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Chemistry & Drug Discovery

Supporting Information

Discovery of Vilaprisan (BAY 1002670): A Highly Potent and Selective Progesterone Receptor Modulator Optimized for Gynecologic Therapies

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Supplementary Material

Chemistry

Materials and methods. All commercially available starting materials and solvents were purchased and used without further purification. Flash column chromatography was performed using prepacked flash chromatography columns PF-15-SIHP (purchased from Interchim) or KP-Sil (purchased from Biotage) using a Biotage Isolera separation system. ^{1}H NMR spectra were recorded at room temperature on Bruker Avance spectrometers operating at 300 or 400 MHz. NMR signal multiplicities are reported as they appeared, without considering higher-order effects. Chemical shifts (δ) are given in ppm with the residual solvent signal used as a reference ($CDCl_3$: s, 7.26 ppm; DMSO-d_6: quint, 2.50 ppm). LC-MS spectra were recorded on a Waters Acquity UPLC-MS SQD 3001 spectrometer, using an Acquity UPLC BEH C18 1.7 50x2.1 mm column, with acetonitrile and water + 0.1% formic acid as eluents at 60°C, a flow of 0.8 mL/min, an injection volume of 2 µL, with DAD scan at 210–400 nm, ELSD. All tested compounds were at least 95% pure, as determined by ^{1}H NMR spectroscopy.

Test compounds 1, 3, 4, 5, 6, 8, 14, and 17 were synthesized from intermediates 24a–-e, 24j, 24k, and 24l by acidic cleavage of the protecting group(s) and concomitant elimination of the 5α-hydroxy group according to the general procedure 3a), 3b) or 3c) (see Experimental Part of main publication):

1: (11β,17α)-20,20,21,21,21-Pentafluoro-11-(4-glycoloylphenyl)-17-hydroxy-19-norpregna-4,9-dien-3-one
Method c
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (br d, *J*=8.34 Hz, 2 H) 7.35 (br d, *J*=8.34 Hz, 2 H) 5.79 - 5.86 (m, 1 H) 4.84 (s, 2 H) 4.46 - 4.56 (m, 1 H) 2.68 - 2.79 (m, 1 H) 2.20 - 2.66 (m, 10 H) 2.02 - 2.15 (m, 2 H) 1.74 - 1.91 (m, 4 H) 1.40 - 1.59 (m, 3 H) 0.57 (s, 3 H) ppm.
LC-MS (ESI+): *R*t=1.90 min, m/z 525 $[M+H]^+$.

3: (11β,17α)-11-[4-(1,2-Dihydroxyethyl)phenyl]-20,20,21,21,21-pentafluoro-17-hydroxy-19-norpregna-4,9-dien-3-one – mixture of isomers

Method c

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.21 - 7.29 (m, 2 H) 7.16 (d, *J*=8.07 Hz, 2 H) 5.78 (s, 1 H) 4.72 - 4.80 (m, 1 H) 4.40 - 4.48 (m, 1 H) 4.12 (d, *J*=7.34 Hz, 1 H) 3.68 - 3.76 (m, 1 H) 3.56 - 3.65 (m, 1 H) 2.89 - 2.98 (m, 1 H) 2.68 - 2.76 (m, 1 H) 2.37 - 2.67 (m, 9 H) 2.21 - 2.36 (m, 2 H) 2.05 - 2.09 (m, 1 H) 1.76 - 1.85 (m, 3 H) 1.41 - 1.56 (m, 2 H) 1.26 (t, *J*=7.15 Hz, 2 H) 0.57 (d, *J*=5.14 Hz, 3 H) ppm.

LC-MS (ESI+): *R*t=1.70 min, m/z 527 $[M+H]^+$.

4: (11β,17α)-20,20,21,21,21-Pentafluoro-17-hydroxy-11-phenyl-19-norpregna-4,9-dien-3-one

Method b

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 - 7.33 (m, 2 H) 7.14 - 7.22 (m, 3 H) 5.74 - 5.81 (m, 1 H) 4.40 - 4.51 (m, 1 H) 2.68 - 2.81 (m, 1 H) 2.26 - 2.66 (m, 10 H) 2.08 (s, 2 H) 1.80 (br s, 4 H) 1.40 - 1.56 (m, 2 H) 0.60 (s, 3 H) ppm.

LC-MS (ESI+): *R*t=1.49 min, m/z 467 $[M+H]^+$.

