Supporting Information

Cyclooxygenase-1-Selective Inhibitors Based on the (*E*)-2′-*Des*-methyl-sulindac Sulfide Scaffold

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Contents:

Experimental Section

General:
The purity of the investigated compounds is ≥ 95%, if not denoted otherwise. The analytical quality was evaluated by HPLC, LCMS (UV detection along with ELSD detection) and/or ^{1}H NMR. Given systematic compound names were generated with ChemDraw Ultra Vers. 12.0.3.1216

Materials and methods:
i) *Solvents and Reagents:*
All reagents and solvents were of commercial quality and were used without further purification. HPLC grade solvents obtained from Fischer (Pittsburg, PA) were used for chromatographic separations. Column chromatography was performed using standard grade silica gel from Sorbent Technologies, Twinsburg, OH (Catalog #: 10930-5, Porosity: 60 A, Particle Size: 32-63 mm, 230x450 mesh, pH range 6.5-7.5). Flash chromatography was conducted on a Biotage SP1 automated flash chromatography system equipped with a fixed wavelength UV detector (λ = 254 nm) using prefabricated 'Flash KP-SIL' columns (size according to requirements). Preparative TLC purification was accomplished on PLC Silica Gel 60 F$_{254}$, 2mm, 20x20 cm plates (EMD No. 5717-7). Analytical thin-layer chromatography (TLC) analyses were performed on fluorescent silica gel 60 F$_{254}$ plates (250 μm) from Whatman (Partisil® LK6D, Cat. No. 4865-821). Spots were visualized under natural light, and UV illumination at λ = 254 and 365 nm.

ii) *Instrumental Analysis:*
^{1}H and ^{13}C spectra were collected on a Bruker AV-400 with sample changer (BACS 60) at 400 and 100 MHz, respectively. Chemical shifts are reported in ppm relative to residual solvent peaks as an internal standard set to δ 2.52 and δ 40.45 (DMSO-d_6). ^{19}F NMR spectra were collected on a Bruker AV-300 at 282 MHz. Data is reported as follows: chemical shift, multiplicity (s = singlet, d = douplet, t = triplet, q = quartet, p = pentet, sext = sextet, sept = septet, br = broad, dd = douplet of douplets, dq = douplet of quartets, td = triplet of douplets, pd = pentet of douplets, m = multiplet), coupling constant (Hz), and integration.
Electrospray ionization (ESI) mass spectrometry (MS) was accomplished by direct injection practice on a Finnigan TSQ 7000 triple-quadrupole spectrometer (ionization mode: positive or negative according to requirements). Alternatively, low-resolution mass analyses (LCMS) were carried out on an Agilent 1200 LCMS system with electrospray ionization (Agilent 6130 quadrupole analyzer, positive ion mode). ESI-MS results are given as m/z ratio ([M+1]$^+$ and/or [M+Na]$^+$ or [M-1]$^+$). Purity of compounds was determined by analytical high performance liquid chromatography (HPLC) on a Supelco Supelcosil LC-18 column (15 cm x 3 mm, 5 μm) '*method 1*' or a YMC J'sphere H-80 S-4 column (3.0 x 50 mm) '*method 2*', which were eluted with a gradient (see time tables below) with a MeOH-0.01 M KH$_2$PO$_4$ system at a flow rate of 1.0 mL/min or an ACN-H$_2$O (plus 0.1 % TFA) system at a flow rate of 1.4 mL/min, respectively. (HP)LC was performed either on a Waters HPLC system^a with PDA detector (UV detection essentially at 288 and 347 nm) or an Agilent 1200 analytical LCMS with UV detection at 214 and 254 nm along with ELSD detection. LC results are presented as tR (min) and relative purity (%). The purity of all tested compounds is >95%, if not denoted otherwise.

^{a}equipped with a Waters 1525 Binary HPLC Punmp, a Waters 2996 Photodiode Detector and a Waters 717plus Autosampler as well as a Shimadzu CTO-6A Column Oven.

HPLC samples were diluted to a final concentration of about 0.1 – 0.2 mg/ml using MeOH. ESI samples (for direct detector injection) were diluted to similar concentrations using 0.5 % TFA in MeOH for measuring in the positive ionization mode and 0.5 % NH$_4$$^+$-acetate in MeOH for measuring in the negative ionization mode. If required, samples were filtered through a Spartan-Filter 13/0,45 RC into the 1 ml HPLC glass vials in order to separate from particulate material.

Method 1:

Waters 1525 binary pump and Shimadzu CTO-6A thermostat settings:

Solvent A: 60.0 % (0.01 M KH_2PO_4)[b]

Solvent B: 40.0 % (methanol)

Gradient

Time	Solv. B	Flow
0.01	40.0	1.400
0.25	40.0	
8.00	85.0	
13.00	85.0	
14.00	40.0	

Stop time: 18.0 min

Pressure Limits (psi)

Minimum pressure: 0

Maximum pressure: 4000

Column temperature: 35 ˚C

[b]Monobasic potassium phosphate solution 0.01 M (pH 2.3) was prepared by dissolving 1.361 g of monobasic potassium phosphate in 800 mL of water (bidest.), adjusting to pH 2.3 with 10% H_3PO_4 (v/v) and diluting to 1000 mL with water.

HPLC mobile phases (Fisher, HPLC grade, submicron filtered) were degassed by vacuum filtration through a Nylon Membrane Filter (Nyaflo®, 0.45 mm, 47 mm, P/N 66608) from Pall Life Sciences Inc. before usage. HPLC results are presented as retention times (min) and relative chemical purity (%). The Empower Pro software (Copyright® 2002, Waters Corporation) was used for the instrument control and data analysis.

Method 2:

Agilent 1200 binary pump and thermostat settings:

Solvent A: 95 % (water (0.1% TFA)

Solvent B: 5.0 % (Acetonitrile)

Gradient

Time	Solv. B	Flow
0.00	5.0	1.400
3.60	100.0	
4.00	100.0	
4.05	5.0	

Stop time: 4.20 min

Pressure Limits (bar)

Minimum pressure: 0

Maximum pressure: 400

Column temperature: 45 ˚C

Method 3 (for OVCAR-3 drug metabolism with selected compounds):
Waters Alliance 2695 HPLC System equipped with a Waters 2487 Dual λ Absorbance Detector
Column: Waters NovaPak C18 15x0.39
Waters 2695 binary binary pump and thermostat settings:
Solvent A: 50 % (water)*
Solvent B: 50 % (3:2 methanol/acetonitrile)*
*each with 0.1% HOAc

Gradient

Time	Solv. B	Flow
	50.0	0.80
0.50	50.0	
12.50	90.0	
14.00	90.0	
15.00	50.0	

Stop time: 20.00 min

Pressure Limits (psi)
Minimum pressure: 0
Maximum pressure: 4000
Column temperature: 35 ˚C

Synthetic procedures:
The synthetic procedures and analytical data of compounds **2**, **11a-o**, **12a-f**, **13a, b** and **14** have been published elsewhere.[1, 2]

General Methods:
General Procedure A. Alkylation of the indanone scaffolds with different ethyl alkanoates.[3]
In a 250 mL round bottom flask, flame-dried under argon, lithiumdiisopropylamine (2 M, 51.0 mmol) was placed in dry THF (50.0 mL) at -75 ˚C (acetone/dry ice). The appropriate ethyl alkanoate (50.0 mmol) was added and the mixture was stirred for 20 min, at which point 1-indanone (50.0 mmol) was added. The solution was stirred for 2 h at the low temperature. After warming the solution to 0 ˚C, HCl (3 M) was carefully added to quench the reaction. The organic layer was then washed twice with a saturated aqueous sodium chloride solution and was dried with magnesium sulfate. HPLC analysis (see Methods) indicated the formation of the product, but also remaining amounts of the starting indanone (depending on the reagents). The solvent was removed and the mixture was carried onto the next step without purification.

General Procedure B: Dehydration of the tertiary alcohols.
The crude (1-hydroxy-indan-1-yl)-acetic acid ethyl esters (3.0 g), p-TsOH•H_2O (4.8 g, 25.2 mmol), and $CaCl_2$•$2H_2O$ (3.49 g, 23.7 mmol) in toluene (66 mL) were refluxed overnight (Cave: foam formation!). The cold solutions were filtered through a glass frit (Por. 3 or 4) and the solid residues washed exhaustively with a little additional toluene. The combined organics were concentrated under reduced pressure and the residual oils either directly separated *via* column chromatography or washed with water, $NaHCO_3$, water, dried ($MgSO_4$), filtered and concentrated in vacuo prior to chromatography. Purification using 5+1 Hexane/EtOAC (silica gel) afforded the indene derivatives (isomer mixtures) as viscous masses, which consistently crystallized upon cooling on ice to give orange solids (yields: 30-60 % over two reaction steps). The pure products were stored at 4 ˚C.

General Procedure C: Knoevenagel condensation of the indene intermediates with different (hetero)arylmethyl aldehydes.

To a solution of the ethyl 2-(1H-inden-3-yl)alkanoate (1 equiv.) and the appropriate aldehyde (1.2 equiv.) in methanol (2.2 mL/0.5 mmol) was added 1 N NaOH (1.1 mL/0.5 mmol). The mixture was stirred at reflux (70 °C) for 2-3 h and then slowly brought back to RT. The suspension was further stirred overnight at RT, diluted with water, washed with diethylether (3 x 30 mL), neutralized with 50% acetic acid, and extracted with CH_2Cl_2 (3× 30 mL). The combined organics were optionally washed with water, $NaHCO_3$, water, dried ($MgSO_4$), filtered, and then concentrated in vacuo. All purifications were performed *via* preparative TLC, column chromatography or flash chromatography on SiO_2 using 0.5 % AcOH in ethylacetate/hexanes as mobile phase to afford typically amorphous, yellow solids.

General Procedure D: Aldol condensation reaction with alternative product workup via isolatable alkali metal salts or as stable ethyl esters.

Step 1: The 'aldol condensation reaction' between the individual reagents was accomplished as described in general procedure C (alike stoichiometry of the reacting agents and identical heating conditions). In comparison to the previously described method, the cold reaction mixtures were then further stirred for several days at ambient temperatures, whereupon the desired lipophilic products (quantitatively) precipitated directly from the alkaline liquor as fine yellow isolable sodium salts or stable ethyl ester derivatives, respectively (in the case of the *alpha*-dimethylated acetic acid derivatives). The particular solids were filtered off and the mud cakes carefully washed with cold water to afford analytically pure compounds, which were either evaluated themselves or continued processing in a second hydrolysis step to yield the corresponding free acid derivatives of the 2′-*des*-methyl sulindac sulfide analogs.

Step 2 (hydrolysis reaction): The 'sodium salts' of the respective 2′-*des*-methyl sulindac sulfide analogs from step 1 were dissolved in the required minimal amount of water (eventually with the aid of ultrasonic checking) and the aqueous mixtures were acidified under external ice cooling with 1.5 N HCl to pH 1-2. The formed suspensions were stirred for another 10-15 min at room temperature to quantity product conversion before collecting the fine-crystalline free acid derivatives by filtration. The products were dried at the vacuum exhauster and usually required no further purification.

General Procedure E: Suzuki-Miyaura Coupling reaction.[4]

A solution of the (E)-2-(1-(bromo(hetero)arylidene)-5-fluoro-1H-inden-3-yl)acetic acid **11i**, the respective (hetero)aryl boronic acid, Pd(Ph₃P)₄, and K_2CO_3 in DME/H_2O 2:1 was degassed with N_2, the vessel sealed, and heated to 85 °C overnight. The mixture was poured into water, acidified with 50% AcOH, extracted with EtOAc (2x), the organic layer dried ($MgSO_4$), and concentrated. Purification of the residue (silica gel; hexane/EtOAc gradient) provided the pure compound.

General Procedure F: Esterification of different 'free acid' derivatives of 2'-des-methyl sulindac sulfide.[5, 6]

Acidic starting compounds were suspended/dissolved in the appropriate alcohol (15 ml/mmol). After the addition of concentrated H_2SO_4 (ml/mmol) the reaction mixtures were heated to reflux for 5-6 h in a closed glass vial under argon and continuously stirred overnight at room temperature, whereupon the analytically pure ester derivatives precipitated from the liquor. The formed products were filtered off, washed with a little of the respective ice-cold alcohol and dried in high vacuum to afford the desired ester compounds in consistently high yields. Alternatively the mixtures were evaporated and the resulting solids washed with water prior to filtration.

General Procedures G for ester cleavage.[5, 7]

General Procedure G_variant1: The appropriate ester derivative was dissolved in tetrahydrofuran (THF) and two equivalents of LiOH were added as a 1 M aqueous solution. After stirring for 5h at ambient temperature, 2 mL diethyl ether and 2 mL H_2O per 0.1 mmol staring material were added. The aqueous phase was separated and acidified with 2 M HCl (pH 2-3). The acidic solution was extracted with 3 x 3 mL ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated.

General Procedure G_variant2: A yellow solution of the (ethyl) ester derivative (1 eqiv.) and potassium trimethylsilanoate (5 equiv., 90% techn. grade) in tetrahydrofuran (5 mL/mmol) was heated by microwave radiation (90-120 °C) for 10-15 min. The brownish reaction mixture was instantly cooled back to 25 °C and then concentrated in vacuo to remove the organic solvent. A solution of the residue in water (8 mL/mmol) was externally chilled (ice-bath), and adjusted to pH 1 by the addition of 1.5 N HCl. The resulting precipitate was collected by filtration, washed with water and dried to give the (crude) product, which was purified by flash chromatography. Alternatively, the aqueous layer was repeatedly extracted with ethyl actetate. The combined organic extracts were dried over Na_2SO_4 and the solvent removed at reduced pressure prior to column chromatography.

General Procedure H: Synthesis of sulfonimides via CDI carbodiimide coupling.[6, 8]

To an ice-cold mixture (0-5 °C) of the free acid derivative of the respective 2′-*des*-methyl sulindac sulfide analog in dry CH_2Cl_2 (2 mL/0.5 mmol) under argon, one equiv. of 1,1′-carbonyldiimidazole (CDI) was added. After the reaction mixtures were stirred for two hours at 0-5 °C, the appropriate (substituted) aryl or alkyl sulfonamide (1 equiv.) and diazabicyclo[5.4.0]undec-7-ene (DBU) (1 equiv.) were added. The mixtures were left stirring for another 4 to 6 hours at ambient temperature before they were quenched by the addition of glacial acetic acid (60 uL/0.5 mmol) and diluted with CH_2Cl_2 (1 mL/0.5 mmol). The organic layer was separated and washed with 10% NaH_2PO_4 buffer (pH 4) (2 x 2 mL) and water (3 x 2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude residues. Chromatographic purification was carried out on SiO_2 as stationary phase using hexane/ethyl acetate (2:1) as eluent mixture to afford the appropriate acyl sulfonimides.

General Procedure I: Carboxylic acid activation with oxalylchloride.[9]

Oxalyl chloride (1.2 eqiv.) was added dropwise to a solution of the respective free acid derivative of 2′-*des*-methyl sulindac sulfide in dry CH_2Cl_2 (20-25 mL/mmol) under argon at ambient temperature and the reaction mixture was stirred overnight. The completion of the reaction was monitored by TLC (SiO_2, EtOAc+hexane: 1+1 (0.5 % AcOH). The solvent was evaporated under reduced pressure and, if required, the crude product repeatedly washed with a little ice-cold hexane. Typically the crude material was directly applied to the following reaction step without further purification.

*General Procedure J: Preparation of alkyl-/arylsulfonimides from the indene acetic acid chlorides.*[10]

The reactive 'acid chloride derivative' and 1.5 equivalents of the respective (substituted) sulfonamide were dissolved in 1,2-DCE or CH_2Cl_2 (20 mL/mmol) under argon and constant stirring. Then, pyridine (1 equiv.) was added and the reaction aged overnight at 25 °C. The reaction mixture was washed with diluted $NaHCO_3$ and water and the organic layer was dried over Na_2SO_4, filtered, concentrated and chromatographed over silica gel using an EtOAc/hexane (0.5% AcOH)-gradient to afford the pure 'sulfonimide' compounds.
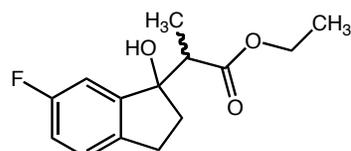
Synthesis of the tertiary alcohols 9:
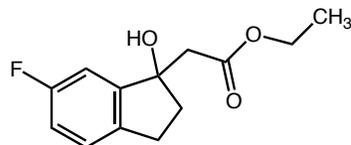
Ethyl 2-(6-fluoro-1-hydroxy-2,3-dihydro-1*H*-inden-1-yl)acetate (9a).
According to general procedure A, the title compound was obtained from ethylacetate (4.41 g, 50.0 mmol) and 6-fluoro-2,3-dihydro-1*H*-inden-1-one (7.51 g, 50.0 mmol) after 2 h at -75 ˚C. The crude product (oil) was used in the next reaction step without purification: $C_{13}H_{15}FO_3$, M_r = 238.26; HPLC (method 1) tR: 6.10 min.
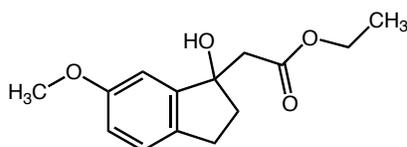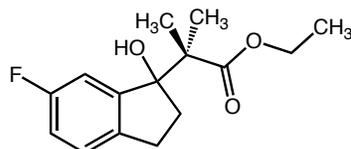

Ethyl 2-(1-hydroxy-6-methoxy-2,3-dihydro-1*H*-inden-1-yl)acetate (9b).[11]
According to general procedure A, the title compound was obtained from ethylacetate (2.73 g, 31.0 mmol) and 6-methoxy-2,3-dihydro-1*H*-inden-1-one (5.02 g, 31.0 mmol) after 2 h at -75 ˚C. The crude product (6.34 g, oil) was used in the next reaction step without purification: $C_{14}H_{18}O_4$, M_r = 250.29.

Ethyl 2-(6-fluoro-1-hydroxy-2,3-dihydro-1*H*-inden-1-yl)propanoate (9c).
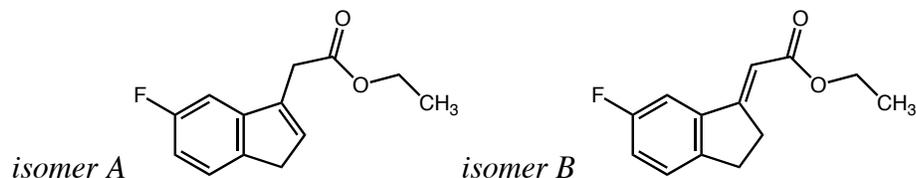According to general procedure A, the title compound was obtained from ethylpropionate (3.06 g, 30.0 mmol) and 6-fluoro-2,3-dihydro-1*H*-inden-1-one (4.50 g, 30.0 mmol) after 2 h at -75 ˚C. The crude product (8.05 g, oil) was used in the next reaction step without purification: $C_{14}H_{17}FO_3$, M_r = 252.29; HPLC (method 1) tR: 6.63 min and 7.14 min.

Ethyl 2-(6-fluoro-1-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-2-methylpropanoate (9d).
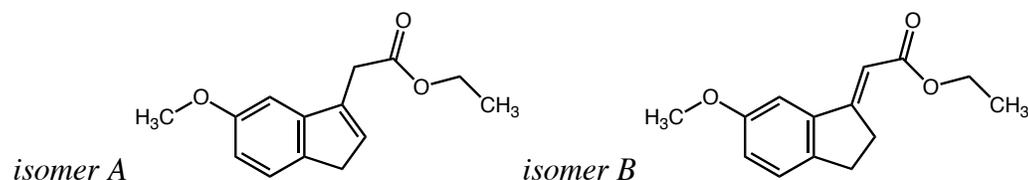According to general procedure A, the title compound was obtained from ethylisobutyrate (2.90 g, 25.0 mmol) and 6-fluoro-2,3-dihydro-1*H*-inden-1-one (3.75 g, 25.0 mmol) after 2 h at -75 ˚C. The crude product (5.4 g, oil) was used in the next reaction step without purification: $C_{15}H_{19}FO_3$, M_r = 266.13; HPLC (method 1) tR: 8.17 min.

Synthesis of the indene intermediates 10 (table S1):

*isomer A*   *isomer B*

Mixture of ethyl 2-(5-fluoro-1*H*-inden-3-yl)acetate (*isomer A*) and ethyl 2-(6-fluoro-2,3-dihydro-1*H*-inden-1-ylidene)acetate (*isomer B*) (10a).

According to general procedure B, the title compounds were formed from **9a** (3.0 g) after heating to reflux for 16 h. The crude product was purified by column chromatography (ethyl acetate/hexanes 1+5) to yield 1.84 g (66%) of **10a** (isomer mixture): $C_{13}H_{13}FO_2$, M_r = 220.25; *isomer A* (endocyclic DB): ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.18 (t, *J*=7.2 Hz, 3H), 3.36 (s, 2H), 3.63 (d, *J*=1.2 Hz, 2H), 4.09 (q, *J*=7.2 Hz, 2H), 6.48 (t, *J*=2.8 Hz, 1H), 6.99 (dt, *J*=2.4/8.8 Hz, 1H), 7.15 (dd, *J*=2.4/9.6 Hz, 1H), 7.42 (dd, *J*=5.0/8.2 Hz, 1H); *isomer B* (exocyclic DB): ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.24 (t, *J*=7.2 Hz, 3H), 2.99 (t, *J*=6.0 Hz, 2H), 3.19-3.22 (m, 2H), 4.14 (q, *J*=7.2 Hz, 2H), 6.55 (s, 1H), 7.22 (dt, *J*=2.4/8.8 Hz, 1H), 7.45 (dd, *J*=5.2 /8.0 Hz, 1H), 7.70 (dd, *J*=2.4/9.4 Hz, 1H); HPLC (method 1) *t*R: 8.12 min (*isomer A*) and *t*R: 9.44 min (*isomer B*); LCMS (ESI) (method 2) *t*R: 2.81 and 3.05 min (UV220, UV254), *m/z*: 221.2 [M+1]$^+$.

isomer A   *isomer B*

Mixture of ethyl 2-(5-methoxy-1*H*-inden-3-yl)acetate (*isomer A*) and ethyl 2-(6-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)acetate (*isomer B*) (10b).
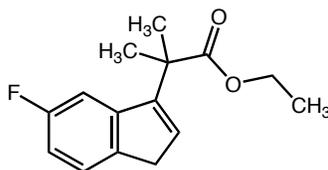
According to general procedure B, the title compounds were formed from **9b** (6.24 g) after heating to reflux for 16 h. The crude product was purified by column chromatography (ethyl acetate/hexanes 1+4) to yield 1.82 g (25%) of **10b** (isomer mixture): $C_{14}H_{16}O_3$, M_r = 232.28; *isomer A* (endocyclic DB): ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.18 (t, *J*=7.2 Hz, 3H), 3.28 (d, *J*=1.2 Hz, 2H), 3.60 (d, *J*=1.2 Hz, 2H), 4.10 (q, *J*=7.2 Hz, 2H), 6.45 (s, 1H), 6.76 (dd, *J*=2.4/8.0 Hz, 1H), 6.91 (d, *J*=2.4 Hz, 1H), 7.33 (d, *J*=8.0 Hz, 1H); *isomer B* (exocyclic DB): ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.24 (t, *J*=7.2 Hz, 3H), 2.94 (t, *J*=6.0 Hz, 2H), 3.16-3.20 (m, 2H), 3.77 (s, 3H), 4.13 (q, *J*=7.2 Hz, 2H), 6.45 (s, 1H), 6.98 (dd, *J*=2.4/8.4 Hz, 1H), 7.29 (d, *J*=8.0 Hz, 1H), 7.37 (d, *J*=2.4 Hz, 1H); HPLC (method 1) *t*R: 6.92 min (*isomer A*) and *t*R: 9.05 min (*isomer B*); LCMS (ESI) (method 2) *t*R: 2.71 and 2.98 min (UV220, UV254), *m/z*: 233.2 [M+1]$^+$.
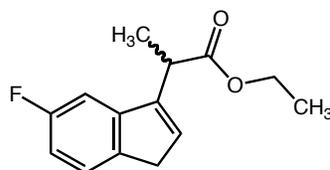
(*R/S*)-ethyl 2-(5-fluoro-1*H*-inden-3-yl)propanoate (10c).

