Supporting Information

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

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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 ¹H 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 F₂₅₄, 2mm, 20x20 cm plates (EMD No. 5717-7). Analytical thin-layer chromatography (TLC) analyses were performed on fluorescent silica gel 60 F₂₅₄ 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:
¹H and ¹³C 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 2.25 and δ 40.45 (DMSO-d₆). ¹³F NMR spectra were collected on a Bruker AV-300 at 282 MHz. Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, sept = septet, br = broad, dd = doublet of doublets, dq = doublet of quadruplets, td = triplet of doublet, pd = pentet of doublets, 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 KH₂PO₄ system at a flow rate of 1.0 mL/min or an ACN-H₂O (plus 0.1 % TFA) system at a flow rate of 1.4 mL/min, respectively. (HP)LC was performed either on a Waters HPLC system⁴ 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 dR (min) and relative purity (%). The purity of all tested compounds is >95%, if not denoted otherwise.

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 % NH₄⁺-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$_2$PO$_4$)
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

\[^{a}\text{Monobasic potassium phosphate solution 0.01 M (pH 2.3) was prepared by dissolving 1.361 g of monobasic potassium phosphate in 800 mL of water (bidest.), adjusting to pH 2.3 with 10% H}_3\text{PO}_4 \text{(v/v) and diluting to 1000 mL with water.}\]

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

| Time   | Solv. B | Flow |
|--------|---------|------|
| 50.0   | 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.¹²

**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•H₂O (4.8 g, 25.2 mmol), and CaCl₂•2H₂O (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, NaHCO₃, water, dried (MgSO₄), 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 G: Knoevenagel condensation of the indene intermediates with different (hetero)arylalkyl 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 CH2Cl2 (3 x 30 mL). The combined organics were optionally washed with water, NaHCO3, water, dried (MgSO4), filtered, and then concentrated in vacuo. All purifications were performed via preparative TLC, column chromatography or flash chromatography on SiO2 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 exhaster and usually required no further purification.

General Procedure E: Suzuki-Miyaura Coupling reaction.

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(PPh3)4, and K2CO3 in DME/H2O 2:1 was degassed with N2, 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 (MgSO4), 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.

Acidic starting compounds were suspended/dissolved in the appropriate alcohol (15 ml/mmol). After the addition of concentrated H2SO4 (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.

General Procedure G-variant: 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 H2O per 0.1 mmol starting 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 Na2SO4 and evaporated.
**General Procedure G**

A yellow solution of the (ethyl) ester derivative (1 equiv.) 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 acetate. The combined organic extracts were dried over Na$_2$SO$_4$ and the solvent removed at reduced pressure prior to column chromatography.

**General Procedure H:** *Synthesis of sulfonimides via CDI carbodiimide coupling.*

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$_2$Cl$_2$ (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$_2$Cl$_2$ (1 mL/0.5 mmol). The organic layer was separated and washed with 10% NaH$_2$PO$_4$ buffer (pH 4) (2 x 2 mL) and water (3 x 2 mL), dried over Na$_2$SO$_4$, 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.*

Oxalyl chloride (1.2 equiv.) was added dropwise to a solution of the respective free acid derivative of 2′-des-methyl sulindac sulfide in dry CH$_2$Cl$_2$ (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.*

The reactive ‘acid chloride derivative’ and 1.5 equivalents of the respective (substituted) sulfonamide were dissolved in 1,2-DCE or CH$_2$Cl$_2$ (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$_2$SO$_4$, 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-1H-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-1H-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) t_R: 6.10 min.

**Ethyl 2-(1-hydroxy-6-methoxy-2,3-dihydro-1H-inden-1-yl)acetate (9b).**
According to general procedure A, the title compound was obtained from ethylacetate (2.73 g, 31.0 mmol) and 6-methoxy-2,3-dihydro-1H-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-1H-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-1H-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) t_R: 6.63 min and 7.14 min.

**Ethyl 2-(6-fluoro-1-hydroxy-2,3-dihydro-1H-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-1H-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) t_R: 8.17 min.
Synthesis of the indene intermediates 10 (table S1):

Mixture of ethyl 2-(5-fluoro-1H-inden-3-yl)acetate (isomer A) and ethyl 2-(6-fluoro-2,3-dihydro-1H-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_{15}FO_{2}, M_{r} = 220.25; isomer A (endocyclic DB): 1H NMR (400 MHz, DMSO-d_{6}) δ: 1.18 (t, J=7.2 Hz, 3H), 3.28 (s, 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): 1H 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) tR: 6.92 min (isomer A) and tR: 9.44 min (isomer B); LCMS (ESI) (method 2) tR: 2.81 and 3.05 min (UV220, UV254), m/z: 221.2 [M+1]^+.

Mixture of ethyl 2-(5-methoxy-1H-inden-3-yl)acetate (isomer A) and ethyl 2-(6-methoxy-2,3-dihydro-1H-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_{17}O_{3}, M_{r} = 232.28; isomer A (endocyclic DB): 1H 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): 1H 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) tR: 6.92 min (isomer A) and tR: 9.05 min (isomer B); LCMS (ESI) (method 2) tR: 2.71 and 2.98 min (UV220, UV254), m/z: 233.2 [M+1]^+.

