-inden-1-yl)ethyl)acetamide **(16b)**

Starting from **11b** and 4-(trifluoromethyl)benzaldehyde, 39.1% of **16b** was obtained as a yellow solid according to above-mentioned general procedure. mp 148–150 ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.5 Hz, 1H), 7.73–7.68 (m, 4H), 7.63 (d, *J* = 1.7 Hz, 1H), 7.16 (d, *J* = 1.9 Hz, 1H), 7.00 (dd, *J* = 8.5, 2.1 Hz, 1H), 5.17 (br s, 1H), 4.51 (s, 1H), 3.95 (s, 3H), 3.24–3.08 (m, 1H), 2.96–2.82 (m, 1H), 2.22–2.11 (m, 1H), 1.99–1.88 (m, 1H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.71, 170.04, 165.93, 156.19, 141.59, 138.42, 130.80, 130.79 (q, $^{2}J_{C–F}$ = 33.0 Hz, Ar*C*), 130.42, 130.37 (2 x Ar*C*H), 126.44, 125.76 (q, $^{3}J_{C–F}$ = 4.0 Hz, 2 x Ar*C*H), 123.84 (q, $^{1}J_{C–F}$ = 271.0 Hz, *C*F_3), 116.11, 109.12, 55.89, 39.46, 36.22, 31.47, 23.02; HPLC: room temperature; eluent, $CH_3OH–H_2O$ (70:30); flow rate, 1.0 mL/min; t_R = 10.57 min, UV_{254} = 96.2%; HRMS (ESI): m/z calcd for $C_{22}H_{21}F_3NO_3$ (M + H^+): 404.1468, found: 404.1471.



(S,E)-N-(2-(2-(furan-2-ylmethylene)-6-methoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)ethyl)propionamide **(17a)**

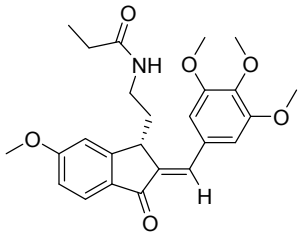
Starting from **11a** and furan-2-carbaldehyde, 39.8% of **17a** was obtained as a pale yellow solid according to above-mentioned general procedure. mp 152–154 ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.5 Hz, 1H), 7.65 (s, 1H), 7.37 (s, 1H), 7.10 (d, *J* = 2.1 Hz, 1H), 6.98-6.94 (m, 1H), 6.77 (d, *J* = 3.3 Hz, 1H), 6.59–6.55 (m, 1H), 5.10 (br s, 1H), 4.41 (s, 1H), 3.94 (s, 3H), 3.33–3.23 (m, 1H), 3.13–2.99 (m, 1H), 2.35–2.00 (m, 4H), 1.05 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.13, 173.50, 165.56, 156.46, 151.51, 145.37, 136.95, 130.94, 126.02, 118.63, 117.48, 115.59, 112.76, 109.22, 55.81, 40.45, 36.42, 33.35, 29.60, 9.64; HPLC: room temperature; eluent, CH_3CN–H_2O (45:55); flow rate, 1.0 mL/min; t_R = 4.73 min, UV_{254} = 95.3%; HRMS (ESI): m/z calcd for $C_{20}H_{22}NO_4$ (M + H^+): 340.1543, found: 340.1557.



(S,E)-N-(2-(2-(furan-2-ylmethylene)-6-methoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)ethyl)acetamide **(17b)**

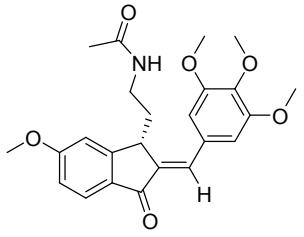
Starting from **11b** and furan-2-carbaldehyde, 83.1% of **17b** was obtained as a pale yellow solid according to above-mentioned general procedure. mp 204–206 ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.5 Hz, 1H), 7.64 (s, 1H), 7.36 (s, 1H), 7.09 (d, *J* = 1.5 Hz, 1H), 6.96 (dd, *J* = 8.5, 1.9 Hz, 1H), 6.76 (d, *J* = 3.4 Hz, 1H), 6.60–6.53 (m, 1H), 5.23 (br s, 1H), 4.39 (s, 1H), 3.93 (s, 3H), 3.32–3.19 (m, 1H), 3.10–2.99 (m, 1H), 2.38–2.27 (m, 1H), 2.27–2.16 (m, 1H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.15, 169.84, 165.55, 156.43, 151.51, 145.39, 136.88, 130.94, 126.05, 118.66, 117.53, 115.62, 112.79, 109.16, 55.83, 40.44, 36.60, 33.26, 23.15; HPLC: room

temperature; eluent, $CH_3CN–H_2O$ (45:55); flow rate, 1.0 mL/min; t_R = 4.14 min, UV_{254} = 95.2%; HRMS (ESI): m/z calcd for $C_{19}H_{20}NO_4$ ($M + H^+$): 326.1387, found: 326.1397.