According to general procedure B, the title compound was formed from **9c** (8.0 g) as a single product (endo-olefin) after heating to reflux for 16 h. The crude product was purified by column chromatography (ethyl acetate/hexanes 1+5) to yield 1.80 g (26%) of **10c** (isomer mixture): $C_{14}H_{15}FO_2$, M_r = 234.27; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.13 (t, *J*=7.0 Hz, 3H), 1.41 (d, *J*=6.8 Hz, 3H), 3.35 (d,

J=0.8 Hz, 2H), 3.84 (dq, J=1.1/7.2 Hz, 1H), 4.08 (dq, J=1.0/7.0 Hz, 2H), 6.52 (s, 1H), 7.00 (td, J=2.4/8.8 Hz, 1H), 7.18 (dd, J=2.4/9.6 Hz, 1H), 7.45 (dd, J=5.2/8.4 Hz, 1H); HPLC (method 1) tR: 8.92 min; LCMS (ESI) (method 2) tR: 3.00 min (UV220, UV254), m/z: 235.2 [M+1]$^+$.

Ethyl 2-(5-fluoro-1*H*-inden-3-yl)-2-methylpropanoate (10d).
According to general procedure B, the title compound was formed from **9d** (5.35 g) as a single product (endo-olefin) after heating to reflux for 16 h. The crude product was purified by column chromatography (ethyl acetate/hexanes 1+5) to yield 2.89 g (47%) of **10d** (isomer mixture): $C_{15}H_{17}FO_2$, M_r = 248.30; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.05 (t, J=7.2 Hz, 3H), 1.49 (s, 6H), 3.35 (s, 2H), 4.06 (q, J=7.2 Hz, 2H), 6.56 (t, J=2.0 Hz, 1H), 6.91 (dd, J=2.4/9.8 Hz, 1H), 6.99 (dtd, J=0.8/2.4/8.2 Hz, 1H), 7.46 (dd, J=5.2/8.0 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -115.43 (d, 1F, C5'-F); HPLC (method 1) tR: 9.30 min; LCMS (ESI) (method 2) tR: 3.13 min (UV220, UV254), m/z: 249.2 [M+1]$^+$.

Synthesis of 2′-*des*-methyl sulindac sulfide analogues 12g, 13c, d, 13 g-j & 17a-f (table 2):
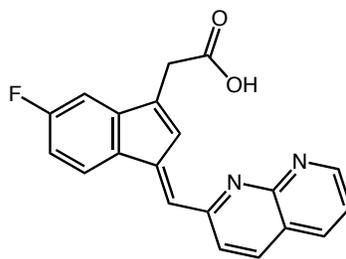
(*E*)-2-(1-((1,8-naphthyridin-2-yl)methylene)-5-fluoro-1*H*-inden-3-yl)acetic acid (12g).
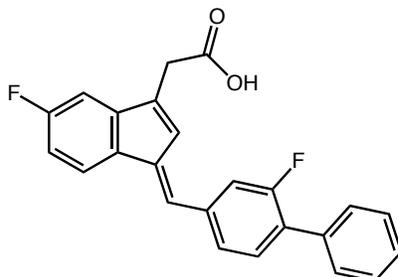According to general procedure C, the title compound was obtained from the isomer mixture **10a** (0.05 g, 0.23 mmol) and 1,8-naphthyridine-2-carbaldehyde (0.039 g, 0.25 mmol) after heating to 70 ˚C for 3 h and subsequent stirring at ambient temperature overnight. The crude product was purified by preparative thin-layer chromatography (SiO$_2$, EtOAc/hexane, 0.5% AcOH) to afford 19.5 mg (26%) of **12g**: $C_{20}H_{13}FN_2O_2$, M_r = 332.34; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.71 (s, 2H), 7.08 (td, J=2.4/9.2 Hz, 1H), 7.18 (dd, J=2.4/8.8 Hz, 1H), 7.64 (dd, J=4.0/8.0 Hz, 1H), 7.74 (s, 1H), 7.88-7.91 (m, 2H), 8.01 (s, 1H), 8.46 (dd, J=2.0/8.0 Hz, 1H), 8.53 (d, J=8.4 Hz, 1H), 9.12 (dd, J=2.0/4.4 Hz, 1H); HPLC (method 1) tR: 6.76 min (95%, UV347); LCMS (ESI) (method 2) tR: 1.74 min (>99%, ELSD), m/z: 333.2 [M+1]$^+$.
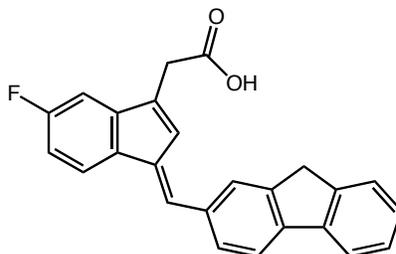
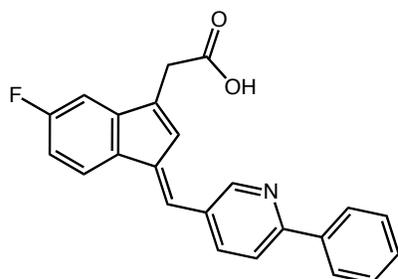**(*E*)-2-(1-((9*H*-fluoren-2-yl)methylene)-5-fluoro-1*H*-inden-3-yl)acetic acid (13c).**
According to general procedure C, the title compound was obtained from the isomer mixture **10a** (0.10 g, 0.45 mmol) and 9*H*-fluorene-2-carbaldehyde (0.097 g, 0.50 mmol) after heating to 65 ˚C for 3 h and

subsequent stirring at ambient temperature overnight. The crude product was purified by preparative thin-layer chromatography (SiO$_2$, EtOAc/hexane, 0.5% AcOH) to afford 45 mg (27%) of **13c**: C$_{25}$H$_{17}$FO$_2$, M$_r$ = 368.41; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.69 (s, 2H), 4.00 (s, 2H), 7.05 (td, J=2.4/8.4 Hz, 1H), 7.15 (dd, J=2.5/9.2 Hz, 1H), 7.22 (s, 1H), 7.32-7.42 (m, 2H), 7.61 (d, J=7.2 Hz, 1H), 7.70 (m, 2H), 7.82-7.87 (m, 1H), 7.93-8.00 (m, 3H); HPLC (method 1) tR: 11.95 min (95%, UV347); ESI/MS: calcd: 367, found: 367.20 ([M-1]$^+$, 35%), 323.27 ([M-1]$^+$-CO$_2$, 100%).
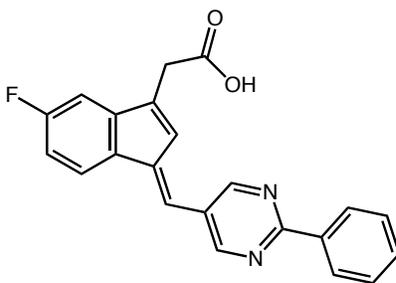

(*E*)-2-(5-fluoro-1-((2-fluorobiphenyl-4-yl)methylene)-1*H*-inden-3-yl)acetic acid (13d).
According to general procedure C, the title compound was obtained from the isomer mixture **10a** (0.05 g, 0.23 mmol) and 2-fluorobiphenyl-4-carbaldehyde (0.05 g, 0.25 mmol) after heating to 65 °C for 3 h and subsequent stirring at ambient temperature overnight. After acidification of the rxn mixture and repeated extraction with dichloro methane the organic layers were combined and concentrated *in vacuo*. The remaining yellow solid material revealed good analytical quality and required no further purification. Yield: 63 mg (74%): C$_{24}$H$_{16}$F$_2$O$_2$, M$_r$ = 374.39; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.70 (s, 2H), 7.08 (dtd, J=1.2/2.4/8.4 Hz, 1H), 7.16-7.19 (m, 2H), 7.41-7.45 (m, 1H), 7.49-7.53 (m, 2H), 7.58-7.67 (m, 6H), 7.84 (dd, J=5.2/8.0 Hz, 1H); HPLC (method 1) tR: 11.30 min (>99%, UV347); ESI/MS: calcd: 373, found: 373.13 ([M-1]$^+$, 22%), 329.27 ([M-1]$^+$-CO$_2$, 100%).
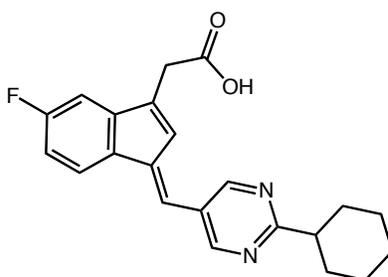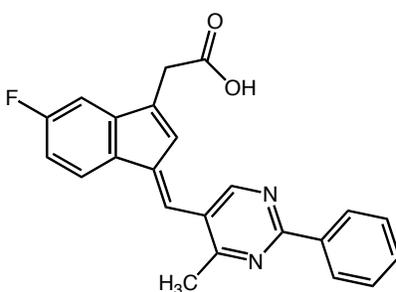

(*E*)-2-(5-fluoro-1-((6-phenylpyridin-3-yl)methylene)-1*H*-inden-3-yl)acetic acid (13g).
According to general procedure C, the title compound was obtained from the isomer mixture **10a** (0.05 g, 0.23 mmol) and 6-phenylnicotinaldehyde (0.046 g, 0.25 mmol) after heating to 65 °C for 3 h and subsequent stirring at ambient temperature overnight. The crude product was purified by preparative thin-layer chromatography (SiO$_2$, EtOAc/hexane, 0.5% AcOH) to afford 17.5 mg (22%) of **13g**: C$_{23}$H$_{16}$FNO$_2$, M$_r$ = 357.39; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.70 (s, 2H), 7.09 (td, J=2.4/8.4 Hz, 1H), 7.17 (s, 1H), 7.19 (d, J=2.4 Hz, 1H), 7.45-7.55 (m, 4H), 7.67 (s, 1H), 7.87 (dd, J=5.2/8.4 Hz, 1H), 8.09 (d, J=8.4 Hz, 1H), 8.15-8.20 (m, 3H), 8.92 (d, J=2.0 Hz, 1H); HPLC (method 1) tR: 9.62 min (95%, UV347); ESI/MS: calcd: 356, found: 356.13 ([M-1]$^+$, 35%), 312.27 ([M-1]$^+$-CO$_2$, 100%).

(*E*)-2-(5-fluoro-1-((2-phenylpyrimidin-5-yl)methylene)-1*H*-inden-3-yl)acetic acid (13h).
According to general procedure C, the title compound was obtained from the isomer mixture **10a** (0.10 g, 0.47 mmol) and 2-phenylpyrimidine-5-carbaldehyde (0.095 g, 0.52 mmol) after heating to 65 ˚C for 2 h and subsequent stirring at ambient temperature overnight. The crude product was purified by preparative thin-layer chromatography (SiO$_2$, EtOAc/hexane, 0.5% AcOH) to afford 39 mg (24%) of **13h**: C$_{22}$H$_{15}$FN$_2$O$_2$, M$_r$ = 358.38; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 3.70 (s, 2H), 7.10 (td, *J*=2.4/9.2 Hz, 1H), 7.17-7.20 (m, 2H), 7.55-7.58 (m, 3H), 7.64 (s, 1H), 7.86 (dd, *J*=5.2/8.2, 1H), 8.43-8.47 (m, 2H), 9.16 (s, 2H); HPLC (method 1) *t*R: 9.84 min (97%, UV347); ESI/MS: calcd: 357, found: 357.13 ([M-1]$^+$, 37%), 313.27 ([M-1]$^+$-CO$_2$, 100%).

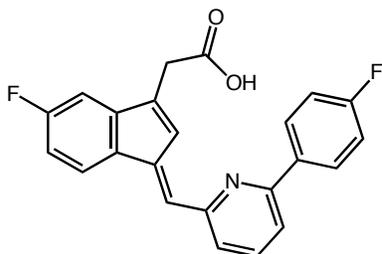**(*E*)-2-(1-((2-cyclohexylpyrimidin-5-yl)methylene)-5-fluoro-1*H*-inden-3-yl)acetic acid (13i).**
According to general procedure C, the title compound was obtained from the isomer mixture **10a** (0.05 g, 0.23 mmol) and 2-cyclohexylpyrimidine-5-carbaldehyde (0.048 g, 0.25 mmol) after heating to 65 ˚C for 3 h and subsequent stirring at ambient temperature overnight. The crude product was purified by preparative thin-layer chromatography (SiO$_2$, EtOAc/hexane, 0.5% AcOH) to afford 32 mg (39%) of **13h**: C$_{22}$H$_{21}$FN$_2$O$_2$, M$_r$ = 364.42; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 1.23-1.99 (m, 10H), 2.86 (tt, *J*=3.6/11.6 Hz, 1H), 3.68 (s, 2H), 7.06-7.11 (m, 2H), 7.17 (dd, *J*=2.4/9.2 Hz, 1H), 7.57 (s, 1H), 7.83 (dd, *J*=5.2/8.4 Hz, 1H), 8.97 (s, 2H); HPLC (method 1) *t*R: 9.89 min (98%, UV347); ESI/MS: calcd: 363, found: 363.20 ([M-1]$^+$, 44%), 319.33 ([M-1]$^+$-CO$_2$, 100%).

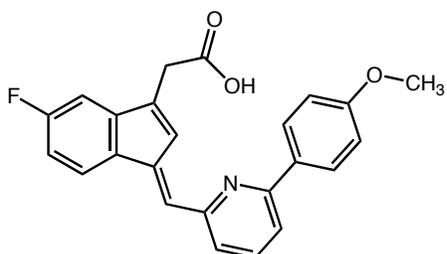**(*E*)-2-(5-fluoro-1-((4-methyl-2-phenylpyrimidin-5-yl)methylene)-1*H*-inden-3-yl)acetic acid (13j).**
According to general procedure C, the title compound was obtained from the isomer mixture **10a** (0.05 g, 0.23 mmol) and 4-methyl-2-phenylpyrimidine-5-carbaldehyde (0.050 g, 0.25 mmol) after heating to 70 ˚C for 3 h and subsequent stirring at ambient temperature overnight. The crude product was purified by preparative thin-layer chromatography (SiO$_2$, EtOAc/hexane, 0.5% AcOH) to afford 43 mg (51%) of **13h**: C$_{23}$H$_{17}$FN$_2$O$_2$, M$_r$ = 372.40; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 2.69 (s, 3H), 3.67 (s, 2H), 6.87 (s,

1H), 7.11 (td, *J*=2.4/8.4 Hz, 1H), 7.18 (dd, *J*=2.4/9.2 Hz, 1H), 7.54-7.56 (m, 3H), 7.75 (s, 1H), 7.98 (dd, *J*=5.2/8.4 Hz, 1H), 8.44-8.47 (m, 2H), 8.82 (s, 1H); HPLC (method 1) *t*R: 10.16 min (97%, UV347); LCMS (ESI) (method 2) *t*R: 2.95 min (97%, ELSD), *m/z*: 373.2 [M+1]$^+$.
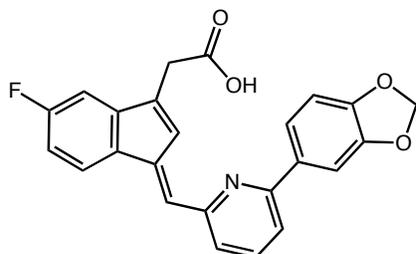

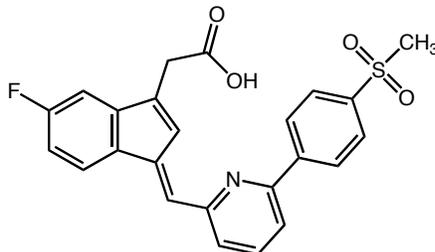**(*E*)-2-(5-fluoro-1-((6-(4-fluorophenyl)pyridin-2-yl)methylene)-1*H*-inden-3-yl)acetic acid (17a).**
According to general procedure C, the title compound was obtained from the isomer mixture **10a** (0.05 g, 0.23 mmol) and 6-(4-fluorophenyl)picolinaldehyde (0.050 g, 0.25 mmol) after heating to 70 ˚C for 3 h and subsequent stirring at ambient temperature overnight. The crude product was purified by preparative thin-layer chromatography (SiO$_2$, EtOAc/hexane, 0.5% AcOH) to afford 17 mg (20%) of **17a**: C$_{23}$H$_{15}$F$_2$NO$_2$, M$_r$ = 375.38; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 3.70 (s, 2H), 7.06 (td, *J*=2.4/8.4 Hz, 1H), 7.15 (dd, *J*=2.4/9.2 Hz, 1H), 7.36-7.41 (m, 2H), 7.58 (s, 1H), 7.61 (dd, *J*=1.2/7.4 Hz, 1H), 7.84-7.86 (m, 1H), 7.91-7.98 (m, 3H), 8.20-8.24 (m, 2H); HPLC (method 1) *t*R: 10.26 min (97%, UV347); LCMS (ESI) (method 2) *t*R: 2.98 min (95%, ELSD), *m/z*: 376.2 [M+1]$^+$.

(*E*)-2-(5-fluoro-1-((6-(4-methoxyphenyl)pyridin-2-yl)methylene)-1*H*-inden-3-yl)acetic acid (17b).
According to general procedure C, the title compound was obtained from the isomer mixture **10a** (0.05 g, 0.23 mmol) and 6-(4-methoxyphenyl)picolinaldehyde (0.053 g, 0.25 mmol) after heating to 70 ˚C for 3 h and subsequent stirring at ambient temperature overnight. The crude product was purified by preparative thin-layer chromatography (SiO$_2$, EtOAc/hexane, 0.5% AcOH) to afford 13 mg (15%) of **17b**: C$_{24}$H$_{18}$FNO$_3$, M$_r$ = 387.41; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 3.69 (s, 2H), 3.84 (s, 3H), 7.05 (td, *J*=2.4/8.4 Hz, 1H), 7.10-7.13 (m, 2H), 7.16 (dd, *J*=2.4/9.4 Hz, 1H), 7.53-7.55 (m, 2H), 7.83-7.92 (m, 3H), 7.97 (s, 1H), 8.11-8.14 (m, 2H); HPLC (method 1) *t*R: 10.17 min (93%, UV347); ESI/MS: calcd: 386, found: 386.13 ([M-1]$^+$, 17%), 342.27 ([M-1]$^+$-CO$_2$, 100%).

(*E*)-2-(1-((6-(benzo[*d*][1,3]dioxol-5-yl)pyridin-2-yl)methylene)-5-fluoro-1*H*-inden-3-yl)acetic acid (17c).
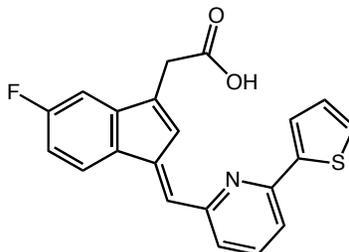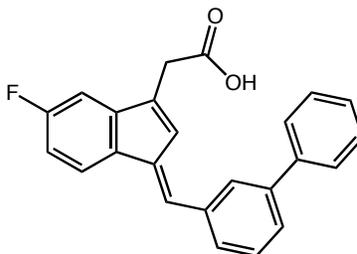According to general procedure C, the title compound was obtained from the isomer mixture **10a** (0.05 g, 0.23 mmol) and 6-(benzo[*d*][1,3]dioxol-5-yl)picolinaldehyde (0.057 g, 0.25 mmol) after heating to 70

°C for 3 h and subsequent stirring at ambient temperature overnight. The crude product was purified by preparative thin-layer chromatography (SiO$_2$, EtOAc/hexane, 0.5% AcOH) to afford 23 mg (25%) of **17c**: C$_{24}$H$_{16}$FNO$_4$, M$_r$ = 401.40; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.68 (s, 2H), 6.11 (s, 2H), 7.03-7.09 (m, 2H), 7.17 (dd, J=2.4/9.2 Hz, 1H), 7.55-7.57 (m, 2H), 7.69 (d, J=1.6 Hz, 1H), 7.73 (dd, J=1.6/8.2 Hz, 1H), 7.84-7.93 (m, 4H); HPLC (method 1) tR: 10.15 min, (~70%, UV347); LCMS (ESI) (method 2) tR: 2.80 min (>99%, ELSD), m/z: 402.2 [M+1]$^+$.

(E)-2-(5-fluoro-1-((6-(4-(methylsulfonyl)phenyl)pyridin-2-yl)methylene)-1H-inden-3-yl)acetic acid (17d).

According to general procedure C, the title compound was obtained from the isomer mixture **10a** (0.05 g, 0.23 mmol) and 6-(4-(methylsulfonyl)phenyl)picolinaldehyde (0.065 g, 0.25 mmol) after heating to 70 °C for 3 h and subsequent stirring at ambient temperature overnight. The crude product was thoroughly washed with methanol to afford 25 mg (25%) of analytically pure **17d**: C$_{24}$H$_{18}$FNO$_4$S, M$_r$ = 435.48; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.29 (s, 3H), 3.72 (s, 2H), 7.07 (td, J=2.4/8.4 Hz, 1H), 7.17 (dd, J=2.4/9.0 Hz, 1H), 7.61 (s, 1H), 7.70 (dd, J=1.6/6.8 Hz, 1H), 7.86 (dd, J=5.2/8.4 Hz, 1H), 7.99-8.08 (m, 3H), 8.12 (d, J=8.4 Hz, 2H), 8.43 (d, J=8.8 Hz, 2H); HPLC (method 1) tR: 8.76 min (93%, UV347); LCMS (ESI) (method 2) tR: 2.64 min (>99%, ELSD), m/z: 436.0 [M+1]$^+$.

(E)-2-(5-fluoro-1-((6-(thiophen-2-yl)pyridin-2-yl)methylene)-1H-inden-3-yl)acetic acid (17e).
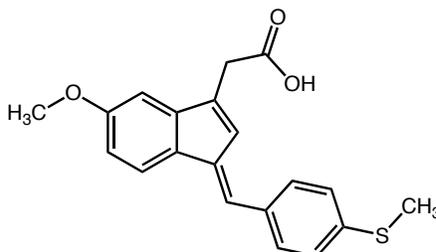
According to general procedure C, the title compound was obtained from the isomer mixture **10a** (0.05 g, 0.23 mmol) and 6-(thiophen-2-yl)picolinaldehyde (0.047 g, 0.25 mmol) after heating to 70 °C for 3 h and subsequent stirring at ambient temperature overnight. The crude product was purified by preparative thin-layer chromatography (SiO$_2$, EtOAc/hexane, 0.5% AcOH) to afford 29 mg (35%) of **17e**: C$_{21}$H$_{14}$FNO$_2$S, M$_r$ = 363.41; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.67 (s, 2H), 7.06 (td, J=2.4/8.4 Hz, 1H), 7.17 (dd, J=2.4/9.2 Hz, 1H), 7.21 (dd, J=3.6/5.0 Hz, 1H), 7.50-7.52 (m, 2H), 7.69 (dd, J=1.2/5.0 Hz, 1H), 7.82-7.94 (m, 4H), 7.99 (s, 1H); HPLC (method 1) tR: 9.88 min (98%, UV347); LCMS (ESI) (method 2) tR: 2.92 min (>99%, ELSD), m/z: 364.0 [M+1]$^+$.