(R/S)-ethyl 2-(5-fluoro-1H-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; 1H 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,
\[ J=0.8 \text{ Hz}, 2H), 3.84 \text{ (dq, } J=1.1/7.2 \text{ Hz, 1H)}, 4.08 \text{ (dq, } J=1.0/7.0 \text{ Hz, 2H)}, 6.52 \text{ (s, 1H)}, 7.00 \text{ (td, } J=2.4/8.8 \text{ Hz, 1H)}, 7.18 \text{ (dd, } J=2.4/9.6 \text{ Hz, 1H)}, 7.45 \text{ (dd, } J=5.2/8.4 \text{ Hz, 1H}); \text{HPLC (method 1) } t_R: 8.92 \text{ min; LCMS (ESI) (method 2) } t_R: 3.00 \text{ min (UV220, UV254), } m/z: 235.2 \text{ [M+1]}.\]

**Ethyl 2-(5-fluoro-1H-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): \(C_{15}H_{17}FO_2, M_r = 248.30; ^1H\) NMR (400 MHz, DMSO-\(d_6\)) \(\delta: 1.05 \text{ (t, } J=7.2 \text{ Hz, 3H)}, 1.49 \text{ (s, 6H)}, 3.35 \text{ (s, 2H)}, 4.06 \text{ (q, } J=7.2 \text{ Hz, 2H)}, 6.56 \text{ (t, } J=2.0 \text{ Hz, 1H)}, 6.91 \text{ (dd, } J=2.4/9.8 \text{ Hz, 1H}), 6.99 \text{ (dt, } J=0.8/2.4/8.2 \text{ Hz, 1H)}, 7.46 \text{ (dd, } J=5.2/8.0 \text{ Hz, 1H}); ^19F\) NMR (282 MHz, DMSO-\(d_6\)) \(\delta: -115.43 \text{ (d, } 1F, C_5'F); \text{HPLC (method 1) } t_R: 9.30 \text{ min; LCMS (ESI) (method 2) } t_R: 3.13 \text{ min (UV220, UV254), } m/z: 249.2 \text{ [M+1]+}.

**Synthesis of 2’-des-methyl sulindac sulfide analogues 12g, 13c, d, 13 g-j & 17a-f (table 2):**

\((E)-2-(1-(1,8-naphthyridin-2-yl)methylene)-5-fluoro-1H-inden-3-yl)acetic acid (12g).\)

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 \(12g\): \(C_{20}H_{13}FN_2O_2, M_r = 332.34; ^1H\) NMR (400 MHz, DMSO-\(d_6\)) \(\delta: 3.71 \text{ (s, 2H)}, 7.08 \text{ (td, } J=2.4/9.2 \text{ Hz, 1H}), 7.18 \text{ (dd, } J=2.4/8.8 \text{ Hz, 1H}), 7.64 \text{ (dd, } J=4.0/8.0 \text{ Hz, 1H)}, 7.74 \text{ (s, 1H)}, 7.88-7.91 \text{ (m, 2H)}, 8.01 \text{ (s, 1H)}, 8.46 \text{ (dd, } J=2.0/8.0 \text{ Hz, 1H}), 8.53 \text{ (d, } J=8.4 \text{ Hz, 1H)}, 9.12 \text{ (dd, } J=2.0/4.4 \text{ Hz, 1H}); \text{HPLC (method 1) } t_R: 6.76 \text{ min (95%, UV347); LCMS (ESI) (method 2) } t_R: 1.74 \text{ min (>99%, ELSD), } m/z: 333.2 \text{ [M+1]+}.

\((E)-2-(1-(9H-fluoren-2-yl)methylene)-5-fluoro-1H-inden-3-yl)acetic acid (13c).\)

According to general procedure C, the title compound was obtained from the isomer mixture \(10a\) (0.10 g, 0.45 mmol) and 9H-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)-1H-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 (dt, $J=1.2/2.4/8.4$ 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)-1H-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)-1H-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 (SiO₂, EtOAc/hexane, 0.5% AcOH) to afford 39 mg (24%) of 13h: C₂₂H₁₅FN₂O₂, Mᵣ = 358.38; ¹H NMR (400 MHz, DMSO-d₆) 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) tR: 9.84 min (97%, UV347); ESI/MS: calcd: 357, found: 357.13 ([M-1]+, 37%), 313.27 ([M-1]+-CO₂, 100%).

(E)-2-(1-((2-cyclohexylpyrimidin-5-yl)methylene)-5-fluoro-1H-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 (SiO₂, EtOAc/hexane, 0.5% AcOH) to afford 32 mg (39%) of 13i: C₂₂H₂₁FN₂O₂, Mᵣ = 364.42; ¹H NMR (400 MHz, DMSO-d₆) 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) tR: 9.89 min (98%, UV347); ESI/MS: calcd: 363, found: 363.20 ([M-1]+, 44%), 319.33 ([M-1]-CO₂, 100%).