(S,E)-N-(2-(6-methoxy-3-oxo-2-(3,4,5-trimethoxybenzylidene)-2,3-dihydro-1H-inden-1-yl)ethyl)propionamide **(18a)**

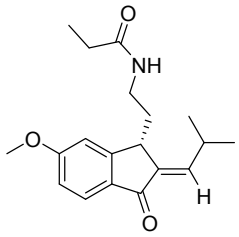
Starting from **11a** and 3,4,5-trimethoxybenzaldehyde, 39.9% of **18a** was obtained as a pale yellow solid according to above-mentioned general procedure. mp 180–181 ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 1H), 7.56 (s, 1H), 7.12 (s, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.85 (s, 2H), 5.09 (br s, 1H), 4.46 (s, 1H), 3.94 (s, 3H), 3.92 (s, 9H), 3.21–3.10 (m, 1H), 2.99–2.87 (m, 1H), 2.32–2.21 (m, 1H), 2.17–2.06 (m, 1H), 1.97 (q, *J* = 7.6 Hz, 2H), 1.00 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.07, 173.52, 165.63, 156.08, 153.40 (2 x Ar*C*), 139.64, 138.36, 133.11, 130.73, 130.16, 126.26, 115.91, 109.09, 108.24 (2 x Ar*C*H), 61.02, 56.39 (2 x O*C*H$_3$), 55.85, 39.90, 36.20, 31.17, 29.47, 9.56; HPLC: room temperature; eluent, $CH_3CN–H_2O$ (45:55); flow rate, 1.0 mL/min; t_R = 6.89 min, UV_{254} = 96.7%; HRMS (ESI): m/z calcd for $C_{25}H_{29}NO_6Na$ ($M + Na^+$): 462.1887, found: 462.1898.



(S,E)-N-(2-(6-methoxy-3-oxo-2-(3,4,5-trimethoxybenzylidene)-2,3-dihydro-1H-inden-1-yl)ethyl)acetamide **(18b)**

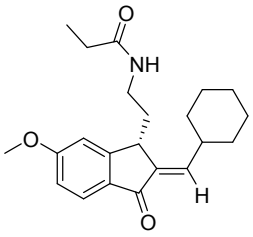
Starting from **11b** and 3,4,5-trimethoxybenzaldehyde, 40.0% of **18b** was obtained as a pale yellow solid according to above-mentioned general procedure. mp 138–140 ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 1H), 7.56 (s, 1H), 7.13 (s, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.85 (s, 2H), 5.13 (br s, 1H), 4.46 (s, 1H), 3.94 (s, 3H), 3.92 (s, 9H), 3.24–3.11 (m, 1H), 2.97–2.87 (m,

1H), 2.30–2.05 (m, 2H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.11, 170.00, 165.64, 156.08, 153.39 (2 x Ar*C*), 139.63, 138.39, 133.12, 130.70, 130.17, 126.28, 115.99, 109.05, 108.23 (2 x Ar*C*H), 61.03, 56.40 (2 x O*C*H_3), 55.86, 39.82, 36.36, 31.15, 23.04; HPLC: room temperature; eluent, CH_3CN–H_2O (45:55); flow rate, 1.0 mL/min; t_R = 5.21 min, UV_{254} = 99.5%; HRMS (ESI): m/z calcd for $C_{24}H_{27}NO_6Na$ (M + Na^+): 448.1731, found: 448.1729. **NOESY NMR** Interaction observed between 6.85 (s, 2H, Ar'C*H*), 4.46 (s, 1H, C*H*C=CH) and 2.30–2.05 (m, 2H, CH_2CHC=CH) to confirm *E* configuration.



(S,E)-N-(2-(6-methoxy-2-(2-methylpropylidene)-3-oxo-2,3-dihydro-1H-inden-1-yl)ethyl)propionamide **(19a)**

Starting from **11a** and isobutyraldehyde, 30.1% of **19a** was obtained as a white needle-like crystal according to above-mentioned general procedure. mp 101–104 ºC, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.5 Hz, 1H), 7.00–6.90 (m, 2H), 5.58 (br s, 1H), 5.03 (d, *J* = 9.4 Hz, 1H), 3.89 (s, 3H), 3.55–3.01 (m, 4H), 2.45–2.30 (m, 1H), 2.19 (q, *J* = 7.6 Hz, 2H), 1.81–1.69 (m, 7H), 1.15 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.77, 173.72, 165.56, 159.18, 136.93, 129.14, 125.77, 121.80, 115.69, 108.61, 55.74, 54.71, 44.23, 37.77, 34.71, 29.73, 25.89, 18.69, 9.80; HPLC: room temperature; eluent, CH_3OH–H_2O (70:30); flow rate, 1.0 mL/min; t_R = 7.38 min, UV_{254} = 95.1%; HRMS (ESI): m/z calcd for $C_{19}H_{26}NO_3$ (M + H^+): 316.1917, found: 316.1911.



(S,E)-N-(2-(2-(cyclohexylmethylene)-6-methoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)ethyl)propionamide **(20a)**

Starting from **11a** and cyclohexanecarbaldehyde, 14.1% of **20a** was obtained as a white solid according to above-mentioned general procedure. mp 149–150 ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.5Hz, 1H), 7.00 (d, *J* = 1.9 Hz, 1H), 6.94 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.63 (dd, *J* = 10.7, 1.5 Hz, 1H), 5.10 (br s, 1H), 4.05 (s, 1H), 3.91 (s, 3H), 3.14–3.06 (m, 2H), 2.47–2.36 (m, 1H), 2.30–2.19 (m, 1H), 2.13–1.97 (m, 3H), 1.83–1.63 (m, 5H), 1.38–1.22 (m, 5H), 1.03 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.22, 173.53, 165.44, 155.91, 142.08, 137.78, 131.35, 126.16, 115.58, 109.06, 55.78, 39.15, 38.61, 36.08, 33.68, 32.14, 31.89, 29.57, 25.77, 25.46, 25.45, 9.61; HPLC: room temperature; eluent, CH_3CN–H_2O (45:55); flow rate, 1.0 mL/min; t_R = 13.33 min, UV_{254} = 95.9%; HRMS (ESI): m/z calcd for $C_{22}H_{30}NO_3$ ($M + H^+$): 356.2220, found: 356.2219.

References and notes

1. L. Vincent, W. Cohen, P. Delagrange, J.A. Boutin, O. Nosjean, *J. Pineal. Res*., **2010**, *48*, 222-229.