(*E*)-2-(1-([1,1′-biphenyl]-3-ylmethylene)-5-fluoro-1*H*-inden-3-yl)acetic acid (17f).

According to general procedure C, the title compound was obtained from the isomer mixture **10a** (0.05 g, 0.23 mmol) and [1,1′-biphenyl]-3-carbaldehyde (0.046 g, 0.25 mmol) after heating to 70 ˚C for 3 h and subsequent stirring at ambient temperature overnight. The crude product was chromatographed over a silica gel column, (EtOAc/hexane=1+1 (0.5% AcOH as eluent mixture), however the title compound could not be afforded with the required purity. $C_{24}H_{17}FO_2$, M_r = 356.39; LCMS (ESI) (method 2) tR: 3.17 min (ELSD), *m/z*: 357.2 [M+1]$^+$.

Synthesis of 2′-*des*-methyl sulindac sulfide analogue 15a (table S3):

(*E*)-2-(5-methoxy-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)acetic acid (15a).

According to general procedure C, the title compound was obtained from the isomer mixture **10b** (0.050 g, 0.22 mmol) and 4-(methylthio)benzaldehyde (0.036 g, 0.24 mmol) after heating to 70 ˚C for 3 h and subsequent stirring at ambient temperature overnight. The crude product was washed with a 1:1 mixture of DCM and hexane and then recrystallized from little methanol to give 22 mg (27%) of a pure yellow solid: $C_{20}H_{18}O_3S$, M_r = 338.42; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.51 (s, 3H), 3.54 (s, 2H), 3.78 (s, 3H), 6.77 (dd, *J*=2.4/8.2 Hz, 1H), 6.91 (d, *J*=2.4 Hz, 1H), 6.96 (s, 1H), 7.32 (d, *J*=8.4 Hz, 2H), 7.38 (s, 1H), 7.58 (d, *J*=8.4 Hz, 2H), 7.67 (d, *J*=8.4 Hz, 1H); LCMS (ESI) (method 2) tR: 2.87 min (95%, UV254; >99%, ELSD), *m/z*: 339.2 [M+1]$^+$.

Synthesis of 2′-*des*-methyl sulindac sulfide analogues (sodium salts) 13a(Na), 13b(Na), 15b(Na) & 15c(Na) (table S2):
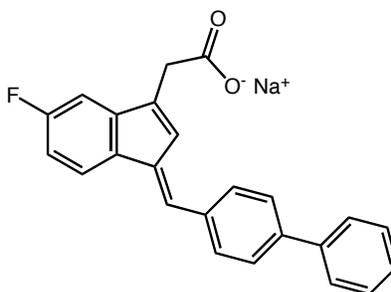
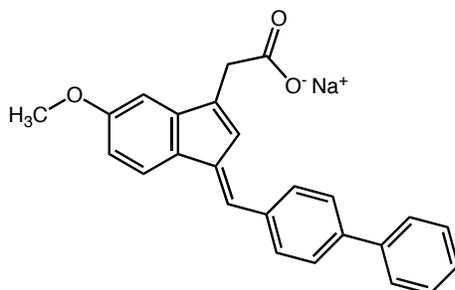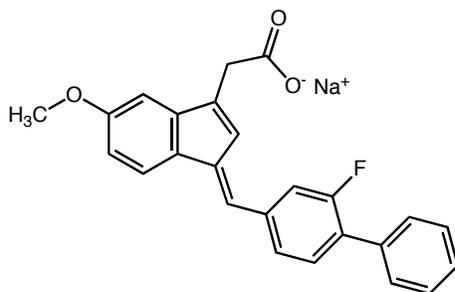**sodium (*E*)-2-(1-([1,1′-biphenyl]-4-ylmethylene)-5-fluoro-1*H*-inden-3-yl)acetate (13a(Na)).**

The title compound was prepared by the aldol condensation reaction specified in general procedure D (step 1) from the isomer mixture **10b** (0.10 g, 0.45 mmol) and commercially available [1,1′-biphenyl]-4-

carbaldehyde (0.091 g, 0.50 mmol). After stirring for 72 h at room temperature the accumulated product precipitate was filtered off and washed with little ice-cold methanol. The title compound was obtained as yellow solid (Na-salt) in 67 % yield (115 mg): $C_{24}H_{16}FNaO_2$, M_r = 378.37; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.25 (s, 2H), 6.95-7.00 (m, 2H), 7.20 (dd, J=2.4/9.6 Hz, 1H), 7.38 (tt, J=1.2/9.6 Hz, 1H), 7.47-7.50 (m, 3H), 7.73-7.79 (m, 7H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -113.78 (t, 1F, C5′-F), LCMS (ESI) (method 2) tR: 2.95 min (96%, ELSD), m/z: 375.2 [M+1]$^+$ (undissociated acid).
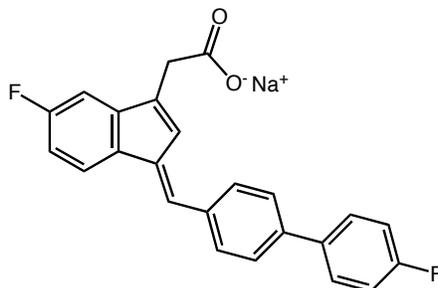
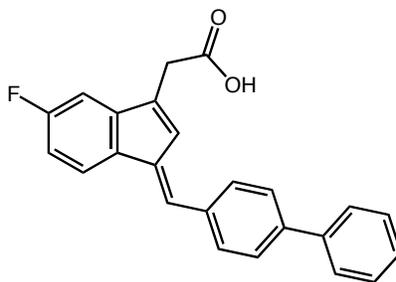**sodium (*E*)-2-(5-fluoro-1-((4′-fluoro-[1,1′-biphenyl]-4-yl)methylene)-1*H*-inden-3-yl)acetate (13e(Na)).**

The title compound was prepared by the aldol condensation reaction specified in general procedure D (step 1) from the isomer mixture **10a** (0.05 g, 0.23 mmol) and commercially available 4′-fluoro-[1,1′-biphenyl]-4-carbaldehyde (0.050 g, 0.25 mmol). After stirring for 72 h at room temperature the accumulated product precipitate was filtered off and washed with little ice-cold methanol. The title compound was obtained as yellow solid (Na-salt) in 71 % yield (64 mg): $C_{24}H_{15}F_2NaO_2$, M_r = 396.36; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.24 (s, 2H), 6.94-7.00 (m, 2H), 7.20 (dd, J=2.4/9.6 Hz, 1H), 7.29-7.33 (m, 2H), 7.47 (s, 1H), 7.74-7.80 (m, 7H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -113.81 (t, 1F, C5′-F), -113.16 (s, 1F, 4′-fluoro-biphenyl).

sodium (*E*)-2-(1-([1,1′-biphenyl]-4-ylmethylene)-5-methoxy-1*H*-inden-3-yl)acetate (15b(Na)).
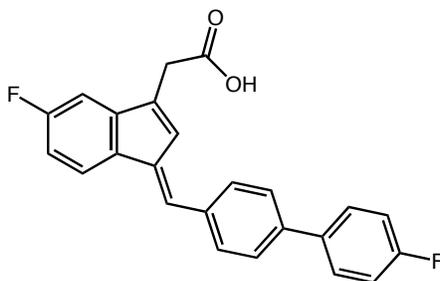
The title compound was prepared by the aldol condensation reaction specified in general procedure D (step 1) from the isomer mixture **10b** (0.050 g, 0.22 mmol) and commercially available [1,1′-biphenyl]-4-carbaldehyde (0.043 g, 0.24 mmol). After stirring for 72 h at room temperature the accumulated product precipitate was filtered off and washed first with little ice-cold methanol and then with diethylether. The title compound was obtained as yellow solid (Na-salt) in 37 % yield (31.5 mg): $C_{25}H_{19}NaO_3$, M_r = 390.41; ^1H NMR (300 MHz, DMSO-d_6) δ: 3.23 (s, 2H), 3.79 (s, 3H), 6.74 (dd, J=2.22/8.22 Hz, 1H), 6.89 (s, 1H), 6.99 (d, J=2.22 Hz, 1H), 7.34-7.41 (m, 2H), 7.47-7.52 (m, 2H), 7.65 (d, J=8.22 Hz, 1H), 7.73-7.79 (m, 6H).

sodium (*E*)-2-(1-((2-fluoro-[1,1′-biphenyl]-4-yl)methylene)-5-methoxy-1*H*-inden-3-yl)acetate (15c(Na)).

The title compound was prepared by the aldol condensation reaction specified in general procedure D (step 1) from the isomer mixture **10b** (0.050 g, 0.22 mmol) and commercially available 2-fluoro-[1,1′-biphenyl]-4-carbaldehyde (0.047 g, 0.24 mmol). After stirring for 72 h at room temperature the accumulated product precipitate was filtered off and first washed with little ice-cold methanol and then with diethylether. The title compound was obtained as yellow solid (Na-salt) in 18 % yield (16 mg): $C_{25}H_{18}FNaO_3$, M_r = 408.40; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.24 (s, 2H), 3.79 (s, 3H), 6.74 (dd, *J*=2.2/8.2 Hz, 1H), 6.86 (s, 1H), 6.98 (d, *J*=2.4 Hz, 1H), 7.32 (s, 1H), 7.40-7.65 (m, 9H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -116.41 (q, 1F, biphenyl).

Synthesis of 2′-*des*-methyl sulindac sulfide analogues (free acids) 13a, 13e & 15b (tabl. 1, 2 & S3):

(*E*)-2-(1-([1,1′-biphenyl]-4-ylmethylene)-5-fluoro-1*H*-inden-3-yl)acetic acid (13a).

The title compound was prepared according to general procedure D (step 2) using 200 μL 1.5 N HCl starting from **13a(Na)** (0.030 g, 0.079 mmol) in 1 mL H_2O. Yield: 25.5 mg (90%): $C_{24}H_{17}FO_2$, M_r = 356.39; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.69 (s, 2H), 7.07 (td, *J*=2.4/9.2 Hz, 1H), 7.15-7.18 (m, 2H), 7.39 (tt, *J*=1.2/2.0/7.6 Hz, 1H), 7.49 (td, *J*=2.0/7.1 Hz, 2H), 7.68 (s, 1H), 7.73-7.81 (m, 6H), 7.86 (dd, *J*=5.2/8.4 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -113.14 (d, 1F, C5′-F); LCMS (ESI) (method 2) *t*R: 3.17 min (>99%, ELSD), *m/z*: 358.2 [M+1]+.

(*E*)-2-(5-fluoro-1-((4′-fluoro-[1,1′-biphenyl]-4-yl)methylene)-1*H*-inden-3-yl)acetic acid (13e).

The title compound was prepared according to general procedure D (step 2) using 200 μL 1.5 N HCl starting from **13e(Na)** (0.030 g, 0.076 mmol) in 1 mL H_2O. Yield: 26 mg (92%): $C_{24}H_{16}F_2O_2$, M_r =

374.38; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.66 (s, 2H, -CH$_2$-), 7.06 (td, J=2.4/8.9 Hz, 1H), 7.15-7.18 (m, 2H), 7.32 (t, J=8.8 Hz, 2H, ar-H biphenyl), 7.66 (s, 1H), 7.50-7.81 (m, 6H), 7.85 (dd, J=5.2/8.2 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -113.15 (1F, C4′-F biphenyl), -112.97 (1F, C[5]-F); LCMS (ESI) (method 2) tR: 3.20 min (>99%, ELSD), m/z: 375.2 [M+1]$^+$.
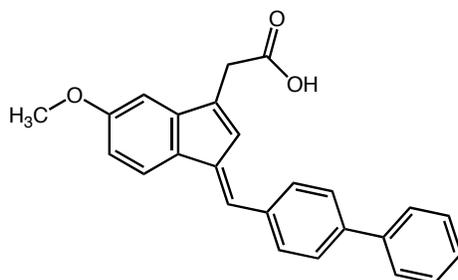
(E)-2-(1-([1,1′-biphenyl]-4-ylmethylene)-5-methoxy-1H-inden-3-yl)acetic acid (15b).
The title compound was prepared according to general procedure D (step 2) using 200 μL 1.5 N HCl starting from **15b(Na)** (0.016 g, 0.041 mmol) in 1 mL H$_2$O. Yield: 13 mg (86%): C$_{25}$H$_{20}$O$_3$, M$_r$ = 368.42; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.64 (s, 2H), 3.80 (s, 3H), 6.81 (dd, J=2.4/8.2 Hz, 1H), 6.92 (d, J=2.0 Hz, 1H), 7.05 (s, 1H), 7.39 (tt, J=0.8/2.0/7.2 Hz, 1H), 7.47-7.51 (m, 3H), 7.72-7.79 (m, 7H); LCMS (ESI) (method 2) tR: 3.14 min (≥95%, ELSD), m/z: 369.2 [M+1]$^+$.

Synthesis of 2′-*des*-methyl sulindac sulfide analogues 13f & 13k (table 2):
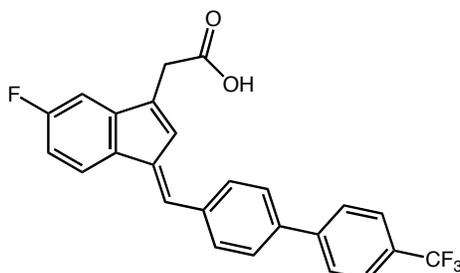
**(E)-2-(5-fluoro-1-((4′-(trifluoromethyl)-[1,1′-biphenyl]-4-yl)methylene)-1H-inden-3-yl)acetic acid (13f).**
According to general procedure E, the title compound was obtained from (E)-2-(1-(4-bromobenzylidene)-5-fluoro-1H-inden-3-yl)acetic acid **11i** (0.050 g, 0.14 mmol) and (4-(trifluoromethyl)phenyl)boronic acid (0.032 g, 0.17 mmol) after 14 h at 90 °C. The crude product (0.035 g, yellow precipitate) could be acceptably purified by multiple elutriating with hexanes. Yield: 24 mg (41%), bright yellow solid: C$_{25}$H$_{16}$F$_4$O$_2$, M$_r$ = 424.39; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.69 (s, 2H), 7.07 (td, J=2.4/8.4 Hz. 1H), 7.16-7.18 (m, 2H), 7.70 (s, 1H), 7.80-7.89 (m, 7H), 7.97 (d, J=8.0 Hz, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -112.94 (d, 1F, C5′-F), -59.06 (s, 3F, -CF$_3$); HPLC (method 1) tR: 11.97 min; LCMS (ESI) (method 2) tR: 3.10 min (≥95%, ELSD), m/z: 425 [M+1]$^+$.
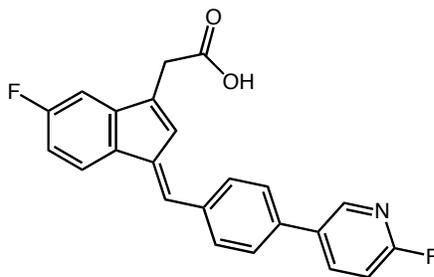
(*E*)-2-(5-fluoro-1-(4-(6-fluoropyridin-3-yl)benzylidene)-1*H*-inden-3-yl)acetic acid (13k).
According to general procedure E, the title compound was obtained from (*E*)-2-(1-(4-bromobenzylidene)-5-fluoro-1*H*-inden-3-yl)acetic acid **11i** (0.50 g, 0.14 mmol) and 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.037 g, 0.17 mmol) after 14 h at 90 ˚C. The crude product was purified by recrystallization from MeOH/hexanes. Yield: 25 mg (48%), bright yellow solid: $C_{23}H_{15}F_2NO_2$, M_r = 375.37; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.69 (s, 2H), 7.07 (td, *J*=(1.2)2.4/8.8 Hz, 1H), 7.15-7.18 (m, 2H), 7.31 (dd, *J*=2.8/8.8 Hz, 1H), 7.69 (s, 1H), 7.79-7.88 (m, 5H), 8.36 (td, *J*=2.8/8.2 Hz, 1H), 8.63 (d, *J*=2.8 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -112.96 (d, 1F, C5′-F), -68.78 (d, 1F, Pyr-F); HPLC (method 1) *t*R: 9.75 min; LCMS (ESI) (method 2) *t*R: 2.70 min (≥95%, ELSD), *m/z*: 376.0 [M+1]$^+$.

Synthesis of different ester derivatives 16a-e of 2′-*des*-methyl sulindac sulfide (table 3):
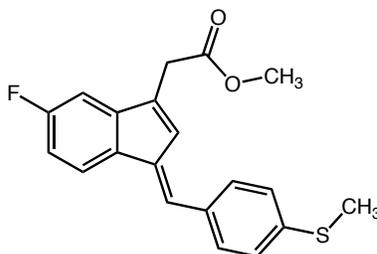
(*E*)-methyl 2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)acetate (16a).
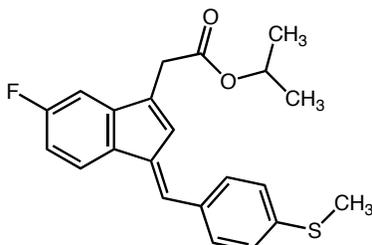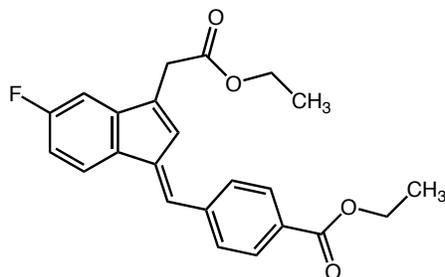According to general procedure F, (*E*)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)acetic acid **2** (100 mg, 0.31 mmol) was subjected to reaction with ethanol (5 mL) to afford **16a** as fluffy yellow solid. Yield: 96 mg (92%). $C_{20}H_{17}FO_2S$, M_r = 340.41; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.52 (s, 3H), 3.64 (s, 2H), 3.79 (s, 3H), 7.05 (td, *J*=2.4/8.9 Hz, 1H), 7.14-7.17 (m, 2H), 7.35 (d, *J*=8.4 Hz, 2H), 7.60-7.64 (m, 3H), 7.83 (dd, *J*=5.2/8.4 Hz, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 14.65 (s, -SCH$_3$), 33.33 (s, -CH$_2$-), 52.24 (s, -OCH$_3$), 107.03 (d, *J*=24.0 Hz, C4′), 112.10 (d, *J*=23.0 Hz, C6′), 121.04 (d, *J*=9.0 Hz, C7′), 126.23 (s, phenyl), 129. 18 (s), 130.93 (s, phenyl), 133.01 (s), 134.23 (s), 136.44 (s), 139.83 (d, *J*=2.0 Hz), 140.25 (s), 143.31 (d, *J*=9.0 Hz, C3a′), 162.52 (d, *J*=240.0 Hz, C5′), 170.92 (s, >C=O); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -113.30 (1F, C5′-F); LCMS (ESI) 3.34 min (>99%, ELSD), *m/z*: 341.2 [M+1]$^+$.
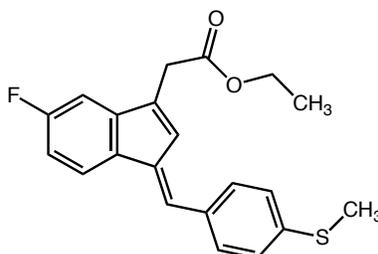

(*E*)-ethyl 2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)acetate (16b).
According to general procedure F, (*E*)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)acetic acid **2** (200 mg, 0.61 mmol) was subjected to reaction with ethanol (10 mL) to afford **16b** as fluffy

yellow solid. Yield: 202 mg (93%). C$_{21}$H$_{19}$FO$_2$S, M$_r$ = 354.44; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.19 (t, J=7.0 Hz, 3H), 2.52 (s, 3H), 3.76 (s, 2H), 4.11 (q, J=7.0 Hz, 2H), 7.05 (td, J=2.4/9.0 Hz, 1H), 7.14-7.17 (m, 2H), 7.35 (d, J=8.8 Hz, 2H), 7.60-7.64 (m, 3H), 7.83 (dd, J=5.0/8.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.47 (s, -CH$_3$), 14.65 (s, -SCH$_3$), 33. 61 (s, -CH$_2$-), 60.84 (s, -O-CH$_2$-), 107.05 (d, J=24.0 Hz), 112.09 (d, J=23.0 Hz), 121.03 (d, J=9.0 Hz), 126.13 (s), 126.23 (s), 129.13 (s), 130.92 (s), 133.02 (s), 134.26 (s), 136.46 (s), 139.93 (s), 140.24 (s), 143.32 (d, J=9.0 Hz), 162.48 (d, J=238.0 Hz), 170.41 (s); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -113.32 (1F, C5′-F); LCMS (ESI) 3.50 min (>99%, ELSD), m/z: 355.2 [M+1]$^+$.

(E)-isopropyl 2-(5-fluoro-1-(4-(methylthio)benzylidene)-1H-inden-3-yl)acetate (16c).
According to general procedure F, (E)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1H-inden-3-yl)acetic acid **2** (100 mg, 0.31 mmol) was subjected to reaction with 2-propanol (5 mL) to afford **16c** as fluffy yellow solid. Yield: 118 mg (100%). C$_{22}$H$_{21}$FO$_2$S, M$_r$ = 368.46; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 400 MHz: 1.19 (d, J=6.4 Hz, 6H), 2.52 (s, 3H), 3.72 (s, 2H), 4.94 (sept, J=6.4 Hz, 1H), 7.05 (td, J=(1.2)2.4/8.9 Hz, 1H), 7.13-7.15 (m, 2H), 7.35 (d, J=8.4 Hz, 2H), 7.59-7.64 (m, 3H), 7.83 (dd, J=5.2/8.4 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -113.39 (1F, C5′-F); LCMS (ESI) 3.60 min (>99%, ELSD), m/z: 369.2 [M+1]$^+$.

**(E)-ethyl 4-((3-(2-ethoxy-2-oxoethyl)-5-fluoro-1H-inden-1-ylidene)methyl)benzoate (16d).**
According to general procedure F, (E)-4-((3-(carboxymethyl)-5-fluoro-1H-inden-1-ylidene)methyl) benzoic acid **11n** (100 mg, 0.31 mmol) was subjected to reaction with ethanol (5 mL) to afford **16d** as yellow solid. Yield: 55 mg (47%). C$_{23}$H$_{21}$FO$_4$, M$_r$ = 380.41; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.19 (t, J=7.2 Hz, 3H), 1.33 (t, J=7.0 Hz, 3H), 3.77 (s, 2H), 4.11 (q, J=7.1 Hz, 2H), 4.33 (q, J=7.1 Hz, 2H), 7.06-7.11 (m, 2H), 7.17 (dd, J=2.4/9.2 Hz, 1H), 7.71 (s, 1H), 7.79 (d, J=8.0 Hz, 2H), 7.87 (dd, J=5.2/8.4 Hz, 1H), 8.03 (d, J=8.4 Hz, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -112.33 (1F, C5′-F); LCMS (ESI) 3.45 min (99%, ELSD), m/z: 381.2 [M+1]$^+$.
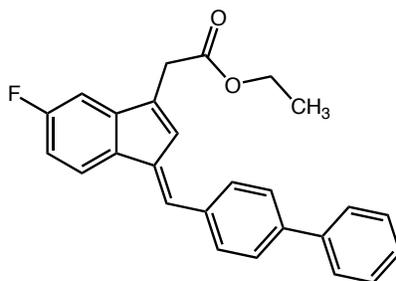
(*E*)-ethyl 2-(1-([1,1′-biphenyl]-4-ylmethylene)-5-fluoro-1*H*-inden-3-yl)acetate (16e).
According to general procedure F, (*E*)-2-(1-([1,1′-biphenyl]-4-ylmethylene)-5-fluoro-1*H*-inden-3-yl)acetic acid **13a** (10 mg, 0.028 mmol) was subjected to reaction with ethanol (0.8 mL) to afford **16e** as yellow solid. Yield: 7 mg (65%). $C_{26}H_{21}FO_2$, M_r = 384.44; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.20 (t, *J*=7.2 Hz, 3H), 3.79 (s, 2H), 4.12 (q, *J*=7.2 Hz, 2H), 7.08 (td, *J*=8.4 Hz, 1H), 7.16-7.19 (m, 2H), 7.40 (t, *J*=7.2 Hz, 1H), 7.50 (t, *J*=7.2 Hz, 2H), 7.69 (s, 1H), 7.74-7.82 (m, 6H), 7.87 (dd, *J*=5.2/8.4 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -113.06 (1F, C5′-F); LCMS (ESI) 3.63 min (>99%, UV254), *m/z*: 385.2 [M+1]$^+$.