(E)-2-(5-fluoro-1-((4-methyl-2-phenylpyrimidin-5-yl)methylene)-1H-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 (SiO₂, EtOAc/hexane, 0.5% AcOH) to afford 43 mg (51%) of 13j: C₂₃H₁₇FN₂O₂, Mᵣ = 372.40; ¹H NMR (400 MHz, DMSO-d₆) 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) tR: 10.16 min (97%, UV347); LCMS (ESI) (method 2) tR: 2.95 min (97%, ELSD), m/z: 373.2 [M+1]+.

(E)-2-(5-fluoro-1-((6-(4-fluorophenyl)pyridin-2-yl)methylene)-1H-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)picilinaldehyde (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 (SiO₂, EtOAc/hexane, 0.5% AcOH) to afford 17 mg (20%) of 17a: C₂₃H₁₅F₂NO₂, Mᵣ = 375.38; ¹H NMR (400 MHz, DMSO-d₆) 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) tR: 10.26 min (97%, UV347); LCMS (ESI) (method 2) tR: 2.98 min (95%, ELSD), m/z: 376.2 [M+1]+.

(E)-2-(5-fluoro-1-((6-(4-methoxyphenyl)pyridin-2-yl)methylene)-1H-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)picilinaldehyde (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 (SiO₂, EtOAc/hexane, 0.5% AcOH) to afford 13 mg (15%) of 17b: C₂₄H₁₈FNO₃, Mᵣ = 387.41; ¹H NMR (400 MHz, DMSO-d₆) 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) tR: 10.17 min (93%, UV347); ESI/MS: calcd: 386, found: 386.13 ([M-1]⁺, 17%), 342.27 ([M-1]⁺-CO₂, 100%).

(E)-2-(1-((6-(benzo[d][1,3]dioxol-5-yl)pyridin-2-yl)methylene)-5-fluoro-1H-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)picilinaldehyde (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 (SiO₂, EtOAc/hexane, 0.5% AcOH) to afford 23 mg (25%) of 17c: C₂₄H₁₈FNO₄, Mᵋ = 401.40; ¹H NMR (400 MHz, DMSO-d₆) 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: C₂₄H₁₈FNO₄S, Mᵋ = 435.48; ¹H NMR (400 MHz, DMSO-d₆) 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 (SiO₂, EtOAc/hexane, 0.5% AcOH) to afford 29 mg (35%) of 17e: C₂₁H₁₄FNO₂S, Mᵋ = 363.41; ¹H NMR (400 MHz, DMSO-d₆) 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]+.
\[ (E)-2-(1-([1,1']-biphenyl)-3-ylmethene)-5-fluoro-1H-inden-3-yl)acetic\ acid\ (17f).\]

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):

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

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; ^1H 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-ylmethene)-5-fluoro-1H-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; 'H 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); '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)-1H-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}FNaO_2, M_r = 396.36; 'H 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); 'F NMR (282 MHz, DMSO-d_6) δ: -113.16 (s, 1F, 4′-fluoro-biphenyl).

sodium (E)-2-(1-([1,1′-biphenyl]-4-ylmethylene)-5-methoxy-1H-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; 'H 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-((2\text{-fluoro-[1,1′-biphenyl]-4-yl)methylene})-5\text{-methoxy-1H-inden-3-yl})\text{acacetate (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):  

\[
\text{C}_{25}\text{H}_{18}\text{FNaO}_3, \text{Mr} = 408.40; \quad ^1\text{H} \text{NMR (300 MHz, DMSO-}d_6) \delta: 3.24 (s, 2H), 3.79 (s, 3H), 6.74 (dd, \text{J} = 2.2/8.2 \text{ Hz}, 1H), 6.86 (s, 1H), 6.98 (d, \text{J} = 2.4 \text{ Hz}, 1H), 7.32 (s, 1H), 7.40-7.65 (m, 9H); \quad ^{19}\text{F} \text{NMR (282 MHz, DMSO-}d_6) \delta: -116.41 (q, 1F, biphenyl).
\]

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

\((E)-2-((1,1′\text{-biphenyl}-4-yl)methylene)-5\text{-fluoro-1H-inden-3-yl})\text{acetic acid (13a).}\n
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\textsubscript{2}O. Yield: 25.5 mg (90%):  

\[
\text{C}_{24}\text{H}_{17}\text{FO}_2, \text{Mr} = 356.39; \quad ^1\text{H} \text{NMR (400 MHz, DMSO-}d_6) \delta: 3.69 (s, 2H), 7.07 (td, \text{J} = 2.4/9.2 \text{ Hz}, 1H), 7.15-7.18 (m, 2H), 7.39 (tt, \text{J} = 1.2/2.0/7.6 \text{ Hz}, 1H), 7.49 (td, \text{J} = 2.0/7.1 \text{ Hz}, 2H), 7.68 (s, 1H), 7.73-7.81 (m, 6H), 7.86 (dd, \text{J} = 5.2/8.4 \text{ Hz}, 1H); \quad ^{19}\text{F} \text{NMR (282 MHz, DMSO-}d_6) \delta: -113.14 (d, 1F, C5′-F); \quad \text{LCMS (ESI) (method 2) \text{rR}: 3.17 min (>99%, ELSD), m/z: 358.2 [M+1].}\n\]

\((E)-2-((5\text{-fluoro-1-((4′\text{-fluoro-[1,1′-biphenyl]-4-yl)methylene})-1H-inden-3-yl})\text{acetic acid (13e).}\n
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\textsubscript{2}O. Yield: 26 mg (92%):  

\[
\text{C}_{24}\text{H}_{16}\text{F}_2\text{O}_2, \text{Mr} = \]
374.38; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\): 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-\(d_6\)) \(\delta\): -113.15 (1F, C\(_4\)′-F biphenyl), -112.97 (1F, C\(_5\)-F); LCMS (ESI) (method 2) \(t_R\): 3.20 min (>99%, ELSD), \(m/z\): 375.2 [M+1]*.

\((E)-2-(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-\(d_6\)) \(\delta\): 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) \(t_R\): 3.14 min (≥95%, ELSD), \(m/z\): 369.2 [M+1]*.

\(1^{st}\)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-\(d_6\)) \(\delta\): 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-\(d_6\)) \(\delta\): -112.94 (d, 1F, C\(_5\)′-F), -59.06 (s, 3F, -CF\(_3\)); HPLC (method 1) \(t_R\): 11.97 min; LCMS (ESI) (method 2) \(t_R\): 3.10 min (≥95%, ELSD), \(m/z\): 425 [M+1]*.
(E)-2-(5-fluoro-1-(4-(6-fluoropyridin-3-yl)benzyldiene)-1H-inden-3-yl)acetic acid (13k).

According to general procedure F, the title compound was obtained from (E)-2-(1-(4-bromobenzylidene)-5-fluoro-1H-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$_{17}$F$_2$NO$_2$, M$_r$ = 375.37; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 3.69 (s, 2H), 7.07 (td, $J$=1.2/4.8 Hz, 1H), 7.14-7.17 (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 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)benzyldiene)-1H-inden-3-yl)acetate (16a).

According to general procedure F, (E)-2-(5-fluoro-1-(4-(methylthio)benzyldiene)-1H-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$_{23}$H$_{19}$FO$_2$S, 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)benzyldiene)-1H-inden-3-yl)acetate (16b).

According to general procedure F, (E)-2-(5-fluoro-1-(4-(methylthio)benzyldiene)-1H-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%). \( \text{C}_{21}\text{H}_{19}\text{FO}_2\text{S} \), \( M_r = 354.44 \); \( ^1\text{H NMR} \) (400 MHz, DMSO-\( d_6 \)) \( \delta \): 1.19 (t, \( J=7.0 \text{ Hz} \), 3H), 2.52 (s, 3H), 3.76 (s, 2H), 4.11 (q, \( J=7.0 \text{ Hz} \), 2H), 7.05 (td, \( J=2.4/9.0 \text{ Hz} \), 1H), 7.14-7.17 (m, 2H), 7.35 (d, \( J=8.8 \text{ Hz} \), 2H), 7.60-7.64 (m, 3H), 7.86 (dd, \( J=5.0/8.2 \text{ Hz} \), 1H); \( ^{13}\text{C NMR} \) (100 MHz, DMSO-\( d_6 \)) \( \delta \): 14.47 (s, -CH\(_3\)), 16.85 (s, -SCH\(_3\)), 33.01 (s, -CH\(_2\)), 60.84 (s, -O-CH\(_2\)-), 107.05 (d, \( J=24.0 \text{ Hz} \)), 112.09 (d, \( J=23.0 \text{ Hz} \)), 121.03 (d, \( J=9.0 \text{ Hz} \)), 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, \( J=9.0 \text{ Hz} \)), 162.48 (d, \( J=238.0 \text{ Hz} \)), 170.41 (s); \( ^{19}\text{F NMR} \) (282 MHz, DMSO-\( d_6 \)) \( \delta \): -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%). \( \text{C}_{22}\text{H}_{23}\text{FO}_2\text{S} \), \( M_r = 368.46 \); \( ^1\text{H NMR} \) (400 MHz, DMSO-\( d_6 \)) \( \delta \): 400 MHz: 1.19 (d, \( J=6.4 \text{ Hz} \), 6H), 2.52 (s, 3H), 3.72 (s, 2H), 4.94 (sept, \( J=6.4 \text{ Hz} \), 1H), 7.05 (td, \( J=1.2/2.4/8.9 \text{ Hz} \), 1H), 7.13-7.15 (m, 2H), 7.35 (d, \( J=8.4 \text{ Hz} \), 2H), 7.59-7.64 (m, 3H), 7.83 (dd, \( J=5.2/8.4 \text{ Hz} \), 1H); \( ^{19}\text{F NMR} \) (282 MHz, DMSO-\( d_6 \)) \( \delta \): -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%). \( \text{C}_{23}\text{H}_{25}\text{FO}_2\text{S} \), \( M_r = 380.41 \); \( ^1\text{H NMR} \) (400 MHz, DMSO-\( d_6 \)) \( \delta \): 1.19 (t, \( J=7.2 \text{ Hz} \), 3H), 1.33 (t, \( J=7.0 \text{ Hz} \), 3H), 3.77 (s, 2H), 4.11 (q, \( J=7.1 \text{ Hz} \), 2H), 4.33 (q, \( J=7.1 \text{ Hz} \), 2H), 7.06-7.11 (m, 2H), 7.17 (dd, \( J=2.4/9.2 \text{ Hz} \), 1H), 7.71 (s, 1H), 7.79 (d, \( J=8.0 \text{ Hz} \), 2H), 7.87 (dd, \( J=5.2/8.4 \text{ Hz} \), 1H), 8.03 (d, \( J=8.4 \text{ Hz} \), 2H); \( ^{19}\text{F NMR} \) (282 MHz, DMSO-\( d_6 \)) \( \delta \): -112.33 (1F, C5’-F); LCMS (ESI) 3.45 min (99%, ELSD), \( m/z \): 381.2 [M+1]*.
(E)-ethyl 2-((1,1′-biphenyl)-4-ylmethylene)-5-fluoro-1H-inden-3-yl)acetate (16e).
According to general procedure F, (E)-2-((1,1′-biphenyl)-4-ylmethylene)-5-fluoro-1H-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<sub>26</sub>H<sub>21</sub>F<sub>2</sub>O, M<sub>r</sub> = 384.44; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) 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); <sup>19</sup>F NMR (282 MHz, DMSO-d<sub>6</sub>) δ: -113.06 (1F, C<sub>5′</sub>-F); LCMS (ESI) 3.63 min (>99%, UV254), m/z: 385.2 [M+1]<sup>+</sup>.