Synthesis of compounds 18a & 18b (table 4):
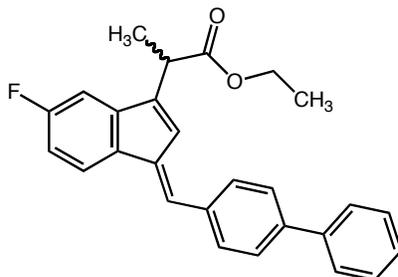
(*E*)-ethyl 2-(1-([1,1′-biphenyl]-4-ylmethylene)-5-fluoro-1*H*-inden-3-yl)propanoate (18a).
The title compound accumulated as a major product (precipitate) in the synthesis of **18b** and could be filtered off from the alkaline mother liquor after several days at room temperature and prior to the described acidic workup. Yield: 8 mg (5%): $C_{27}H_{23}FO_2$, M_r = 398.47; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.15 (t, *J*=7.2 Hz, 3H), 1.48 (d, *J*=6.8 Hz, 3H), 3.99 (q, *J*=7.2 Hz, 1H), 4.07 (dq, *J*=1.2/7.2 Hz, 2H), 7.06-7.10 (m, 2H), 7.20 (dd, *J*=2.4/9.2 Hz, 1H), 7.40 (t, *J*=7.2 Hz, 1H), 7.50 (t, *J*=7.2 Hz, 2H), 7.71-7.82 (m, 7H), 7.89 (dd, *J*=5.2/8.4 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -112.88 (d, 1F, C5′-F); LCMS (ESI) (method 2) *t*R: 3.86 min (85%*, ELSD), *m/z*: 399.2 [M+1]$^+$.
* impurity: 15% *alpha*-demethylated product m/z=384 and traces of its free acid m/z=356
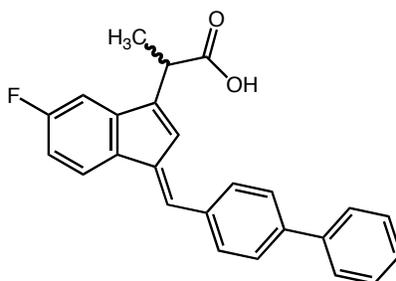
(*E*)-2-(1-([1,1′-biphenyl]-4-ylmethylene)-5-fluoro-1*H*-inden-3-yl)propanoic acid (18b).
The title compound was repeatedly formed in non-isolable traces as minor by-product to **18a** (see above) according to general procedure C from (*R/S*)-ethyl 2-(5-fluoro-1*H*-inden-3-yl)propanoate **10c** (0.10 g, 0.43 mmol) and [1,1′-biphenyl]-4-carbaldehyde (0.086 g, 0.47 mmol) after 3 h at 70 ˚C and

subsequent acidic workup: $C_{25}H_{19}FO_2$, $M_r = 370.42$; LCMS (ESI) (method 2) tR: 3.35 min (~8%, MSD), m/z: 371.0 [M+1]$^+$.

**Synthesis of compounds 19b, 19d-j and 20a, b (table 4):**
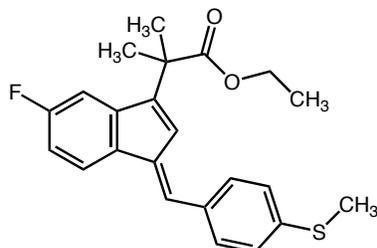
(*E*)-ethyl 2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)-2-methylpropanoate (19b).
The title compound was prepared by the aldol condensation reaction specified in general procedure D (step 1) from **10d** (0.050 g, 0.20 mmol) and commercially available 4-(methylthio)benzaldehyde (0.034 g, 0.22 mmol). After stirring for 72 h at room temperature the accumulated product precipitate was filtered off and carefully washed with water. The title compound was obtained as yellow solid (ethyl ester) in 18 % yield (71 mg): $C_{23}H_{23}FO_2S$, $M_r = 382.49$; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.06 (t, J=7.2 Hz, 3H), 1.55 (s, 6H), 2.53 (s, 3H), 4.08 (q, J=7.2 Hz, 2H), 6.88 (dd, J=2.4/9.6 Hz, 1H), 7.03-7.08 (m, 2H), 7.36 (d, J=8.4 Hz, 2H), 7.62-7.68 (m, 3H), 7.86 (dd, J=5.2/8.4 Hz, 1H); LCMS (ESI) (method 2) tR: 3.68 min (>99%, ELSD), m/z: 383.2 [M+1]$^+$.
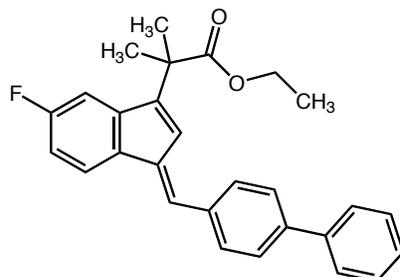
(*E*)-ethyl 2-(1-([1,1′-biphenyl]-4-ylmethylene)-5-fluoro-1*H*-inden-3-yl)-2-methylpropanoate (19d).
The title compound was prepared by the aldol condensation reaction specified in general procedure D (step 1) from **10d** (0.10 g, 0.40 mmol) and commercially available [1,1′-biphenyl]-4-carbaldehyde (0.081 g, 0.44 mmol). After stirring for 72 h at room temperature the accumulated product precipitate was filtered off and carefully washed with water. The title compound was obtained as yellow solid (ethyl ester) in 98 % yield (163 mg): $C_{28}H_{25}FO_2$, $M_r = 412.50$; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.07 (t, J=7.2 Hz, 3H), 1.57 (s, 6H), 4.09 (q, J=7.2 Hz, 2H), 6.90 (dd, J=2.4/9.6 Hz, 1H), 7.05-7.10 (m, 2H), 7.40 (tt, J=7.2 Hz, 1H), 7.50 (t, J=7.2 Hz, 1H), 7.72-7.76 (m, 3H), 7.81 (s, 4H), 7.91 (dd, J=5.2/8.4 Hz, 1H); LCMS (ESI) (method 2) tR: 3.89 min (>99%, ELSD), m/z: 413.2 [M+1]$^+$.
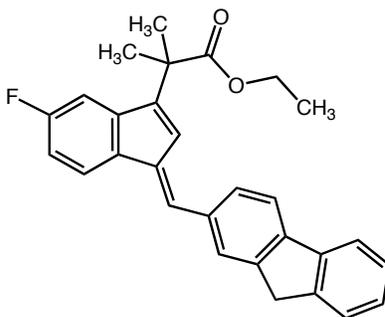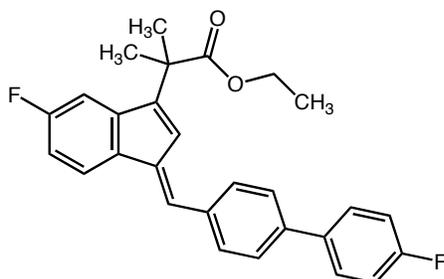
(*E*)-ethyl 2-(1-((9*H*-fluoren-2-yl)methylene)-5-fluoro-1*H*-inden-3-yl)-2-methylpropanoate (19e).
The title compound was prepared by the aldol condensation reaction specified in general procedure D (step 1) from **10d** (0.050 g, 0.20 mmol) and commercially available 9*H*-fluorene-2-carbaldehyde (0.043 g, 0.22 mmol). After stirring for 72 h at room temperature the accumulated product precipitate was filtered off and carefully washed with water. The title compound was obtained as yellow solid (ethyl ester) in 100 % yield (85.5 mg): $C_{28}H_{25}FO_2$, M_r = 412.50; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.07 (t, *J*=7.2 Hz, 3H), 1.58 (s, 6H), 4.03 (s, 2H), 4.09 (q, *J*=7.2 Hz, 2H), 6.90 (dd, *J*=2.4/9.8 Hz, 1H), 7.07 (td, *J*=2.4/9.0 Hz, 1H), 7.14 (s, 1H), 7.36 (td, *J*=1.2/7.4 Hz, 1H), 7.42 (t, *J*=7.0 Hz, 1H), 7.62 (d, *J*=7.2 Hz, 1H), 7.75-7.76 (m, 2H), 7.90 (dd, *J*=5.6/8.2 Hz, 1H), 7.95-7.96 (m, 2H), 8.01 (d, *J*=8.0 Hz, 1H); LCMS (ESI) (method 2) *t*R: 3.95 min (>99%, ELSD), *m/z*: 425.2 [M+1]$^+$.
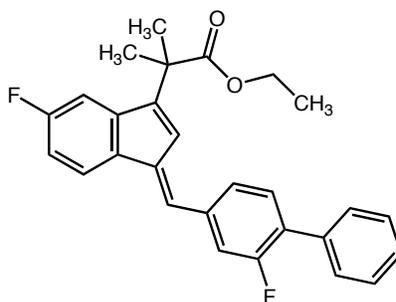
(*E*)-ethyl 2-(5-fluoro-1-((2-fluoro-[1,1′-biphenyl]-4-yl)methylene)-1*H*-inden-3-yl)-2-methyl-propanoate (19f).
The title compound was prepared by the aldol condensation reaction specified in general procedure D (step 1) from **10d** (0.050 g, 0.20 mmol) and commercially available 2-fluoro-[1,1′-biphenyl]-4-carbaldehyde (0.044 g, 0.22 mmol). After stirring for 72 h at room temperature the accumulated product precipitate was filtered off and carefully washed with water. The title compound was obtained as yellow solid (ethyl ester) in 91 % yield (79.3 mg): $C_{28}H_{24}F_2O_2$, M_r = 430.49; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.07 (t, *J*=7.2 Hz, 3H), 1.57 (s, 6H), 4.09 (q, *J*=7.2 Hz, 2H), 6.90 (dd, *J*=2.4/9.6 Hz, 1H), 7.07-7.12 (m, 2H), 7.42-7.45 (m, 1H), 7.49-7.53 (m, 2H), 7.61-7.69 (m, 6H), 7.89 (dd, *J*=5.2/8.4 Hz, 1H); LCMS (ESI) (method 2) *t*R: 3.82 min (>99%, ELSD), *m/z*: 431.1 [M+1]$^+$.
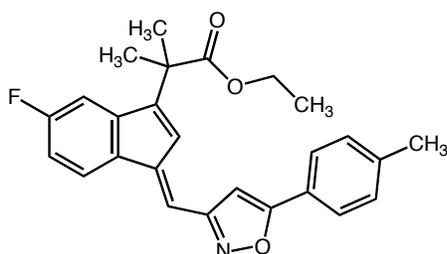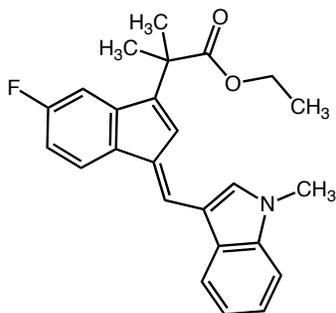

(*E*)-ethyl 2-(5-fluoro-1-((4′-fluoro-[1,1′-biphenyl]-4-yl)methylene)-1*H*-inden-3-yl)-2-methyl-propanoate (19g).

The title compound was prepared by the aldol condensation reaction specified in general procedure D (step 1) from **10d** (0.050 g, 0.20 mmol) and commercially available 4′-fluoro-[1,1′-biphenyl]-4-carbaldehyde (0.044 g, 0.22 mmol). After stirring for 72 h at room temperature the accumulated product precipitate was filtered off and carefully washed with water. The title compound was obtained as yellow solid (ethyl ester) in 93 % yield (80.4 mg): $C_{28}H_{24}F_2O_2$, M_r = 430.49; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.07 (t, J=7.2 Hz, 3H), 1.57 (s, 6H), 4.09 (q, J=7.2 Hz, 2H), 6.90 (dd, J=2.4/9.8 Hz, 1H), 7.05-7.10 (m, 2H), 7.32 (t, J=8.8 Hz, 2H), 7.71 (s, 1H), 7,78-7.81 (m, 6H), 7.90 (dd, J=5.2/8.4 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -112.92 (q, 1F), -112.82 (q, 1F); LCMS (ESI) (method 2) tR: 3.87 min (>99%, ELSD), m/z: 431.2 [M+1]$^+$.
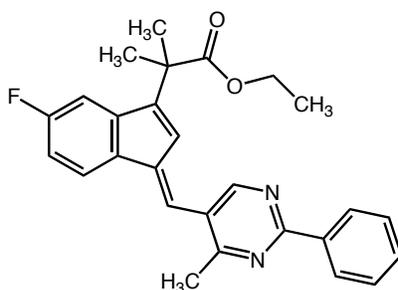
(*E*)-ethyl 2-(5-fluoro-1-((4-methyl-2-phenylpyrimidin-5-yl)methylene)-1*H*-inden-3-yl)-2-methyl-propanoate (19h).

The title compound was prepared by the aldol condensation reaction specified in general procedure D (step 1) from **10d** (0.050 g, 0.20 mmol) and commercially available 4-methyl-2-phenylpyrimidine-5-carbaldehyde (0.044 g, 0.22 mmol). After stirring for 72 h at room temperature the aqueous reaction mixture was combined with DCM (4 mL), the organic layer was separated and the solvent evaporated under reduced pressure. The remaining crude product (91 mg) was carefully washed with little ice-cold methanol, filtered and dried in high vacuum to afford the analytically pure title compound. Yield: 64 mg (74%): $C_{27}H_{25}FN_2O_2$, M_r = 428.50; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.07 (t, J=6.8 Hz, 3H), 1.54 (s, 6H), 2.70 (s, 3H), 4.08 (q, J=7.0 Hz, 2H), 6.83 (s, 1H), 6.90 (dd, J=2.0/9.6 Hz, 1H), 7.12 (td, J=2.4/9.0 Hz, 1H), 7.53-7.57 (m, 3H), 7.78 (s, 1H), 8.02 (dd, J=5.2/8.4 Hz, 1H), 8.44-8.48 (m, 2H), 8.90 (s, 1H); LCMS (ESI) (method 2) tR: 3.69 min (>99%, ELSD), m/z: 429.2 [M+1]$^+$.
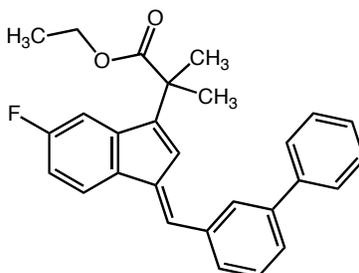

(*E*)-ethyl 2-(5-fluoro-1-((5-(*p*-tolyl)isoxazol-3-yl)methylene)-1*H*-inden-3-yl)-2-methylpropanoate (19i).

The title compound was prepared by the aldol condensation reaction specified in general procedure D (step 1) from **10d** (0.050 g, 0.20 mmol) and commercially available 5-(*p*-tolyl)isoxazole-3-carbaldehyde (0.034 g, 0.22 mmol). After stirring for 72 h at room temperature the accumulated product precipitate was filtered off and carefully washed with water. The title compound was obtained as yellow solid (ethyl ester) in 57 % yield (48 mg): $C_{26}H_{24}FNO_3$, M_r = 417.47; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.07 (t, J=6.8 Hz, 3H), 1.59 (s, 6H), 2.39 (s, 3H), 4.09 (q, J=6.8 Hz, 3H), 6.89 (dd, J=2.4/9.2 Hz, 1H), 7.09 (td, J=2.4/8.6 Hz, 1H), 7.20 (s, 1H), 7.39 (d, J=8.0 Hz, 2H), 7.45 (s, 1H), 7.51 (s, 1H), 7.88 (d, J=8.4 Hz, 2H), 7.96 (q, J=5.2 Hz, 1H); LCMS (ESI) (method 2) tR: 3.78 min (>99%, UV254, ELSD), m/z: 418.2 [M+1]$^+$.
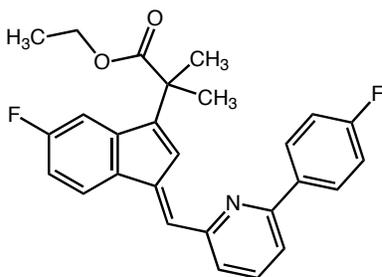
(*E*)-ethyl 2-(5-fluoro-1-((1-methyl-1*H*-indol-3-yl)methylene)-1*H*-inden-3-yl)-2-methylpropanoate (19j).
The title compound was prepared by the aldol condensation reaction specified in general procedure D (step 1) from **10d** (0.050 g, 0.20 mmol) and commercially available 1-methyl-1*H*-indole-3-carbaldehyde (0.035 g, 0.22 mmol). After stirring for 72 h at room temperature the aqueous reaction mixture was combined with DCM (4 mL), the organic layer was separated and the solvent evaporated under reduced pressure. The remaining crude product was purified by flash chromatography (EtOAc+Hex=1+2 (0.5% AcOH, gradient) to afford the analytically pure title compound. Yield: 13 mg (17%). $C_{25}H_{24}FNO_2$, M_r = 389.46; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.07 (t, *J*=7.2 Hz, 3H), 1.60 (s, 6H), 3.92 (s, 3H, N-CH$_3$), 4.07 (q, *J*=7.2 Hz, 2H), 6.88 (dd, *J*=2.4/10.0 Hz, 1H), 7.01 (td, *J*=2.4/9.2 Hz, 1H), 7.19-7.23 (m, 2H), 7.27 (t, *J*=7.2 Hz, 1H, imidazol), 7.53 (d, *J*=8.0 Hz, 1H, imidazol), 7.85 (s, 1H), 7.98 (dd, *J*=5.4/8.2 Hz, 1H), 8.03 (d, *J*=7.6 Hz, 1H, imidazol), 8.22 (s, 1H, imidazol); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -115.26 Hz (s, 1F, C5'-F); LCMS (ESI) (method 2) *t*R: 3.57 min (≥95%, UV254, ELSD), *m/z*: 390.2 [M+1]$^+$.

**(*E*)-ethyl 2-(1-([1,1′-biphenyl]-3-ylmethylene)-5-fluoro-1*H*-inden-3-yl)-2-methylpropanoate (20a).**
The title compound was prepared by the aldol condensation reaction specified in general procedure D (step 1) from **10d** (0.050 g, 0.20 mmol) and commercially available [1,1′-biphenyl]-3-carbaldehyde (0.040 g, 0.22 mmol). After stirring for 72 h at room temperature the basic reaction mixtute was combined with the same volume of water and then extracted thrice with equal amounts of DCM. The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo to afford the pure title compound (ethyl ester) as bright brownish viscous oil that gradually crystallized upon storage at -20 ˚C. Yield: 75.5 mg (91%): $C_{28}H_{25}FO_2$, M_r = 412.50; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.06 (t, *J*=7.2 Hz, 3H), 1.56 (s, 6H), 4.08 (q, *J*=7.2 Hz, 2H), 6.91 (dd, *J*=2.0/9.8 Hz, 1H), 7.05 (s, 1H), 7.09 (td, *J*=2.4/8.9 Hz, 1H), 7.40 (t, *J*=7.4 Hz, 1H), 7.51 (t, *J*=7.6 Hz, 2H), 7.60 (t, *J*=7.6 Hz, 1H), 7.69-7.78 (m, 5H), 7.88-7.92 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -112.69 (q, 1F, C5'-F); LCMS (ESI) (method 2) *t*R: 3.87 min (>99%, UV254, ELSD), *m/z*: 413.2 [M+1]$^+$.

(*E*)-ethyl 2-(5-fluoro-1-((6-(4-fluorophenyl)pyridin-2-yl)methylene)-1*H*-inden-3-yl)-2-methyl-propanoate (20b).

The title compound was prepared by the aldol condensation reaction specified in general procedure D (step 1) from **10d** (0.050 g, 0.20 mmol) and commercially available 6-(4-fluorophenyl)picolin-aldehyde (0.045 g, 0.22 mmol). After stirring for 72 h at room temperature the accumulated product precipitate was filtered off and carefully washed with water. The title compound was obtained as yellow solid (Na-salt) in 83% yield (72.5 mg): $C_{27}H_{23}F_2NO_2$, M_r = 431.47; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.06 (t, *J*=7.2 Hz, 3H), 1.59 (s, 6H), 4.08 (q, *J*=7.2 Hz, 2H), 6.91 (dd, *J*=2.0/9.6 Hz, 1H), 7.07 (td, *J*=2.4/8.8 Hz, 1H), 7.38 (pseudo t, *J*=8.8 Hz, 2H), 7.61-7.63 (m, 2H), 7.87-8.00 (m, 3H), 8.07 (s, 1H), 8.20-8.24 (dd, *J*=5.6/8.8 Hz, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -111.98 (s, 1F), -110.74 (s, 1F); LCMS (ESI) (method 2) *t*R: 3.79 min (>99%, ELSD), *m/z*: 432.2 [M+1]⁺.

Synthesis of compounds 2, 19a & 19c (tables 1 and 4):
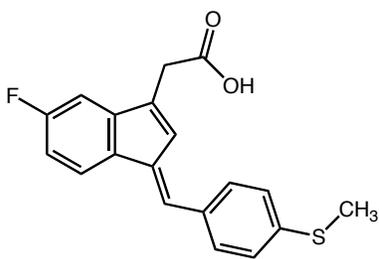
(*E*)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)acetic acid (2).[1, 5]

Ester cleavage as described in general procedure G_variant1 was performed on **16b** (25 mg, 0.071 mmol). The crude product was purified by flash chromatography (ethyl acetate/hexane 1:2, 0.5% HOAc) to give the desired title compound as yellow powder (13 mg, 56%). $C_{19}H_{15}FO_2S$, M_r = 326.38; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 400 MHz: 2.52 (s, 3H), 3.67 (s, 2H), 7.04 (td, *J*=2.4/9.2 Hz, 1H), 7.11 (s, 1H), 7.15 (dd, *J*=9.2 Hz, 1H), 7.35 (d, *J*=8.4 Hz, 2H), 7.58 (s, 1H), 7.63 (d, *J*=8.4 Hz, 2H), 7.82 (dd, *J*=5.2/8.4 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -113.42 (t, 1F, C5′-F); LCMS (ESI) (method 2) *t*R: 2.49 min (>99%, UV254, ELSD), *m/z*: 327.0 [M+1]⁺.
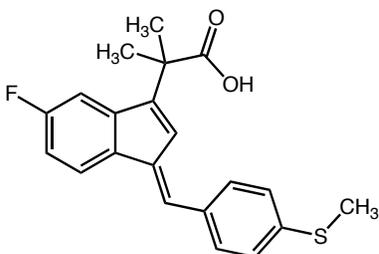
(*E*)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)-2-methylpropanoic acid (19a).