Synthesis of compounds 18a & 18b (table 4):

(E)-ethyl 2-((1,1′-biphenyl)-4-ylmethylene)-5-fluoro-1H-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<sub>27</sub>H<sub>23</sub>F<sub>2</sub>O<sub>2</sub>, M<sub>r</sub> = 398.47; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) 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); <sup>19</sup>F NMR (282 MHz, DMSO-d<sub>6</sub>) δ: -112.88 (d, 1F, C<sub>5′</sub>-F); LCMS (ESI) (method 2) tR: 3.86 min (85%*, ELSD), m/z: 399.2 [M+1]<sup>+</sup>.
* impurity: 15% alpha-demethylated product m/z=384 and traces of its free acid m/z=356

(E)-2-((1,1′-biphenyl)-4-ylmethylene)-5-fluoro-1H-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-1H-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$_{28}$H$_{23}$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)-1H-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$_2$S, 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-1H-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]$^+$. 

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(E)-ethyl 2-(1-((9H-fluoren-2-yl)methylene)-5-fluoro-1H-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 9H-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; ^1H 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)-1H-inden-3-yl)-2-methylpropanoate (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_{2}O_{2}, M_r = 430.49; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.07 (t, J=7.2 Hz, 3H), 1.58 (s, 6H), 4.09 (q, J=7.2 Hz, 2H), 6.90 (dd, J=2.4/9.6 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: 3.82 min (>99%, ELSD), m/z: 431.1 [M+1]^+.

(E)-ethyl 2-(5-fluoro-1-((4′-fluoro-[1,1′-biphenyl]-4-yl)methylene)-1H-inden-3-yl)-2-methylpropanoate (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_{23}H_{22}F_2O_2, M_r = 430.49; \text{^1H NMR} (400 MHz, DMSO-d_6) \delta: 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), 7.80-7.81 (m, 6H), 7.90 (dd, J=5.2/8.4 Hz, 1H); \text{^19F NMR} (282 MHz, DMSO-d_6) \delta: -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)-1H-inden-3-yl)-2-methylpropanoate (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_{22}FNO_2, M_r = 428.50; \text{^1H NMR} (400 MHz, DMSO-d_6) \delta: 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)-1H-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; \text{^1H NMR} (400 MHz, DMSO-d_6) \delta: 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-1H-indol-3-yl)methylene)-1H-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-1H-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%). C25H24FNO2, Mr = 389.46; 1H NMR (400 MHz, DMSO-d6) δ: 1.07 (t, J=7.2 Hz, 3H), 1.60 (s, 6H), 3.92 (s, 3H, N-CH3), 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); 19F NMR (282 MHz, DMSO-d6) δ: -115.26 Hz (s, 1F, C5′-F); LCMS (ESI) (method 2) tR: 3.57 min (>95%, UV254, ELSD), m/z: 390.2 [M+1]+.

(5)-ethyl 2-(1-((1,1′-biphenyl)-3-ylmethylene)-5-fluoro-1H-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 mixture was combined with the same volume of water and then extracted thrice with equal amounts of DCM. The combined organic extracts were dried over Na2SO4 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%): C28H25FO2, Mr = 412.50; 1H NMR (400 MHz, DMSO-d6) 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); 19F NMR (282 MHz, DMSO-d6) δ: -112.69 (q, 1F, C5′-F); LCMS (ESI) (method 2) tR: 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)-1H-inden-3-yl)-2-methylpropanoate (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 (7.25 mg): C_{27}H_{23}F_{2}NO_{2}, M_r = 431.47; ^1H 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); ^19F NMR (282 MHz, DMSO-d_6) δ: -111.98 (s, 1F), -110.74 (s, 1F); LCM S (ESI) (method 2) τR: 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)-1H-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_{2}S, M_r = 326.38; ^1H 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), 7.62 (d, J = 8.4 Hz, 2H), 7.82 (dd, J = 5.2/8.4 Hz, 1H); ^19F NMR (282 MHz, DMSO-d_6) δ: -113.42 (t, 1F, C_5′-F); LCM S (ESI) (method 2) τR: 2.49 min (>99%, UV254, ELSD), m/z: 327.0 [M+1]^+.

(E)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1H-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_{2}S, M_r = 354.44; ^1H 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-\(d_6\)) \(\delta:\) -113.31 (q, 1F, C5′-F); LCMS (ESI) (method 2) \(t_R:\) 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%). \(\text{C}_{26}\text{H}_{21}\text{FNO}_2, M_r = 384.44; \) \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta:\) 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-\(d_6\)) \(\delta:\) -112.96 (d, 1F, C5′-F); LCMS (ESI) (method 2) \(t_R:\) 3.45 min (\(\geq 95\%\), 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 methanesulfonylamine (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%). \(\text{C}_{20}\text{H}_{18}\text{FNO}_3\text{S}_2, M_r = 403.49; \) \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta:\) 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) \(t_R:\) 9.20 min; LCMS (ESI) (method 2) \(t_R:\) 2.83 min (>99%, ELSD), \(m/z:\) 404.0 [M+1].
According to general procedure H, the title compound was obtained from (E)-2-(5-fluoro-1-(4-(methylthio) benzylidene)-1H-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)-1H-inden-3-yl)-N-((trifluoromethyl)sulfonyl)acetamide (21d).

According to general procedure H, the title compound was obtained from (E)-2-(5-fluoro-1-(4-(methylthio) benzylidene)-1H-inden-3-yl)-N-tosylacetamide (21e).
column chromatography (SiO₂, EtOAc:Hexane = 1+1, 0.5%AcOH) to yield 167 mg (57%) of an analytically pure solid: C_{26}H_{22}FNO_{3}S₂, Mᵣ = 479.59; ¹H NMR (400 MHz, DMSO-d₆) 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); ¹⁹F NMR (282 MHz, DMSO-d₆) 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]⁺.

(\textit{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 (\textit{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 (SiO₂, EtOAc:Hexane = 1+1, 0.5%AcOH) to yield 149 mg (47%) of an analytically pure solid: C_{29}H_{22}FNO_{3}S₂, Mᵣ = 515.62; ¹H NMR (400 MHz, DMSO-d₆) 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]⁺.

(\textit{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 (SiO₂, EtOAc:Hexane gradient = 1+1 (0.5% AcOH) and treatment with little diethylether and methanol. Yield: 110 mg (37%), orange solid: C_{25}H_{14}FNO_{3}S₂, Mᵣ = 483.55; ¹H NMR (400 MHz, DMSO-d₆) 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); ¹⁹F NMR (282 MHz, DMSO-d₆) 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]⁺.
\((E)-2-(5\text{-fluoro}-1-(4\text{-methylthio})\text{benzylidene})\text{-1H-inden-3-yl}-N-(4\text{-trifluoromethyl})\text{phenylsulfonyl})\text{acetamide (21h).}\)

According to general procedure H, the title compound was obtained from \((E)-2-(5\text{-fluoro}-1-(4\text{-methylthio})\text{benzylidene})\text{-1H-inden-3-yl})\text{acetic acid 2 (0.20 g, 0.61 mmol) and 4-(trifluoromethyl) benzenesulfonamide (0.138 g, 0.61 mmol) after 20 h at room temperature. The crude product was chromatographed (SiO}_2\text{ column, EtOAc:Hexane = 1+1 (containing 0.5% AcOH) to yield 205 mg (63%) of an analytically pure solid: C}_{26}H_{19}F_4NO_3S_2, M}_w=533.56; ^1H NMR (400 MHz, DMSO-\text{d}_6) \delta:\ 2.52 (s, 3H), 3.68 (s, 2H), 6.86-8.11 (m, 13 H); ^13C NMR (75 MHz, DMSO-\text{d}_6) \delta:\ 14.6 (s, -SCH\text{\_3}), 35.7 (s, -CH\text{\_3}-), 106.7 (d, J=22.5 Hz, C4 indene), 112.1 (d, J=23.3 Hz, C6 indene), 121.1 (d, J=9.0 Hz, C7 indene), 125.5, 126.2 (s, C3/C5 benzenesulfonamide), 126.7 (s, C3/C5 benzenesulfonamide), 129.0 (s, C2/C6 benzenesulfonamide), 129.4 (s, =C-Ar), 130.9 (s, C2/C6 benzylidene), 133.0 (s), ~133.5 (q), 134.0 (s), 136.3 (s), 139.1 (s), 140.4 (s), 143.0 (d), 143.2 (s), ~162 (d, C5 indene), 169.1 (s, >C=O); ^19F NMR (310 MHz, DMSO-\text{d}_6) \delta:\ -113.37 (s, 1F, C5'-F), -60.01 (s, 3F, -CF\text{\_3}); HPLC (method 1) tR: 10.67 min; LCMS (ESI) (method 2) tR: 3.31 min (\geq95%, ELSD), m/z: 534.0 [M+1]^+.\)