Ester cleavage as described in general procedure G_variant2 was performed on **19b** (15 mg, 0.039 mmol). The crude product was purified by flash chromatography (ethyl acetate/hexane 1:1, 0.5% HOAc, gradient). Yield: 12.5 mg (90%). $C_{21}H_{19}FO_2S$, M_r = 354.44; ^{1}H NMR (400 MHz, DMSO-d_6) δ:

1.53 (s, 6H), 2.53 (s, 3H), 6.98 (dd, J=2.4/10.0 Hz, 1H), 7.02-7.07 (m, 2H), 7.36 (d, J=8.8 Hz, 2H), 7.60 (s, 1H), 7.66 (d, J=8.4 Hz, 2H), 7.86 (dd, J=5.4/8.2 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -113.31 (q, 1F, C5′-F); LCMS (ESI) (method 2) tR: 3.12 min (98%, ELSD), m/z: 355.2 [M+1]$^+$.
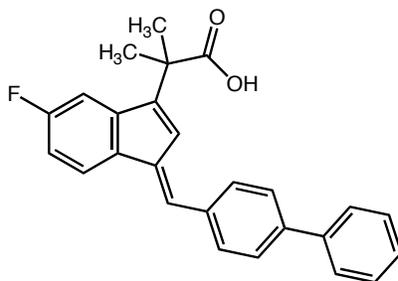

(E)-2-(1-([1,1′-biphenyl]-4-ylmethylene)-5-fluoro-1H-inden-3-yl)-2-methylpropanoic acid (19c).
Ester cleavage as described in general procedure G_variant2 was performed on **19d** (10 mg, 0.024 mmol). The crude product was purified by flash chromatography (ethyl acetate/hexane 1:1, 0.5% HOAc, gradient). Yield: 6 mg (64%). $C_{26}H_{21}FO_2$, M_r = 384.44; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.54 (s, 6H), 7.00 (dd, J=2.4/9.8 Hz, 1H), 7.05-7.10 (m, 2H), 7.40 (tt, J=1.6/7.2 Hz, 1H), 7.50 (t, J=7.4 Hz, 2H), 7.70 (s, 1H), 7.75 (dd, J=1.2/7.2 Hz, 2H), 7.81 (s, 4H), 7.90 (dd, J=5.6/8.2 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -112.96 (d, 1F, C5′-F); LCMS (ESI) (method 2) tR: 3.45 min (≥95%, ELSD, MSD), m/z: 385.2 [M+1]$^+$.
Alternative workup: The crude product (combo precipitate) was repeatedly washed with hexane until residual amounts of the starting material could be no longer detected on TLC (SiO$_2$, ethyl acetate/hexane 1:1, 0.5% HOAc).

Synthesis of compounds 21a, b & 21d-o (table 5):
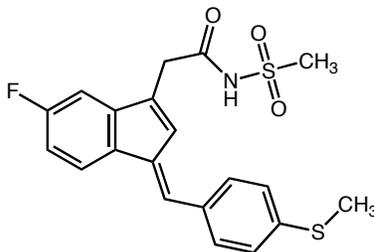
(E)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1H-inden-3-yl)-N-(methylsulfonyl)acetamide (21a).
According to general procedure H, the title compound was obtained from (E)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1H-inden-3-yl)acetic acid **2** (0.20 g, 0.61 mmol) and methanesulfonamide (0.058 g, 0.61 mmol) after 4 h at room temperature. The crude product was washed with little DCM and then recrystallized from MeOH. Yield: 75 mg (30%). $C_{20}H_{18}FNO_3S_2$, M_r = 403.49; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.52 (s, 3H), 3.14 (s, 3H), 3.63 (s, 2H), 7.04 (td, J=2.4/8.4 Hz, 1H), 7.10 (s, 1H), 7.17 (dd, J=2.4/9.2 Hz, 1H), 7.35 (d, J=8.4 Hz, 2H), 7.58 (s, 1H), 7.63 (d, J=8.4 Hz, 2H), 7.82 (dd, J=5.2/8.4 Hz, 1H); HPLC (method 1) tR: 9.20 min; LCMS (ESI) (method 2) tR: 2.83 min (>99%, ELSD), m/z: 404.0 [M+1]$^+$.
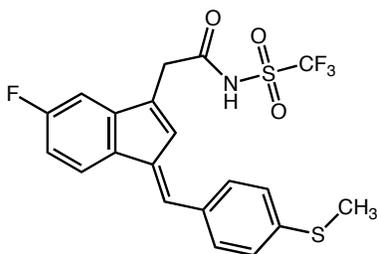
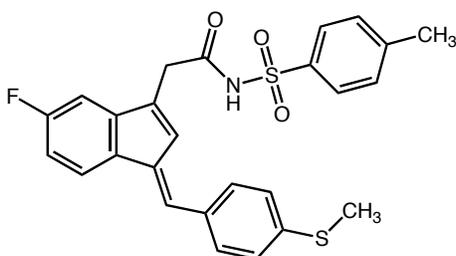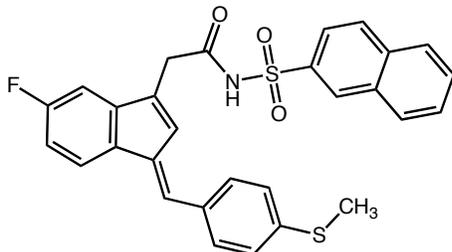**(*E*)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)-*N*-((trifluoromethyl)sulfonyl)-acetamide (21b).**
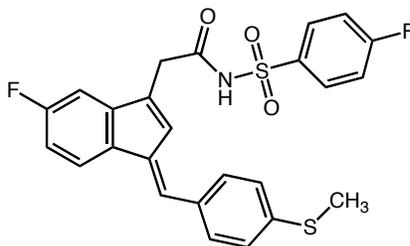
According to general procedure H, the title compound was obtained from (*E*)-2-(5-fluoro-1-(4-(methylthio) benzylidene)-1*H*-inden-3-yl)acetic acid **2** (0.20 g, 0.61 mmol) and trifluoromethane-sulfonamide (0.091 g, 0.61 mmol) after 20 h at room temperature. The crude product was purified by column chromatography (SiO$_2$, EtOAc:Hexane = 1+1, 0.5%AcOH) to yield 50 mg (18%) of an analytically pure yellow solid: C$_{20}$H$_{15}$F$_4$NO$_3$S$_2$, M$_r$ = 457.46; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.52 (s, 3H), 3.46 (s, 2H), 6.97-7.03 (m, 2H), 7.13 (dd, *J*=2.4/9.2 Hz, 1H), 7.33 (d, *J*=8.8 Hz, 2H), 7.50 (s, 1H), 7.62 (d, *J*=8.4 Hz, 2H), 7.78 (dd, *J*=5.2/8.4 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -113.68 (s, 1F, C5'-F), -75.46 (s, 3F, -CF$_3$); HPLC (method 1) *t*R: 9.24 min; LCMS (ESI) (method 2) *t*R: 3.25 min (96%, ELSD), *m/z*: 458.0 [M+1]$^+$.
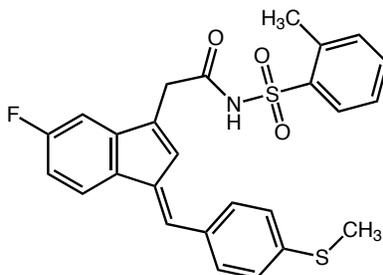
(*E*)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)-*N*-(*o*-tolylsulfonyl)acetamide (21d).

According to general procedure H, the title compound was obtained from (*E*)-2-(5-fluoro-1-(4-(methylthio) benzylidene)-1*H*-inden-3-yl)acetic acid **2** (0.20 g, 0.61 mmol) and 2-methylbenzenesulfonamide (0.105 g, 0.61 mmol) after 20 h at room temperature. The crude product was chromatographed (SiO$_2$ column, EtOAc:Hexane = 1+1 (containing 0.5% AcOH) to yield 131 mg (45%) of an analytically pure solid: C$_{26}$H$_{22}$FNO$_3$S$_2$, M$_r$ = 479.59; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.52 (s, 3H), 2.53 (s, 3H), 3.66 (s, 2H), 6.94-6.97 (m, 2H), 7.02 (dtd, *J*=1.2/2.4/9.2 Hz, 1H), 7.28-7.42 (m, 4H), 7.51 (dt, *J*=1.2/7.5 Hz, 1H), 7.55-7.57 (m, 3H), 7.79 (dd, *J*=5.2/8.4 Hz, 1H), 7.93 (dd, *J*=1.2/8.0 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -113.30 (s, 5'-F); HPLC (method 1) *t*R: 10.39 min; LCMS (ESI) (method 2) *t*R: 3.16 min (>99%, ELSD), *m/z*: 480.0 [M+1]$^+$.
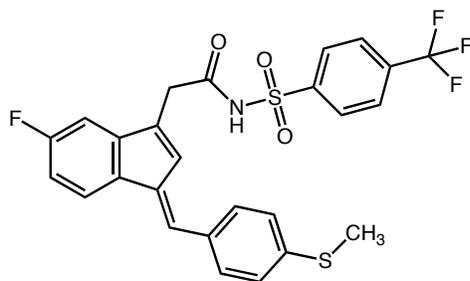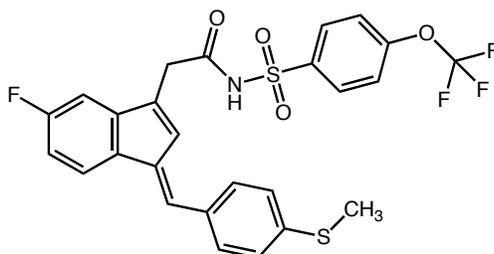

(*E*)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)-*N*-tosylacetamide (21e).

According to general procedure H, the title compound was obtained from (*E*)-2-(5-fluoro-1-(4-(methylthio) benzylidene)-1*H*-inden-3-yl)acetic acid **2** (0.20 g, 0.61 mmol) and 4-methylbenzene-sulfonamide (0.105 g, 0.61 mmol) after 20 h at room temperature. The crude product was purified by

column chromatography (SiO$_2$, EtOAc:Hexane = 1+1, 0.5%AcOH) to yield 167 mg (57%) of an analytically pure solid: C$_{26}$H$_{22}$FNO$_3$S$_2$, M$_r$ = 479.59; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.34 (s, 3H), 2.53 (s, 3H), 3.62 (s, 2H), 6.92 (dd, J=2.0/9.2 Hz, 1H), 6.97 (s, 1H), 7.02 (td, J=2.0/9.0 Hz, 1H), 7.33-7.36 (m, 4H), 7.56-7.58 (m, 3H), 7.76-7.81 (m, 3H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -113.35 (q, 5'-F); HPLC (method 1) tR: 10.25 min; LCMS (ESI) (method 2) tR: 3.18 min (>99%, ELSD), m/z: 480.0 [M+1]$^+$.

(E)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1H-inden-3-yl)-N-(naphthalen-2-ylsulfonyl) acetamide (21f).

According to general procedure H, the title compound was obtained from (E)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1H-inden-3-yl)acetic acid **2** (0.20 g, 0.61 mmol) and naphthalene-2-sulfonamide (0.127 g, 0.61 mmol) after 20 h at room temperature. The crude product was purified by column chromatography (SiO$_2$, EtOAc:Hexane = 1+1, 0.5%AcOH) to yield 149 mg (47%) of an analytically pure solid: C$_{29}$H$_{22}$FNO$_3$S$_2$, M$_r$ = 515.62; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.52 (s, 3H), 3.65 (s, 2H), 6.94-7.01 (m, 3H), 7.28 (d, J=8.4 Hz, 2H), 7.53 (m, 3H), 7.64-7.78 (m, 3H), 7.86 (dd, J=2.0/8.8 Hz, 1H), 8.02 (d, J=8.0 Hz, 1H), 8.08 (d, J=8.8 Hz, 1H), 8.16 (d, J=8.0 Hz, 1H), 8.57 (d, J=1.2 Hz, 1H); HPLC (method 1) tR: 10.79 min; LCMS (ESI) (method 2) tR: 3.28 min (>99%, UV220, ELSD), m/z: 516.0 [M+1]$^+$.

(E)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1H-inden-3-yl)-N-(4-fluorophenylsulfonyl) acetamide (21g).

According to general procedure H, the title compound was obtained from (E)-2-(5-fluoro-1-(4-(methylthio) benzylidene)-1H-inden-3-yl)acetic acid **2** (0.20 g, 0.61 mmol) and 4-fluorobenzene-sulfonamide (0.107 g, 0.61 mmol) after 20 h at room temperature. The crude product was purified by flash chromatography (SiO$_2$, EtOAc:Hexane gradient = 1+1 (0.5% AcOH) and treatment with little diethylether and methanol. Yield: 110 mg (37%), orange solid: C$_{25}$H$_{19}$F$_2$NO$_3$S$_2$, M$_r$ = 483.55; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.53 (s, 3H), 3.64 (s, 2H), 6.89 (dd, J=2.4/9.2 Hz, 1H), 6.96 (s, 1H), 7.02 (td, J=2.4/8.4 Hz, 1H), 7.34 (d, J=8.0 Hz, 2H), 7.41 (pseudo-t, J=8.8 Hz, 2H), 7.55-7.56 (m, 3H), 7.79 (dd, J=4.8/8.4 Hz, 1H), 7.79 (dd, J=4.8/8,4 Hz, 1H), 7.95-7.99 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -113.33 (d, 1F, C5'-F), -102.71 (s, 1F, p-fluorophenyl); HPLC (method 1) tR: 10.21 min; LCMS (ESI) (method 2) tR: 3.12 min (≥95%, ELSD), m/z: 484.0 [M+1]$^+$.
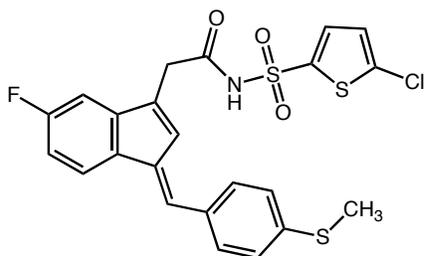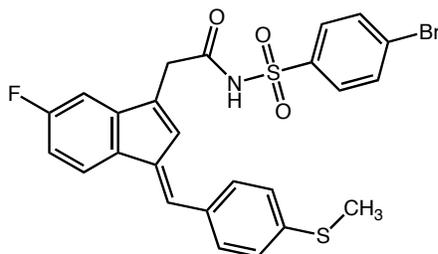
(*E*)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)-*N*-(4-(trifluoromethyl)phenyl-sulfonyl)acetamide (21h).

According to general procedure H, the title compound was obtained from (*E*)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)acetic acid **2** (0.20 g, 0.61 mmol) and 4-(trifluoromethyl) benzenesulfonamide (0.138 g, 0.61 mmol) after 20 h at room temperature. The crude product was chromatographed (SiO$_2$ column, EtOAc:Hexane = 1+1 (containing 0.5% AcOH) to yield 205 mg (63%) of an analytically pure solid: C$_{26}$H$_{19}$F$_4$NO$_3$S$_2$, M$_r$ = 533.56; ^{1}H NMR (400 MHz, DMSO-*d$_6$*) δ: 2.52 (s, 3H), 3.68 (s, 2H), 6.86-8.11 (m, 13 H); ^{13}C NMR (75 MHz, DMSO-*d$_6$*) δ: 14.6 (s, -SCH$_3$), 35.7 (s, -CH$_2$-), 106.7 (d, *J*=22.5 Hz, C4 indene), 112.1 (d, *J*=23.3 Hz, C6 indene), 121.1 (d, *J*=9.0 Hz, C7 indene), 125.5, 126.2 (s, C3/C5 benzylidene), 126.7 (s, C3/C5 benzenesulfonamide), 129.0 (s, C2/C6 benzenesulfonamide), 129.4 (s, =C-Ar), 130.9 (s, C2/C6 benzylidene), 133.0 (s), ~133.5 (q), 134.0 (s), 136.3 (s), 139.1 (s), 140.4 (s), 140.4 (s), 143.0 (d), 143.2 (s), ~162 (d, C5 indene), 169.1 (s, >C=O); ^{19}F NMR (282 MHz, DMSO-*d$_6$*) δ: -113.37 (s, 1F, C5'-F), -60.01 (s, 3F, -CF$_3$); HPLC (method 1) *t*R: 10.67 min; LCMS (ESI) (method 2) *t*R: 3.31 min (≥95%, ELSD), *m/z*: 534.0 [M+1]$^+$.

(*E*)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)-*N*-(4-(trifluoromethoxy) phenylsulfonyl)acetamide (21i).

According to general procedure H, the title compound was obtained from (*E*)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)acetic acid **2** (0.20 g, 0.61 mmol) and 4-(trifluoromethoxy) benzenesulfonamide (0.148 g, 0.61 mmol) after 20 h at room temperature. The crude product was chromatographed (SiO$_2$ column, EtOAc:Hexane = 1+1 (containing 0.5% AcOH) to yield 240 mg (71%) of an analytically pure solid: C$_{26}$H$_{19}$F$_4$NO$_4$S$_2$, M$_r$ = 549.56; ^{1}H NMR (400 MHz, DMSO-*d$_6$*) δ: 2.52 (s, 3H), 3.61 (s, 2H), 6.88 (dd, *J*=2.4/9.2 Hz, 1H), 6.98-7.03 (m, 2H), 7.33 (d, *J*=8.8 Hz, 2H), 7.56-7.58 (m, 5H), 7.78 (dd, *J*=5.2/8.4 Hz, 1H), 8.05 (d, *J*=8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-*d$_6$*) δ: 14.62 (s, -SCH$_3$), 35.61 (s, -CH$_2$-), 106.71 (d, *J*=23.0 Hz, C4 indene), 112.08 (d, *J*=23.0 Hz, C6 indene), 118.89 (s, C1 indene), 121.05 (d, *J*=9.0 Hz, C7 indene), 121.49 (s, 2H, C3/C5 benzenesulfonamide), 126.18 (s, C2/C6 benzenesulfonamide), 126.54 (s, C2 indene), 129.31 (s, =CH-), 130.74 (s, C3/C5 benzylidene), 130.87 (s, C2/C6 benzylidene), 132.95 (s), 134.07 (d, *J*=2.0 Hz, C7a indene), 136.30 (s), 138.09 (s), 139.25 (d, *J*=3.0 Hz, C3 indene), 140.35 (s), 142.93 (d, *J*=9.0 Hz, C3a indene), 152.08 (s, C4); ^{19}F NMR (282 MHz, DMSO-*d$_6$*) δ: -113.39 (d, 1F, C5'-F indene), -54.92 (s, 3F, -OCF$_3$); HPLC (method 1) *t*R: 10.87 min; LCMS (ESI) (method 2) *t*R: 3.33 min (99%, ELSD), *m/z*: 550.0 [M+1]$^+$.
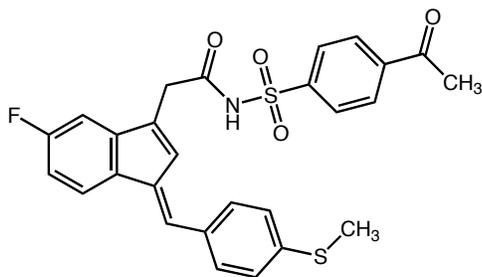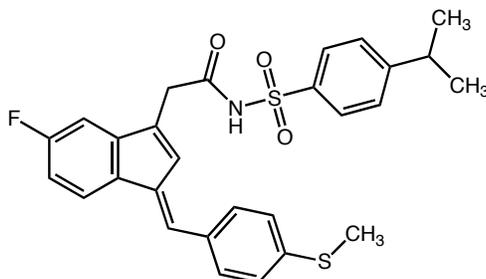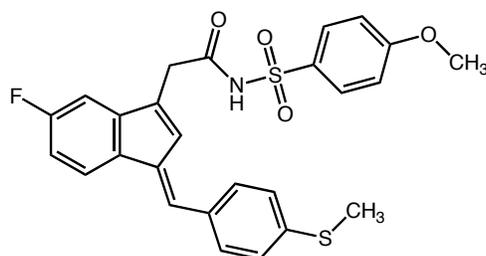
(*E*)-*N*-(5-chlorothiophen-2-ylsulfonyl)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)acetamide (21j).
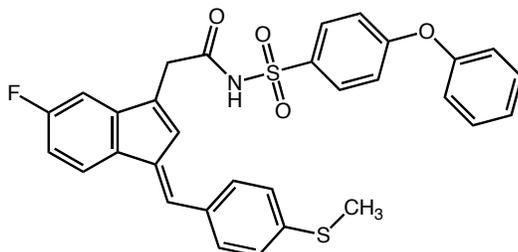
According to general procedure H, the title compound was obtained from (*E*)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)acetic acid **2** (0.20 g, 0.61 mmol) and 5-chlorothiophene-2-sulfonamide (0.121 g, 0.61 mmol) after 20 h at room temperature. The crude product was chromatographed (SiO$_2$ column, EtOAc:Hexane = 1+1 (containing 0.5% AcOH) to give 167 mg (54%) of an analytically pure solid: C$_{23}$H$_{17}$ClFNO$_3$S$_3$, M$_r$ = 506.03; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 2.52 (s, 3H), 3.70 (s, 2H), 6.97-7.05 (m, 3H), 7.22 (d, *J*=4.0 Hz, 1H), 7.34 (d, *J*=8.8 Hz, 2H), 7.57-7.61 (m, 3H), 7.67 (d, *J*=4.0 Hz, 1H), 7.80 (dd, *J*=5.2/8.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ: 14.65 (s, -SCH$_3$), 35.70 (s, -CH$_2$-), 106.79 (d, *J*=24.0 Hz, C4 indene), 112.15 (d, *J*=23.0 Hz, C6 indene), 121.08 (d, *J*=9.0 Hz, C7 indene), 126.19 (s, C3/C5), 126.41 (C2 indene), 128.07 (s), 129.37 (s, =CH-), 130.88 (s, C2/C6 benzylidene), 132.96 (s), 134.10 (s), 134.60 (s), 136.33 (s), 137.30 (s), 137.69 (s), 139.25 (d, *J*=2.0 Hz, C3 indene), 140.37 (s), 142.98 (d, *J*=9.0 Hz, C3a indene), 162.45 (d, *J*=241.0 Hz, C5 indene), 169.13 (s, >C=O); HPLC (method 1) *t*R: 10.49 min; LCMS (ESI) (method 2) *t*R: 3.27 min (>99%, ELSD), *m/z*: 506 [M+1]$^+$.

(*E*)-*N*-(4-bromophenylsulfonyl)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)acetamide (21k).

According to general procedure H, the title compound was obtained from (*E*)-2-(5-fluoro-1-(4-(methylthio) benzylidene)-1*H*-inden-3-yl)acetic acid **2** (0.20 g, 0.61 mmol) and 4-bromobenzene-sulfonamide (0.145 g, 0.61 mmol) after 20 h at room temperature. The crude product was chromatographed (SiO$_2$ column, EtOAc:Hexane = 1+1 (containing 0.5% AcOH) to give 117 mg (35%) of an analytically pure solid: C$_{25}$H$_{19}$BrFNO$_3$S$_2$, M$_r$ = 544.46; ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ: 2.55 (s, 3H), 3.67 (s, 2H), 6.93 (d, *J*=8.34 Hz, 1H), 7.01-7.05 (m, 2H), 7.36-7.37 (m, 2H), 7.58-7.59 (m, 3H), 7.80-7.84 (m, 5H); HPLC (method 1) *t*R: 10.80 min; LCMS (ESI) (method 2) *t*R: 3.29 min (≥95%, ELSD), *m/z*: 547 [M+1]$^+$.