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

According to general procedure H, the title compound was obtained from \((E)-2-(5\text{-fluoro}-1-(4\text{-methylthio})\text{benzylidene})\text{-1H-inden-3-yl})\text{acetic acid 2 (0.148 g, 0.61 mmol) after 20 h at room temperature. The crude product was chromatographed (SiO}_2\text{ column, EtOAc:Hexane = 1+1 (containing 0.5% AcOH) to yield 240 mg (63%) of an analytically pure solid: C}_{26}H_{19}F_4NO_3S_2, M}_w=549.56; ^1H NMR (400 MHz, DMSO-\text{d}_6) \delta:\ 2.52 (s, 3H), 3.61 (s, 2H), 6.88 (dd, J=2.4/9.2 Hz, 1H), 6.98-7.03 (m, 2H), 7.33 (d, J=8.8 Hz, 2H), 7.56-7.58 (m, 5H), 7.78 (dd, J=5.2/8.4 Hz, 1H), 8.04 (d, J=8.8 Hz, 2H); ^13C NMR (100 MHz, DMSO-\text{d}_6) \delta:\ 14.6 (s, -SCH\text{\_3}), 35.61 (s, -CH\text{\_3}-), 106.71 (d, J=23.0 Hz, C4 indene), 112.08 (d, J=23.0 Hz, C6 indene), 118.89 (s, C1 indene), 121.05 (d, J=9.0 Hz, C7 indene), 121.49 (s, 2H, C3/C5 benzenesulfonamide), 126.18 (s, C2/C6 benzenesulfonamide), 126.54 (s, C2 indene), 129.31 (s, =CH\text{-}), 130.74 (s, C3/C5 benzylidene), 130.87 (s, C2/C6 benzylidene), 132.95 (s), 134.07 (d, J=2.0 Hz, C7a indene), 136.30 (s), 138.09 (s), 139.25 (d, J=3.0 Hz, C3 indene), 140.35 (s), 142.93 (d, J=9.0 Hz, C3a indene), 152.08 (s, C4); ^19F NMR (282 MHz, DMSO-\text{d}_6) \delta:\ -113.37 (s, 1F, C5'-F), -60.01 (s, 3F, -CF\text{\_3}); HPLC (method 1) tR: 10.87 min; LCMS (ESI) (method 2) tR: 3.31 min (99%, ELSD), m/z: 550.0 [M+1]^+.\)
(E)-N-(5-chlorothiophen-2-ylsulfonyl)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1H-inden-3-yl)acetamide (21j).

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 5-chlorothiophene-2-sulfonamide (0.121 g, 0.61 mmol) after 20 h at room temperature. The crude product was chromatographed (SiO₂ column, EtOAc:Hexane = 1+1 (containing 0.5% AcOH) to give 167 mg (54%) of an analytically pure solid: C₂₃H₁₇ClFNO₃S₃, Mr = 506.03; ¹H NMR (400 MHz, DMSO-d₆) 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); ¹³C NMR (100 MHz, DMSO-d₆) δ: 14.65 (s, -SCH₃), 35.70 (s, -CH₂-), 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), 128.87 (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) tR: 10.49 min; LCMS (ESI) (method 2) tR: 3.27 min (>99%, ELSD), m/z: 506 [M+1]+.

(21k).

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-bromobenzene-sulfonamide (0.145 g, 0.61 mmol) after 20 h at room temperature. The crude product was chromatographed (SiO₂ column, EtOAc:Hexane = 1+1 (containing 0.5% AcOH) to give 117 mg (35%) of an analytically pure solid: C₂₅H₁₉BrFNO₃S₂, Mr = 544.46; ¹H NMR (600 MHz, DMSO-d₆) 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) tR: 10.80 min; LCMS (ESI) (method 2) tR: 3.29 min (>95%, ELSD), m/z: 547 [M+1]+.
(E)-N-(4-acetylphenyl)sulfonyl)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1H-inden-3-yl)acetamide (21I).

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-acetylbenzene-sulfonamide (0.122 g, 0.61 mmol) after 20 h at room temperature. The crude product was chromatographed (SiO₂ column, EtOAc:Hexane = 1+1 (containing 0.5% AcOH) to give 189 mg (61%) of an analytically pure solid: C₂₇H₂₅FNO₃S₂, M = 507.60; ¹H NMR (400 MHz, DMSO-d₆) δ: 2.53 (s, 3H), 2.60 (s, 3H), 3.66 (s, 2H), 3.95 (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); ¹³C NMR (282 MHz, DMSO-d₆) δ: -113.33 (d, 1F, C5′-F); HPLC (method 1) tR: 11.14 min; LCMS (ESI) (method 2) tR: 3.02 min (>97%, UV254, ELSD), m/z: 508.0 [M+1]⁺.

(2E)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1H-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)-1H-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 (SiO₂ column, EtOAc:Hexane = 1+1 (containing 0.5% AcOH) to give 189 mg (61%) of an analytically pure solid: C₂₇H₂₅FNO₃S₂, M = 507.60; ¹H NMR (400 MHz, DMSO-d₆) 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); ¹³C NMR (282 MHz, DMSO-d₆) δ: -113.27 (q, 1F, C5′-F); HPLC (method 1) tR: 9.70 min; LCMS (ESI) (method 2) tR: 3.38 min (>95%, ELSD), m/z: 508.2 [M+1]⁺.

(E)-2-(5-fluoro-1-(4-(methylthio)benzylidene)-1H-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)-1H-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 (SiO₂, EtOAc:Hexane gradient = 1+1 (0.5% AcOH). Yield: 33 mg (11%), orange solid: C₂₆H₂₂FNO₄S₂, Mᵣ = 495.59; ¹H NMR (400 MHz, DMSO-d₆) 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-phenoxybenzenesulfonamide (0.153 g, 0.61 mmol) after 20 h at room temperature: C₃₁H₂₄FNO₄S, Mᵣ = 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
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. C₂₄H₁₆ClFO, Mᵣ = 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 (SiO₂, EtOAc + Hexane: 1+1 (0.5 % AcOH, gradient) to afford 13.5 mg (52%) as bright yellow solid. C₂₅H₁₇F₄NO₃S, Mᵣ = 487.47; ¹H NMR (400 MHz, DMSO-d₆) 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); ¹⁹F NMR (282 MHz, DMSO-d₆) δ: -115.25 (s, 1F, C₅’-F), -77.31 (s, 3F, -CF₃); LCMS (ESI) (method 2) tR: 3.62 min (>99%, UV254, ELSD), m/z: 488.0 [M+1]⁺.
Biochemical and biological screening methods:

\[^{14}\text{C}}\text{-AA TLC COX activity assay}\]

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 [\(^{14}\text{C}}\text{-AA (~ 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-dependent inhibition of the compounds. The extracts were analyzed for substrate consumption by thin-layer chromatography as previously described. 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 [\(^{14}\text{C}}\text{-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\(_2\)O/CH\(_3\)OH/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\(_2\)Cl\(_2\)/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:

$^1$H NMR of compd 10a
(400 MHz, DMSO-$d_6$)

$^1$H NMR of compd 10b
(400 MHz, DMSO-$d_6$)
$^1$H NMR of compd 10c
(400 MHz, DMSO-$d_6$)

$^1$H 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 2
(400 MHz, DMSO-$d_6$)

$^1$H 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. 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. $^1$H NMR of compd 20b.
Figure S3. 2D Nuclear Overhauser Effect Spectroscopy (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-IC₅₀: 1.8 µM, COX-2: 10% inhibition at 4 µM), 13a (COX-1-IC₅₀: 570 nM, COX-2: n. i. at 4 µM) and 21c (COX-1-IC₅₀: 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. 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. 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 compounds 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
**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. 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. 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.
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 (●, EC₅₀: 209 µM), 13a (■, EC₅₀: 141 µM) or 21b (△, EC₅₀: 215 µM).
Scheme S1. Synthetic route to 2'-des-methyl indene acetic acid derivatives with additional alkyl substituents in \( \alpha \)-position to the carboxylic group.

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                                    | $\geq95\%$        | 1:1 mixture of isomers |
| 8b                | 10b                 | $25\%$ via 9b                                    | $\geq95\%$        | mixture of isomers    |
| 8a                | 10c                 | $26\%$ via 9c                                    | $\geq95\%$        | mixture of enantiomers (racemate) |
| 8a                | 10d                 | $47\%$ via 9d                                    | $\geq95\%$        | single isomer         |
Table S2. Isolated sodium salts of different E-DMSS analogs

![Chemical structure of sodium salts of E-DMSS analogs](image)

| Compd # | R¹ | R² |
|---------|----|----|
| 13a(Na) | F  | ![Structure](image) |
| 13e(Na) | F  | ![Structure](image) |
| 15b(Na) | OMe | ![Structure](image) |
| 15c(Na) | OMe | ![Structure](image) |
Table S3. COX-1 and COX-2 inhibition by 5′-F analogs of E-DMSS.

![Chemical structure]

| Compd # | R\(^1\) | R\(^2\) | oCOX-1 %-inhibition @ 4 µM\(^a\) | mCOX-2 %-inhibition @ 4 µM\(^a\) |
|---------|---------|--------|---------------------------------|---------------------------------|
| 15a     | OMe     | ![Structure] | 16 ± 6 (6)                      | 8 ± 7 (6)                        |
| 15b     | OMe     | ![Structure] | 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.            | No effect up to 25 µM; likewise 5 & 6 ineffective |
| 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; 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; 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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