(*E*)-*N*-(4-acetylphenylsulfonyl)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)acetamide (21l).

According to general procedure H, the title compound was obtained from (*E*)-2-(5-fluoro-1-(4-(methylthio) benzylidene)-1*H*-inden-3-yl)acetic acid **2** (0.20 g, 0.61 mmol) and 4-acetylbenzene-sulfonamide (0.122 g, 0.61 mmol) after 20 h at room temperature. The crude product was chromatographed (SiO$_2$ column, EtOAc:Hexane = 1+1 (containing 0.5% AcOH) to give 132 mg (42%) of an analytically pure solid: C$_{27}$H$_{22}$FNO$_4$S$_2$, M$_r$ = 507.60; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.53 (s, 3H), 2.60 (s, 3H), 3.66 (s, 2H), 6.89 (dd, *J*=2.4/9.2 Hz, 1H), 6.98-7.03 (m, 2H), 7.33 (d, *J*=8.8 Hz, 2H), 7.56-7.58 (m, 3H), 7.78 (dd, *J*=5.2/8.4 Hz, 1H), 8.01 (d, *J*=8.4 Hz, 2H), 8.09 (d, *J*=8.4 Hz, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -113.33 (d, 1F, C5′-F); HPLC (method 1) *t*R: 11.14 min; LCMS (ESI) (method 2) *t*R: 3.02 min (>97%, UV254, ELSD), *m/z*: 508.0 [M+1]$^+$.

(*E*)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)-*N*-((4-isopropylphenyl)sulfonyl)-acetamide (21m).
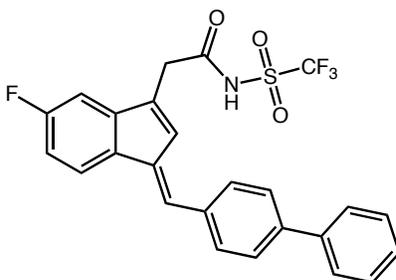
According to general procedure H, the title compound was obtained from (*E*)-2-(5-fluoro-1-(4-(methylthio) benzylidene)-1*H*-inden-3-yl)acetic acid **2** (0.20 g, 0.61 mmol) and 4-isopropylbenzene-sulfonamide (0.122 g, 0.61 mmol) after 20 h at room temperature. The crude product was chromatographed (SiO$_2$ column, EtOAc:Hexane = 1+1 (containing 0.5% AcOH) to give 189 mg (61%) of an analytically pure solid: C$_{28}$H$_{26}$FNO$_3$S$_2$, M$_r$ = 507.64; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.17 (d, *J*=7.2 Hz, 6H), 2.53 (s, 3H), 2.94 (sept, *J*=9.2 Hz, 1H), 3.64 (s, 2H), 6.91 (dd, *J*=2.4/9.2 Hz, 1H), 6.99-7.04 (m, 2H), 7.35 (d, *J*=8.4 Hz, 2H), 7.43 (d, *J*=8.4 Hz, 2H), 7.58-7.60 (m, 3H), 7.77-7.82 (m, 3H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -113.27 (q, 1F, C5′-F); HPLC (method 1) *t*R: 9.70 min; LCMS (ESI) (method 2) *t*R: 3.38 min (≥95%, ELSD), *m/z*: 508.2 [M+1]$^+$.

(*E*)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1*H*-inden-3-yl)-*N*-((4-methoxyphenyl)sulfonyl)-acetamide (21n).

According to general procedure H, the title compound was obtained from (*E*)-2-(5-fluoro-1-(4-(methylthio) benzylidene)-1*H*-inden-3-yl)acetic acid **2** (0.20 g, 0.61 mmol) and 4-methoxybenzene-

sulfonamide (0.115 g, 0.61 mmol) after 20 h at room temperature. The crude product was purified by flash chromatography (SiO$_2$, EtOAc:Hexane gradient = 1+1 (0.5% AcOH). Yield: 33 mg (11%), orange solid: C$_{26}$H$_{22}$FNO$_4$S$_2$, M$_r$ = 495.59; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.53 (s, 3H), 3.62 (s, 2H), 3.81 (s, 3H), 6.92 (dd, J=2.4/9.2 Hz, 1H), 6.96 (s, 1H), 7.02 (td, J=2.4/8.4 Hz, 1H), 7.06-7.09 (m, 2H), 7.34 (d, J=8.4 Hz, 2H), 7.56-7.57 (m, 3H), 7.78-7.85 (m, 3H); HPLC (method 1) tR: 10.09 min; LCMS (ESI) (method 2) tR: 3.09 min (≥95%, ELSD), m/z: 496.0 [M+1]$^+$.

(E)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1H-inden-3-yl)-N-(4-phenoxyphenylsulfonyl) acetamide (21o).
According to general procedure H, the title compound was obtained from (E)-2-(5-fluoro-1-(4-(methylthio) benzylidene)-1H-inden-3-yl)acetic acid **2** (0.20 g, 0.61 mmol) and 4-phenoxybenzene-sulfonamide (0.153 g, 0.61 mmol) after 20 h at room temperature: C$_{31}$H$_{24}$FNO$_4$S$_2$, M$_r$ = 557.65; HPLC (method 1) tR: 10.21 min; LCMS (ESI) (method 2) tR: 3.38 min (ELSD), m/z: 558.1 [M+1]$^+$.

Synthesis of compound 21c *via* (E)-2-(1-([1,1′-biphenyl]-4-ylmethylene)-5-fluoro-1H-inden-3-yl)acetyl chloride (table 5):
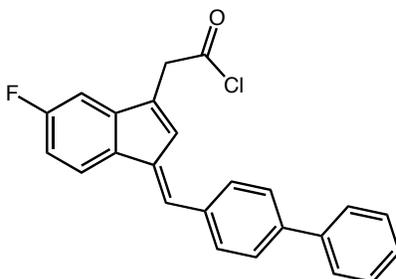
(E)-2-(1-([1,1′-biphenyl]-4-ylmethylene)-5-fluoro-1H-inden-3-yl)acetyl chloride[6]
The title compound was prepared according to general procedure I from **13a** (0.020 g, 0.056 mmol) and was used in the next reaction step without purification. Yield: 20 mg (95%), bright orange solid. C$_{24}$H$_{16}$ClFO, M$_r$ = 374.83.

(E)-2-(1-([1,1′-biphenyl]-4-ylmethylene)-5-fluoro-1H-inden-3-yl)-N-((trifluoromethyl)sulfonyl)-acetamide (21c).
According to general procedure J, (E)-2-(1-([1,1′-biphenyl]-4-ylmethylene)-5-fluoro-1H-inden-3-yl)acetyl chloride (20 mg, 0.053 mmol) was subjected to reaction with trifluoromethanesulfonamide

(11.9 mg, 0.080 mmol). The crude product was purified by flash chromatography (SiO$_2$, EtOAc + Hexane: 1+1 (0.5 % AcOH, gradient) to afford 13.5 mg (52%) as bright yellow solid. C$_{25}$H$_{17}$F$_4$NO$_3$S, M$_r$ = 487.47; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.47 (s, 2H), 7.02 (td, J=2.4/8.8 Hz, 1H), 7.09 (s, 1H), 7.15 (dd, J=2.4/9.4 Hz, 1H), 7.39 (tt, J=1.6/7.2 Hz, 1H), 7.49 (t, J=7.2 Hz, 2H), 7.59 (s, 1H), 7.74 (dd, J=1.6/7.2 Hz, 2H), 7.78 (s, 4H), 7.82 (dd, J=5.2/8.4 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -115.25 (s, 1F, C5′-F), -77.31 (s, 3F, -CF$_3$); LCMS (ESI) (method 2) tR: 3.62 min (>99%, UV254, ELSD), m/z: 488.0 [M+1]$^+$.

Biochemical and biological screening methods:

^{14}C-AA TLC COX activity assay

COX inhibition screening assay to evaluate compounds as competitive inhibitors: time- and concentration-dependent inhibition reactions were performed by pre-incubating inhibitor and hematin-reconstituted enzyme in 100 mM Tris-HCl buffer with 500 μM phenol for 17 min at room temperature followed by a 3 min incubation at 37 °C. Following the addition of 5 μM [1-^{14}C]-AA ($\sim$ K_m of arachidonate), samples were incubated for 30 sec at 37 °C, and the reactions were then terminated by extraction with diethyl ether/methanol/citrate (30:4:1). Some assays were performed at 50 μM to evaluate the time-depending inhibition of the compounds. The extracts were analyzed for substrate consumption by thin-layer chromatography as previously described.[12] All inhibitor concentrations for 50% enzyme activity (IC_{50}) were determined by nonlinear regression analysis using Graphpad Prism software and were the average of at least two independent experiments. All inhibitors were prepared as stock solutions in dimethyl sulfoxide (DMSO), and diluted into reaction buffer so that the final DMSO concentration was 2.5% in all samples. Reactions were run with hematin-reconstituted proteins at final enzyme concentrations adjusted to give approximately 30% substrate consumption. AA was prepared as a stock solution in 0.1 N NaOH.

In Vitro Cell Metabolism Assay:

Human ovarian adenocarcinoma cells, OVCAR-3, passage 8-20, or human head and neck squamous carcinoma cells, HNSCC 1483, passage 19, mycoplasma negative by pcr detection method (Sigma VenorGem) were grown in RPMI 1640 (Invitrogen/Gibco)+10% FBS (Atlas) to 70% confluence. Cells were plated in 6-well plates (Sarstedt) and grown to ~60% confluency. Warm serum-free HBSS (2 ml) was replaced in each well, and the cells were treated with inhibitor dissolved in DMSO (0 – 5 μM, final concentration) for 30 min at 37°C followed by the addition of [1-^{14}C]-arachidonic acid [8 μM, ~55 mCi/mmol, Perkin Elmer] for 30 min at 37°C. Aliquots (400 μl) were removed and the reactions were terminated by solvent extraction in 400 μl ice-cold Et_2O/CH_3OH/1 M citrate, pH 4.0 (30:4:1). The organic phase was spotted on a 20x20 cm TLC plate (EMD Kieselgel 60, VWR). The plate was developed in $EtOAc/CH_2Cl_2$/glacial AcOH (75:25:1), and radiolabeled prostaglandins were quantified with a radioactivity scanner (Bioscan, Inc., Washington, D.C.). The percentage of total products observed at different inhibitor concentrations was divided by the percentage of products observed for cells pre-incubated with DMSO.

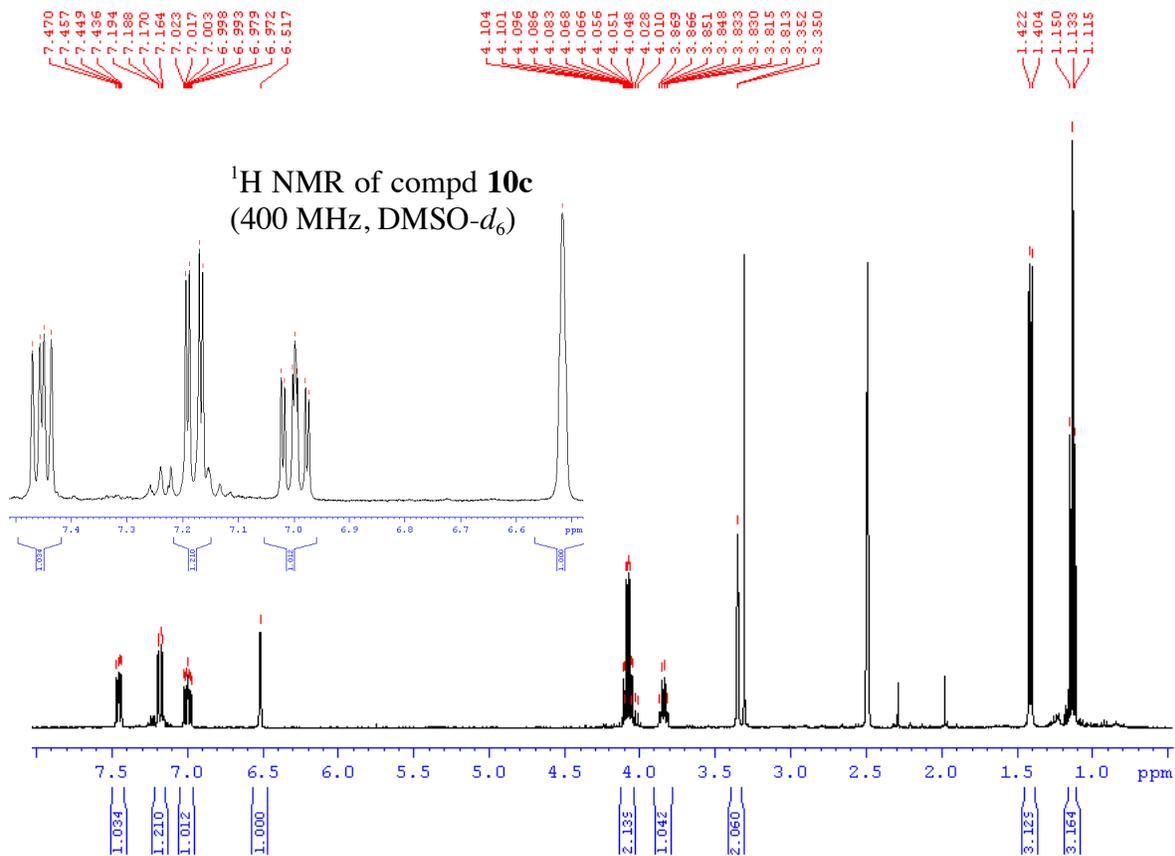*Human cancer cell viability screening assay:*

Human adenocarcinoma cells NIH:OVCAR-3 (HTB-161), SK-OV-3 (HTB-77), and MDA-MB-231 (HTB-26) (ATCC, passage number 8-20, mycoplasma-negative by pcr mycoplasma detection assay) were grown at 37°C in a humidified incubator with 5% CO_2 in RPMI 1640+10% FBS. Cells were plated in growth medium at 8000-10000 cells per well (100 μl) in 96 well plates (Sarstedt) and allowed to attach for 24 hrs. No cells were plated in the first column. Fresh RPMI 1640+10% FBS+penicillin/streptomycin (100 μl) containing the final concentrations of DMSO or test compound dilutions in DMSO (DMSO final concentration, 0.1%) was replaced in each well. After 48 hr of cell growth with respective treatments, WST-1 Cell Proliferation Reagent (Roche, 11644807001) was added (10 μl) to each well for 45-60 min at 37°C. The plates were read (Molecular Devices) at 450 nm for the formazan product and at 690 nm as a reference. Background absorbance (cell-free medium plus WST-1, first column) was averaged and subtracted from all values. Six replicates were used in the calculations per treatment concentration in duplicate experiments. Data was plotted as a percentage of the formazan product formation in vehicle-treated cells.
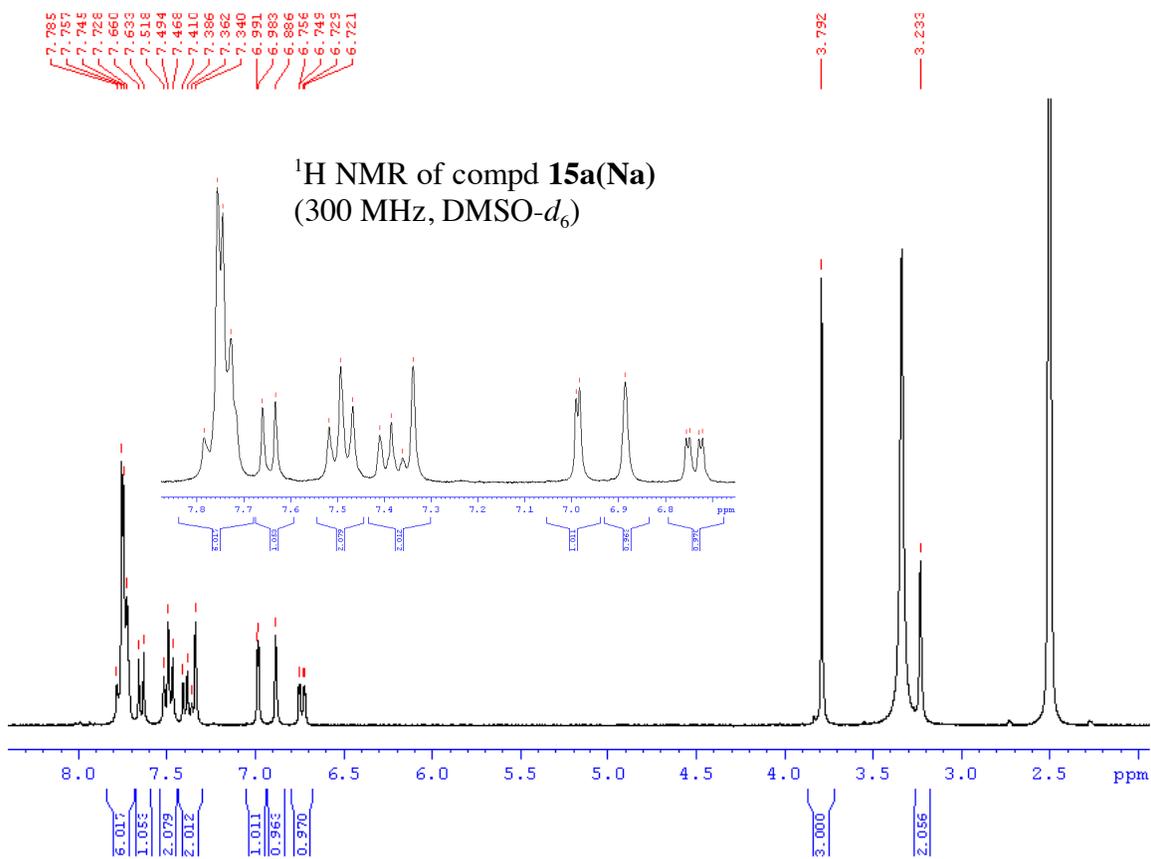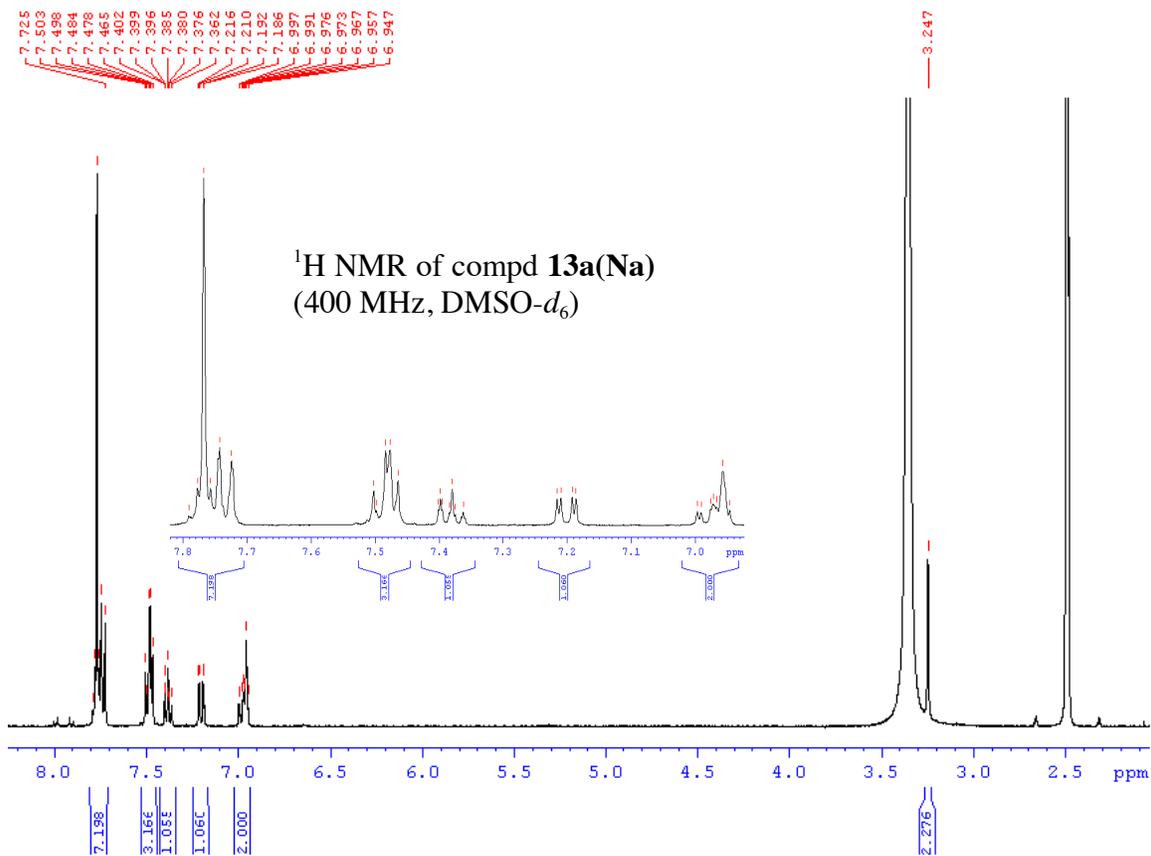
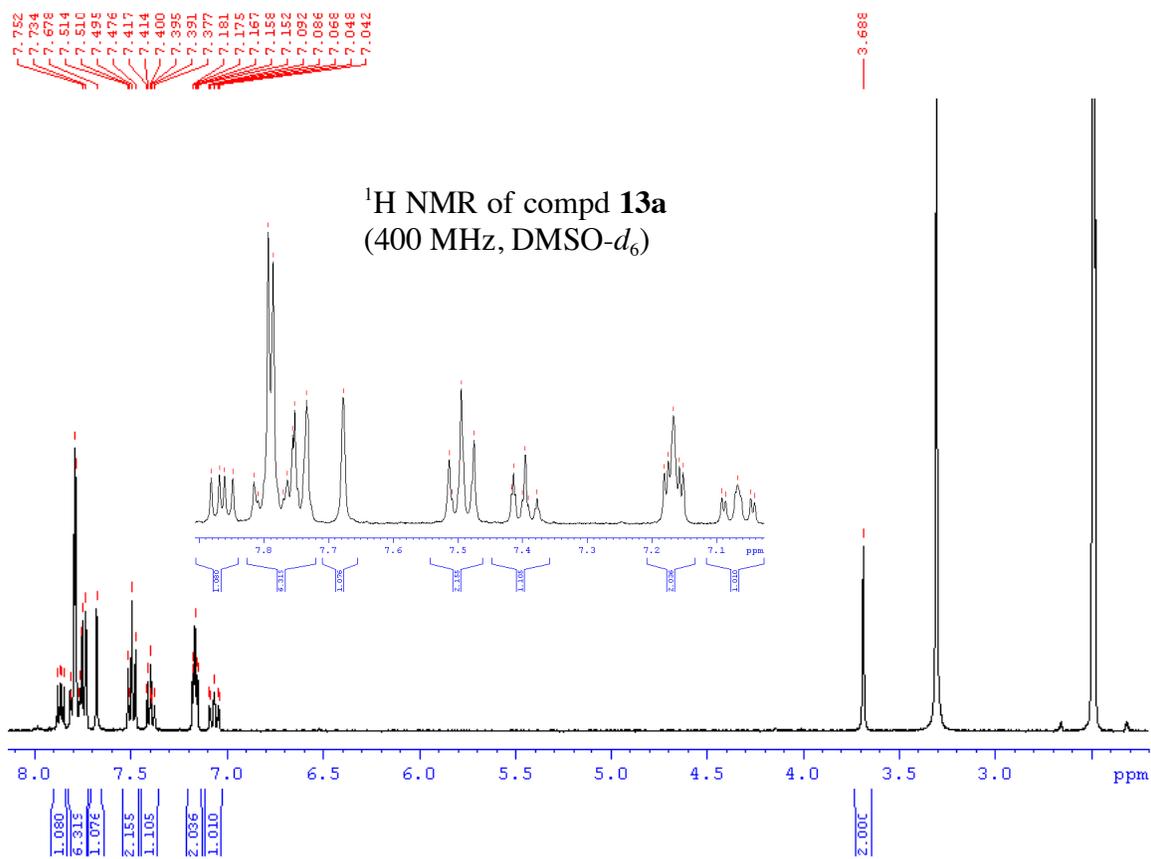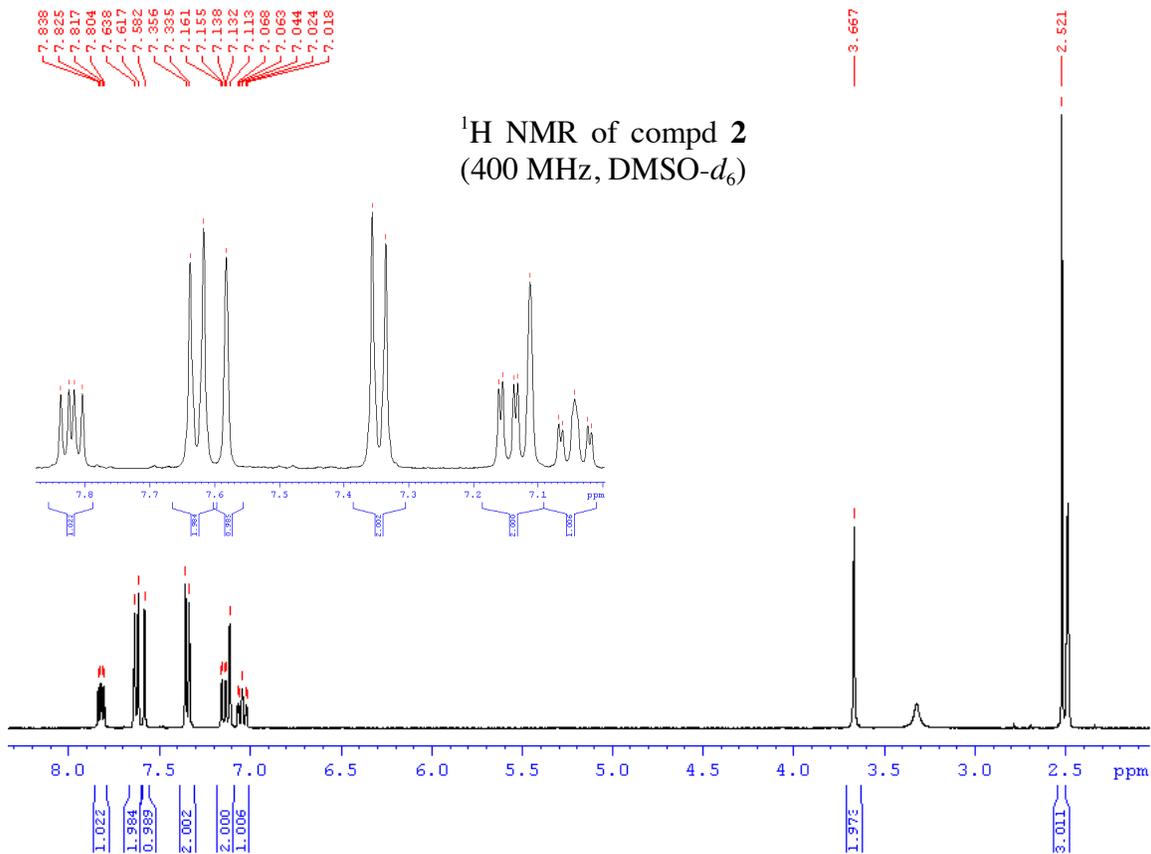*NIH:OVCAR-3 drug metabolism study (with compound **15a**).*

Human ovarian adenocarcinoma cells, OVCAR-3, passage 23, mycoplasma negative by pcr detection method (Sigma VenorGem) were grown in RPMI 1640 (Invitrogen/Gibco)+10% FBS (Atlas) to 60% confluence. Growth medium was removed and warm serum-free RPMI 1640 (Invitrogen/Gibco) (11 ml) was replaced in each flask. Inhibitor dissolved in DMSO (1 μM, final concentration) (11μl) was added to each flask. Aliquots (500 μl) were removed at time points for *t*=0m, 15m, 30m, 1 hr, 2hr, and 4hr. Each aliquot was mixed with 1.5ml ethyl acetate containing 1% acetic acid. For analysis of metabolites in the cell, all media was removed from the flasks and cells were scraped into PBS (5ml) then removed. Each flask was then rinsed with methanol (4ml).

Exemplified NMR spectra:

¹H NMR of compd **10a**
(400 MHz, DMSO-*d*₆)

¹H NMR of compd **10b**
(400 MHz, DMSO-*d*₆)

¹H NMR of compd **10c**
(400 MHz, DMSO-*d*₆)

¹H NMR of compd **10d**
(400 MHz, DMSO-*d*₆)

^{1}H NMR of compd **13a(Na)**
(400 MHz, DMSO-d_6)

^{1}H NMR of compd **15a(Na)**
(300 MHz, DMSO-d_6)

¹H NMR of compd **2**
(400 MHz, DMSO-*d*₆)

¹H NMR of compd **13a**
(400 MHz, DMSO-*d*₆)

^{1}H NMR of compd **13d**
(400 MHz, DMSO-d_6)

^{1}H NMR of compd **13g**
(400 MHz, DMSO-d_6)

^{1}H NMR of compd **13i**
(400 MHz, DMSO-d_6)

^{1}H NMR of compd **13k**
(400 MHz, DMSO-d_6)

^{1}H NMR of compd **15b**
(400 MHz, DMSO-d_6)

^{1}H NMR of compd **16d**
(400 MHz, DMSO-d_6)

^{1}H NMR of compd **17a**
(400 MHz, DMSO-d_6)

^{1}H NMR of compd **18a**
(400 MHz, DMSO-d_6)

^{1}H NMR of compd **19a**
(400 MHz, DMSO-d_6)

^{1}H NMR of compd **19b**
(400 MHz, DMSO-d_6)

^{1}H NMR of compd **19e**
(400 MHz, DMSO-d_6)

^{1}H NMR of compd **19i**
(400 MHz, DMSO-d_6)

^{1}H NMR of compd **20a**
(400 MHz, DMSO-d_6)

^{1}H NMR of compd **21b**
(400 MHz, DMSO-d_6)

^{1}H NMR of compd **21c**
(400 MHz, DMSO-d_6)

^{1}H NMR of compd **21m**
(400 MHz, DMSO-d_6)

Figure S1. Comparison of the HPLC profiles and UV spectra (λ=347 nm; method 1) of **11i** (left hand side) and its isolated Suzuki coupling product **13f** (right hand side). Suzuki couplings were performed on sub-millimolar scale in a sealed glass tube under argon as outlined in Scheme 2.[4] Primarily, 4-bromo benzylidene intermediate **11i** (table 1), which originates from the synthetic route shown in Scheme 1 was reacted with the appropriate boronic acids in 1,2-dimethoxyethane (DME) in the presence of tetrakis(triphenylphosphine)-palladium and potassium carbonate.

Figure S2. ¹H NMR of compd **20b**.
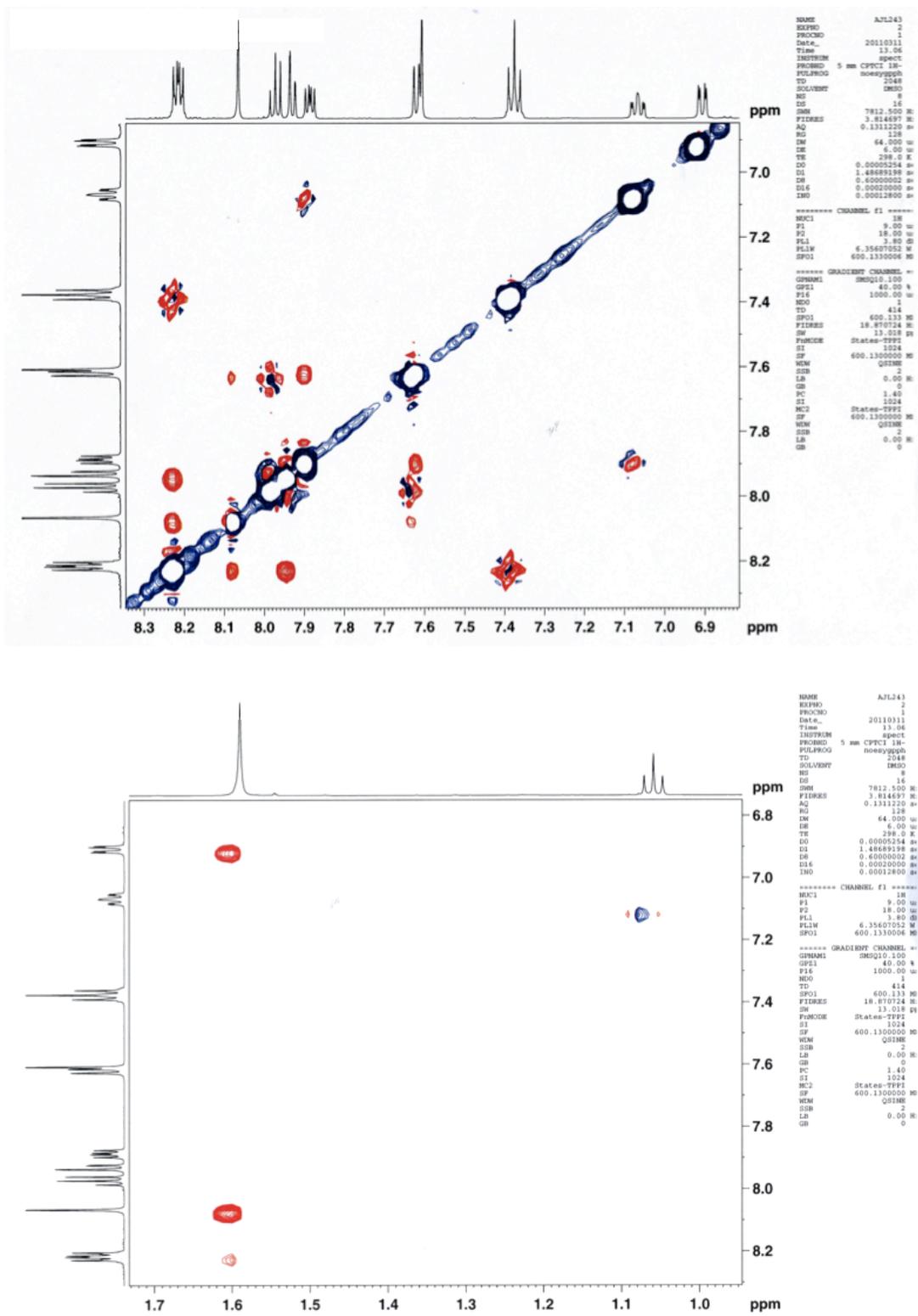
Figure S3. 2D <u>N</u>uclear <u>O</u>verhauser <u>E</u>ffect <u>S</u>pectroscopy (NOESY) of compound **20b**. Based on the recorded ^{1}H NMR peak shifts and splittings and the 2D NOESY spectrum, the stereochemistry of **20b** was understood to be (*E*), as it had been previously established for **2**.[13]
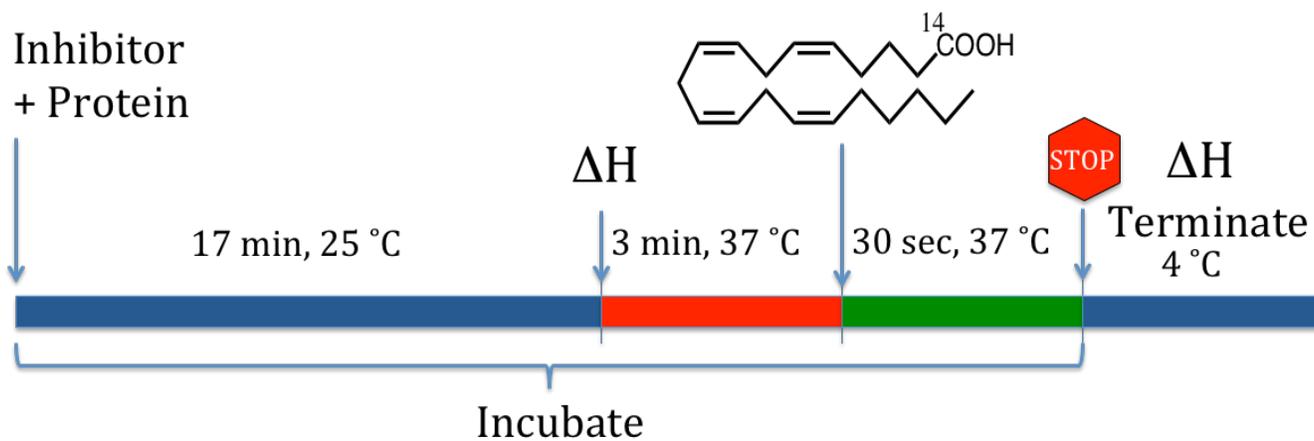
Figure S4. COX inhibition screening assay (experimental timeline)
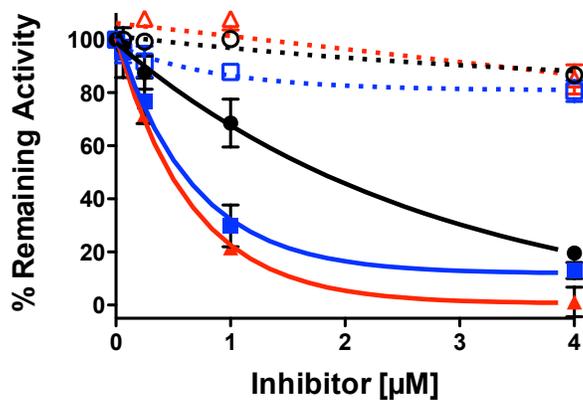
Figure S5. Competitive inhibition of ovine COX-1 and murine COX-2 by *E*-DMSS analogs **2** (COX-1-IC$_{50}$: 1.8 μM, COX-2: 10% inhibition at 4 μM), **13a** (COX-1-IC$_{50}$: 570 nM, COX-2: n. i. at 4 μM) and **21c** (COX-1-IC$_{50}$: 470 nM, COX-2: 15% inhibition at 4 μM) under low arachidonate conditions. (●) COX-1 and **2**, (○) COX-2 and **2**; (■) COX-1 and **13a**, (□) COX-2 and **13a**; (▲) COX-1 and **21c**, (△) COX-2 and **21c**.
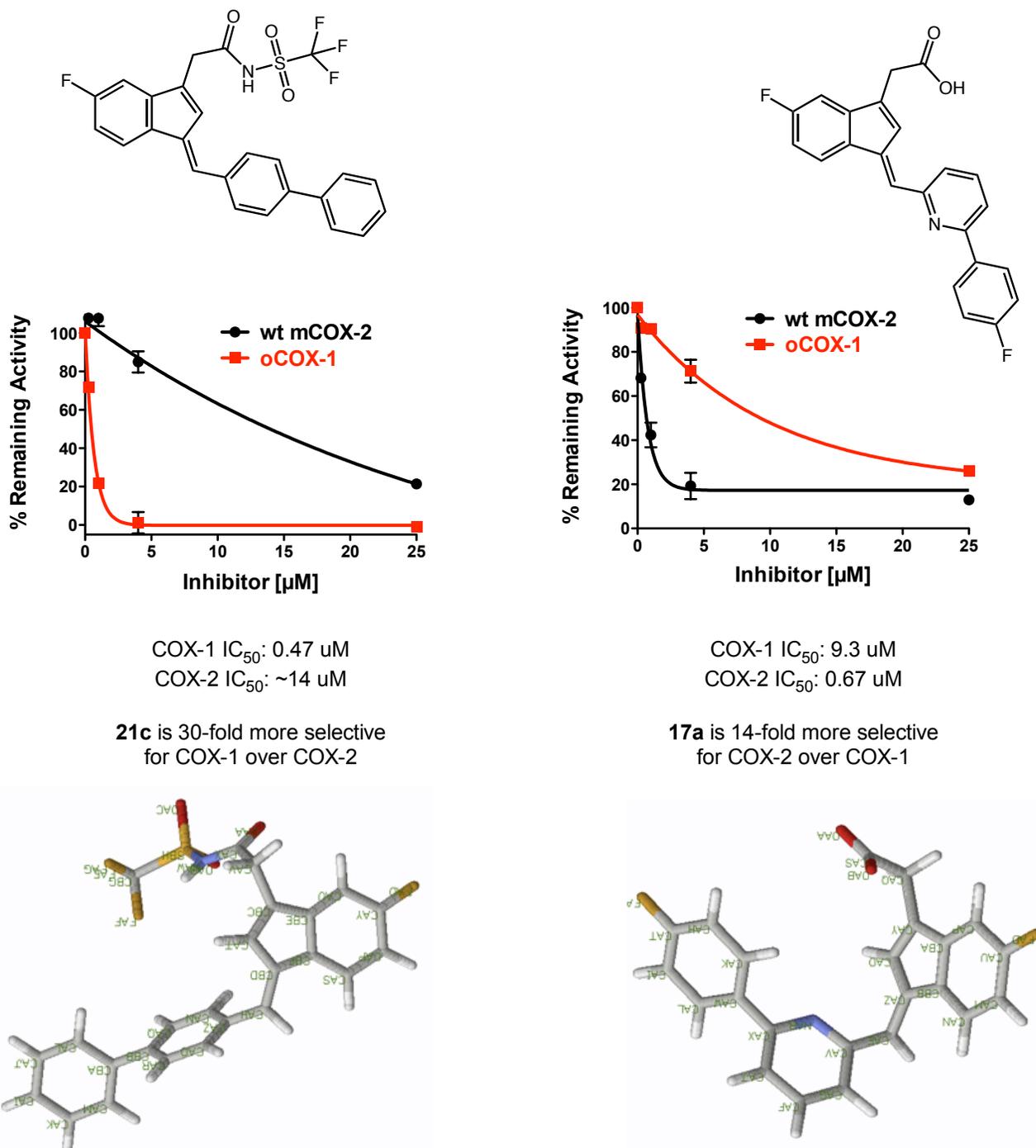
Figure S6. Dose-response curves for the inhibition of recombinant COX by **21c**, a potent COX-1-selective inhibitor (left hand side) and **17a**, a COX-2-selective inhibitor (right hand side) as well as energy minimizations of **21c** and **17a**. Energy minimized PDB coordinates and topology files were generated using Dundee PRODRG2 Server.[14] Without the 2′-methyl group, anchoring the (*E*)-DMSS analogs in the COX active sites, the compounds can be easily competed off of the enzyme by AA.[15] The curve characteristics with increasing inhibitor concentrations (up to 25 μM, e.g. for **21c**, **17a** or in individual cases even 250 μM) are consistent with a rapid reversible (time-independent) binding behaviour with these compounds. The rise in inhibitor concentration came along with the loss of binding prevalence of each compound for one specific COX-isoform and was all but annulled at concentrations above 25 μM, where both COX enzymes are about equally inhibited. The structures of **17** & **20** did not superimpose properly with the more elongate template of coumpounds **13** or **21c** as emulation of the favored *S-trans* form of **5** for COX-1 binding (figure 1). Compounds **17** (& **20**), whose biphenyl-3-ylmethylidene substituent must cause more steric collisions than the other indene derivatives with

para-configurated substituents at their 1′-position, still retain the *E*-configuration at the exocyclic double bond. This was verified for **20b** by 2D-NOESY (see Supplementary Figures S2 & S3). In analogy to celecoxib (**6**), compound **17a** was also unable to block COX-1-mediated AA-metabolism in OVCAR-3 cells (data not shown).
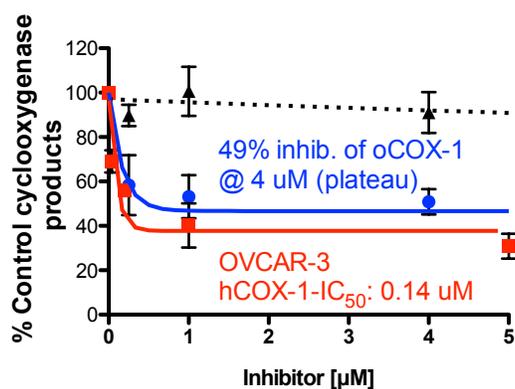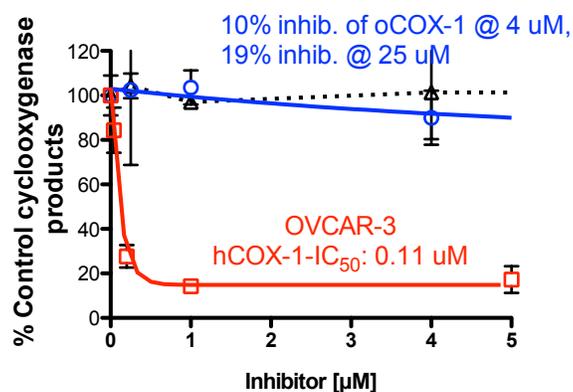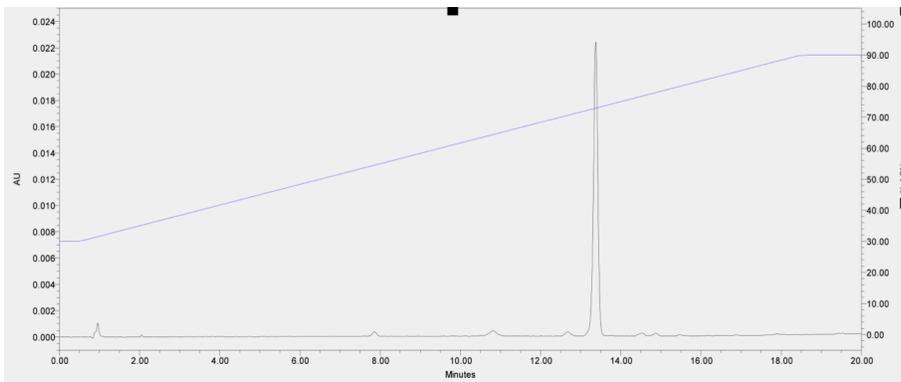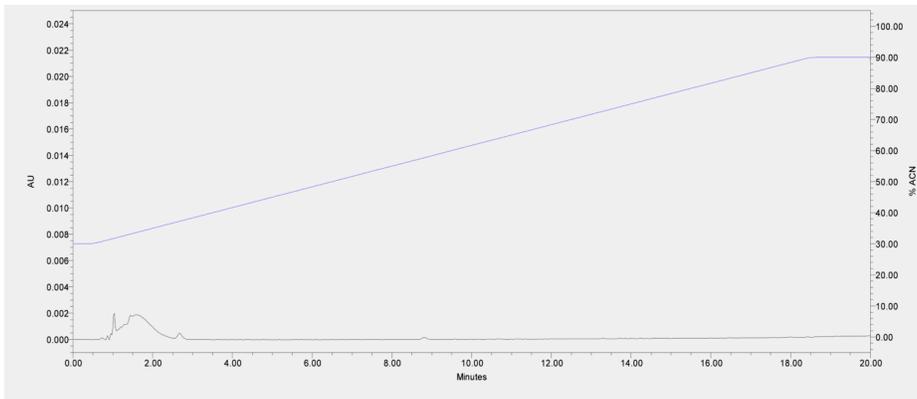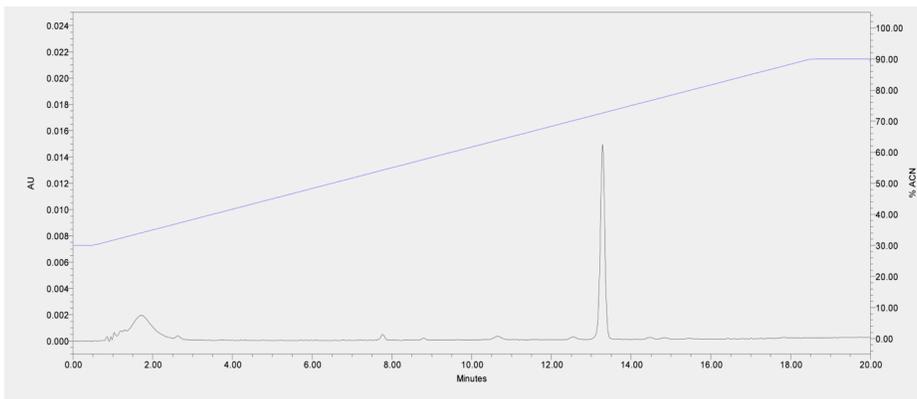
Figure S7. Comparison of the inhibition of recombinant oCOX-1, mCOX-2 (5 μM 14C-AA, 3 min at 37°C) and hCOX-1 in OVCAR-3 cells (8 μM 14C-AA, 30 min at 37°C) by compounds **15a** (upper graph) and **15b** (lower graph). (○) oCOX-1 and **15a**, (△) mCOX-2 and **15a**, (□) hCOX-1 and **15a**; (●) oCOX-1 and **15b**, (▲) mCOX-2 and **15b**, (■) hCOX-1 and **15b**.
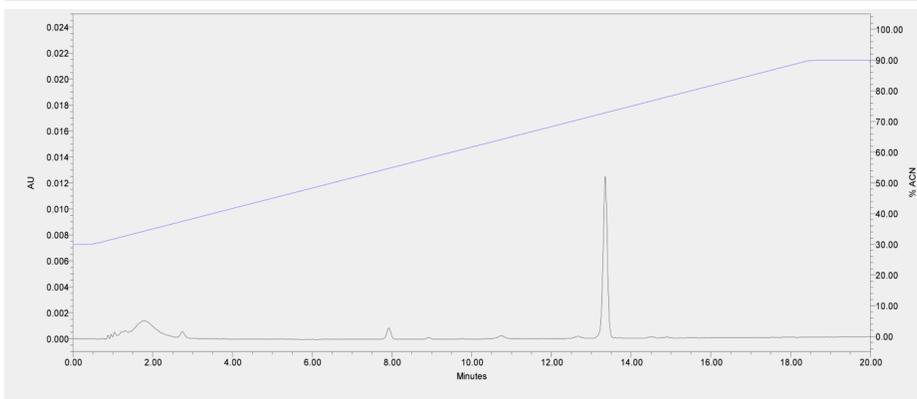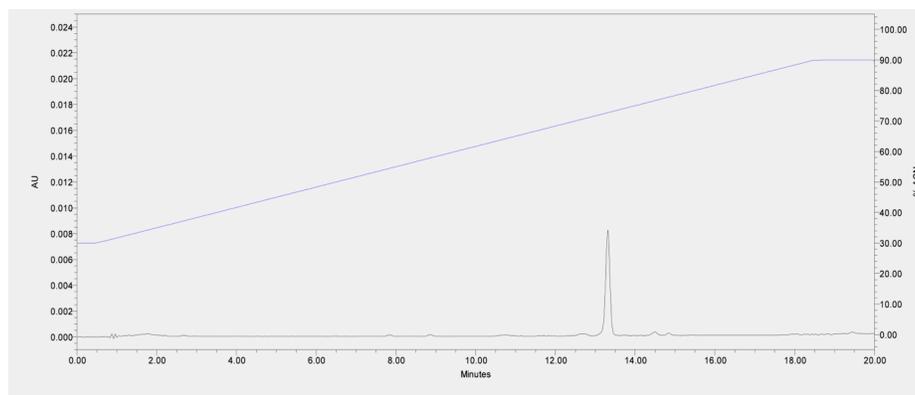
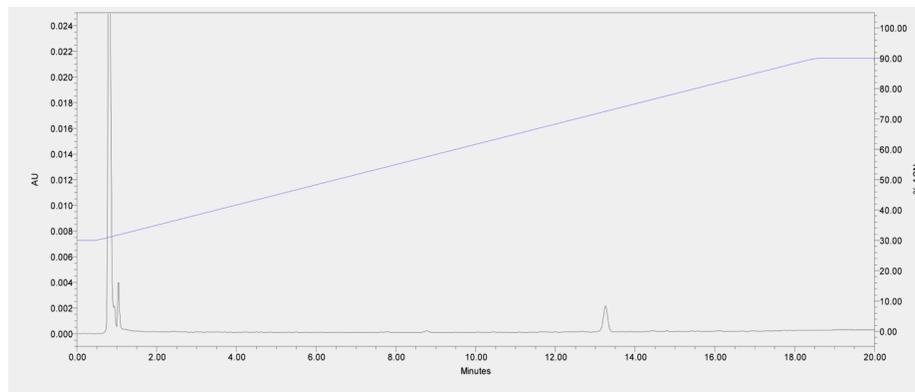standard (**15a**)

fresh culture media

EA extract after 30 min

EA extract after 4 h

cell scrape (PBS)

MeOH rinse (plastic tubes)

Figure S8. HPLC analyses of ethyl acetate (EA) extracts from culture media and scraped whole cells @254 & 375 nm (after incubation with **15a** (1 %) at increasing time points). EA extracts of the culture medium following different incubation experiments with **15a** (at increasing time points, 0', 15', 30', 1h, 2h, 4h) did not show the formation of any metabolite(s). We also scraped the medium-free cells (4h incubation) using PBS and analyzed the organic whole cell extracts with the same negative result. As the applied drug **15a** appeared to be still intact after after 4 h incubation with OVCAR-3 cell-media, other factors than metabolism might be in charge for favoring the intracellular accumulation and the activity seen in OVCAR-3 cells (Fig. S7). Differences in the inhibitory behaviour at the purified oCOX-1 enzyme and in the cells (hCOX-1) could also originate from interindividual sequence variations between the COX-1 enzymes coming from unlike species.
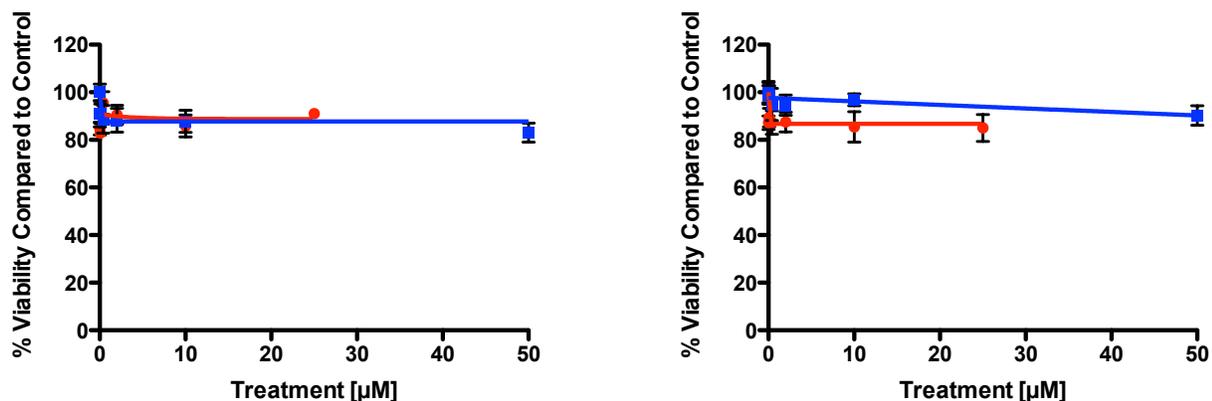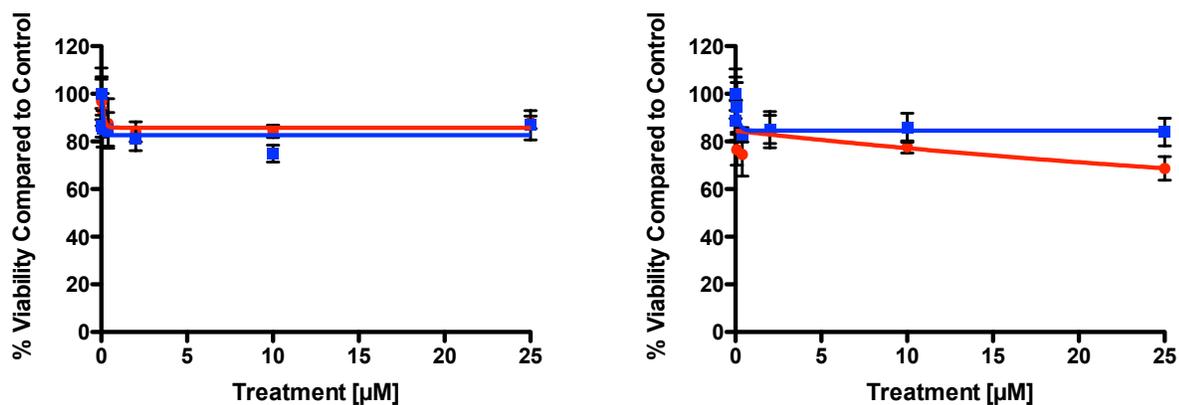
Figure S9a. OVCAR-3 (COX-1-positive cell line, left hand side) and SKOV-3 (COX-1-negative cell line, right hand side) growth inhibition by compounds **2** (■) and **13a** (●) at concentration < 25 (50) μM.[16] Standard assay (see biological methods): drugs added at 20% confluence; growth for 2 days plated at 10,000 cells per well.


Figure S9b. OVCAR-3 (COX-1-positive cell line, left hand side) and SKOV-3 (COX-1-negative cell line, right hand side) growth inhibition by compounds SC-560 (**5**, ■) and indomethacin (**3**, ●) at concentration < 25 μM.[16] Standard assay (see biological methods): drugs added at 20% confluence; growth for 2 days plated at 10,000 cells per well.

Neither the SK-OV-3 cells nor the OVCAR3 cells were sensitive to growth inhibition by any of the drug additions at concentrations < 25(50) μM.
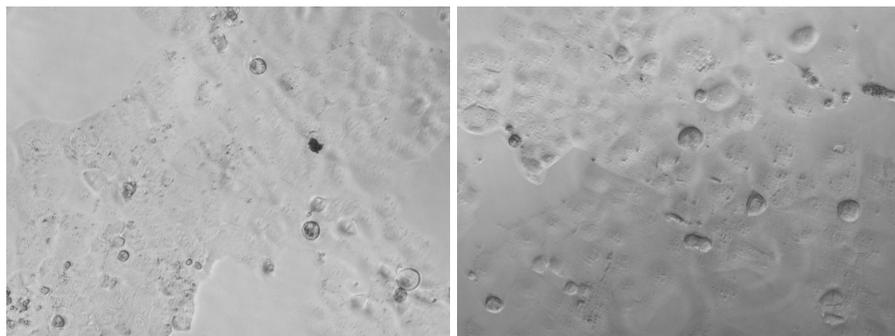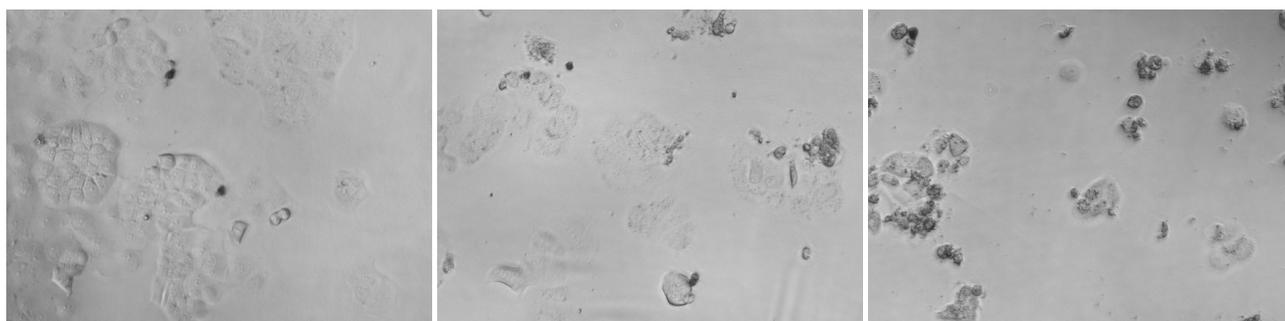
DMSO after 48 h

Sulindac 1 μM   83.3 μM   250 μM
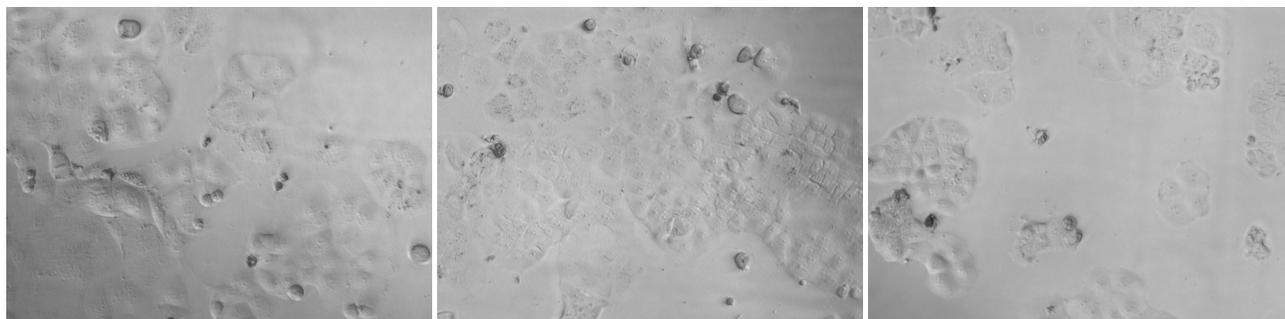
compd **21b** 1 μM   83.3 μM   250 μM

Figure S10. Close-up view on the OVCAR-3 growth inhibition by sulindac (**1a**) & compound **21c** (higher inhibitor concentrations)
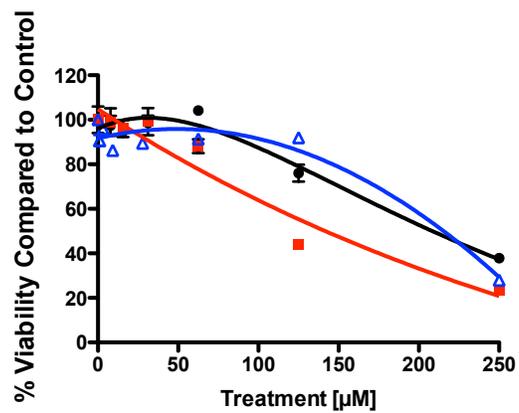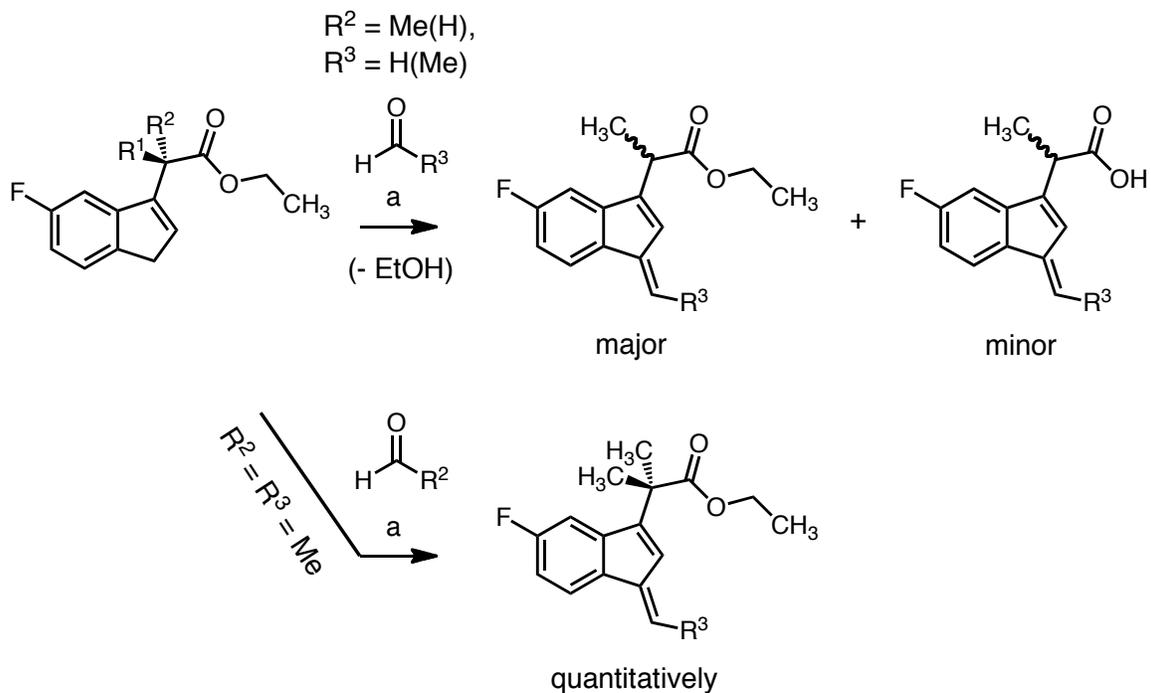
Figure S11. MDA-MB-231 Cell Viability (48 hr treatment) with **1b** (●, EC$_{50}$: 209 μM), **13a** (■, EC$_{50}$: 141 μM) or **21b** (△, EC$_{50}$: 215 μM).

Scheme S1. Synthetic route to *2′-des*-methyl indene acetic acid derivatives with additional alkyl substituents in α-position to the carboxylic group.

R² = Me(H),
R³ = H(Me)

major

+

minor

R² = R³ = Me

a

quantitatively

Reagents and conditions: (a) 1 N NaOH/MeOH, 70 ˚C, 2-3 h then RT overnight

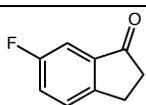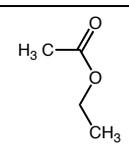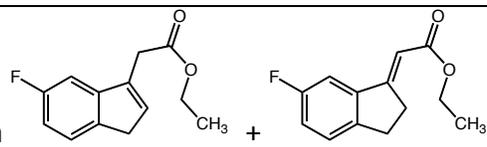**Table S1.** Summary of the synthesized indene intermediates.

Starting Indanone	Alkylation reagent	Isolated Indene Product(s) (after dehydration)		yield over 2 steps	HPLC purity (@254 nm)	Characteriz.
8a	**10a**	+		66% *via* **9a**	≥ 95%	1:1 mixture of isomers
8b	**10b**	+		25% *via* **9b**	≥ 95%	mixture of isomers
8a	**10c**	+		26% *via* **9c**	≥ 95%	mixture of enantiomers (racemate)
8a	**10d**			47% *via* **9d**	≥ 95%	single isomer
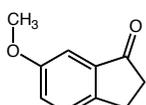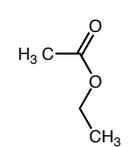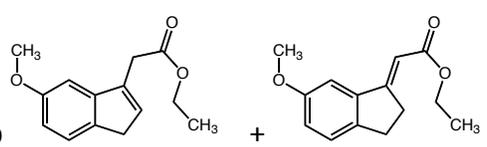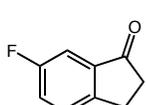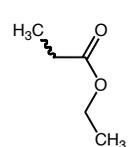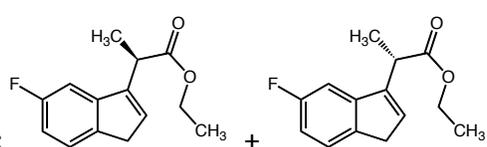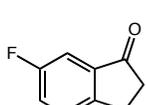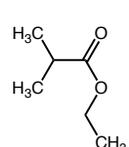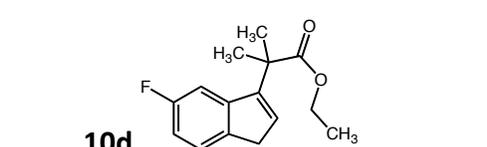
Table S2. Isolated sodium salts of different *E*-DMSS analogs
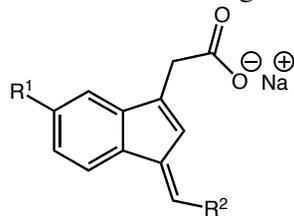
Compd #	R^1	R^2
13a(Na)	F	
13e(Na)	F	
15b(Na)	OMe	
15c(Na)	OMe	

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Table S3. COX-1 and COX-2 inhibition by 5′-F analogs of *E*-DMSS.
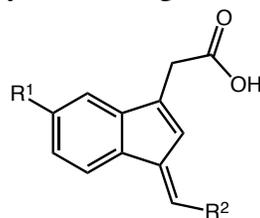
Compd #	R¹	R²	oCOX-1 %-inhibition @ 4 μM[a]	mCOX-2 %-inhibition @ 4 μM[a]
15a	OMe		16 ± 6 (6)	8 ± 7 (6)
15b	OMe		38 ± 7 (4)	2 ± 5 (4)

Compounds were screened at 4 μM. A concentration of 5 μM of AA-substrate was employed.

[a] Mean ± SEM of two (n) experiments.

Table S4. Detailed screening data for exemplified compounds

LM#	oCOX-1-IC$_{50}$ [μM]	% mCOX-2 inhib. @ 4 μM	OVCAR-3 AA-metabolism hCOX-1-IC$_{50}$ [μM][a]	OVCAR-3 growth inhibition (2-day treatment) EC$_{50}$ [μM][b]
2	~2 (complete inhibition)	10	0.12	~223; no inhib. up to 50 μM; likewise SC-560 (**6**) & INDO (**5**) ineffective
11g	3.2	13 (IC$_{50}$: ~26 μM)	n.d.	
13a(Na)	n.d.	n.d.	0.95	No effect up to 25 μM; likewise **5** & **6** ineffective
13a	0.57 (complete inhibition)	1	0.3	~132;[c] sulindac sulfide (**2**): ~210
15a	16% @ 4 μM	8	0.11	
15b	~38-49% @ 4 μM (plateauing)	2	0.14	
16e	1.1	28 (IC$_{50}$: ~10 μM)	n.d.	
17a	17% @ 4 μM	IC$_{50}$: 0.67 μM	>>5	
19a	17% @ 4 μM	16% @ 4 μM	0.49	
19c	2.2	8.5	1.3	
19d	26% @ 4 μM	2	>>5	
21a	21% @ 4 μM	7	0.83	
21b	0.7-1.0 (compl. Inhibition)	15(24)	0.094	~160;[d] sulindac (**1**): no inhib.
21c	0.47	15	0.495	
21e	2.7	20	n.d.	
21f	2.0	26	n.d.	
21h	3.9	19	n.d.	
21j	2.0	34	n.d.	
21n	58% @ 4 μM	8	0.33	

n.d. = not determined

[a] OVCAR-3 hCOX-1-IC$_{50}$ by SC-560: 0.16 μM; Celecoxib (**6**), a COX-2-selective inhibitor, was used as negative control and revealed only 17% inhibition @ 5 μM

[b] SC-560 (**5**), indomethacin (**3**), sulindac (**1a**) or sulindac sulfide (**1b**) were used as reference

[c] MB-231 cell viability reduced with EC$_{50}$=141 μM

[d] MB-231 cell viability reduced with EC$_{50}$=215 μM

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