5: (11β,17α)-20,20,21,21,21-Pentafluoro-17-hydroxy-11-(4-vinylphenyl)-19-norpregna-4,9-dien-3-one

Method a

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J*=8.34 Hz, 2 H) 7.13 (d, *J*=8.08 Hz, 2 H) 6.59 - 6.74 (m, 1 H) 5.78 (s, 1 H) 5.72 (d, *J*=17.43 Hz, 1 H) 5.22 (d, *J*=10.86 Hz, 1 H) 4.40 - 4.48 (m, 1 H) 3.57 - 3.71 (m, 2 H) 2.69 - 2.78 (m, 1 H) 2.51 - 2.64 (m, 4 H) 2.43 (br d, *J*=11.62 Hz, 6 H) 2.04 (s, 2 H) 1.80 (br t, *J*=8.34 Hz, 3 H) 1.37 - 1.62 (m, 3 H) 0.62 (s, 3 H) ppm.

6: (11β,17α)-20,20,21,21,21-Pentafluoro-17-hydroxy-11-[4-(prop-1-en-2-yl)phenyl]-19-norpregna-4,9-dien-3-one

Method a

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39 (d, *J*=8.48 Hz, 2 H) 7.13 (d, *J*=8.10 Hz, 2 H) 5.78 (s, 1 H) 5.37 (s, 1 H) 5.06 (d, *J*=1.32 Hz, 1 H) 4.44 (br d, *J*=6.78 Hz, 1 H) 2.71 (s, 1 H) 2.50 - 2.66 (m, 5 H) 2.24 - 2.48 (m, 6 H) 2.13 (s, 3 H) 2.04 (s, 2 H) 1.71 - 1.89 (m, 3 H) 1.60 (s, 1 H) 1.50 (br d, *J*=9.42 Hz, 2 H) 0.62 (s, 3 H) ppm.

LC-MS (ESI+): *R*t=1.34 min, m/z 525 $[M+H]^+$.

8: (11β,17α)-20,20,21,21,21-Pentafluoro-17-hydroxy-11-[4-(oxetan-3-yl)phenyl]-19-norpregna-4,9-dien-3-one

Method a

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 (s, 4 H) 5.78 (s, 1 H) 4.92 (d, *J*=5.46 Hz, 2 H) 4.63 (d, *J*=5.65 Hz, 2 H) 4.39 - 4.49 (m, 1 H) 2.68 - 2.82 (m, 1 H) 2.39 (s, 11 H) 2.00 - 2.12 (m, 1 H) 1.70 (s, 8 H) 1.37 - 1.56 (m, 2 H) 0.60 (s, 3 H) ppm.

LC-MS (ESI+): *R*t=1.65 min, m/z 537 $[M+H]^+$.

14: (11β,17α)-11-[4-(Dimethylamino)phenyl]-20,20,21,21,21-pentafluoro-17-hydroxy-19-norpregna-4,9-dien-3-one

Method b

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.01 (dbr, *J*=8.8 Hz, 2H) 6.66 (d, J=8.8 Hz, 2H) 5.77 s (1H), 4.38 d (J= 6.5 Hz, 1H) 2.92 s (6H), 0.64 s (3H) ppm.

17: (11β,17α)-20,20,21,21,21-Pentafluoro-17-hydroxy-11-[4-(methylsulfanyl)phenyl]-19-norpregna-4,9-dien-3-one

Method b

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19 - 7.26 (m, 2 H) 7.10 - 7.18 (m, 2 H) 5.83 (s, 1 H) 4.42 - 4.49 (m, 1 H) 2.72 - 2.85 (m, 1 H) 2.51 (s, 13 H) 2.05 (s, 2 H) 1.75 - 1.94 (m, 3 H) 1.43 - 1.57 (m, 2 H) 1.12 - 1.22 (m, 1 H) 0.66 (s, 3 H) ppm.

LC-MS (ESI+): *R*t=1.23 min, m/z 513 $[M+H]^+$.

The intermediates **24a–24k** were synthesized according to general procedure 2) described in the Experimental Part of the main publication. Spectroscopical data for the different intermediates are shown below:

24a: (5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-11-{4-[2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-1,3-dioxolan-2-yl]phenyl}-5',5',13-trimethyl-17-(pentafluoroethyl)-1,2,6,7,8,11,12,13,14,15,16,17-dodecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxane]-5,17(4*H*)-diol

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 - 7.45 (m, 2 H) 7.17 - 7.26 (m, 2 H) 4.44 - 4.50 (m, 1 H) 4.33 - 4.39 (m, 1 H) 4.10 - 4.19 (m, 2 H) 3.88 - 3.96 (m, 2 H) 3.79 (s, 2 H) 3.45 - 3.62 (m,

2 H) 2.17 - 2.57 (m, 8 H) 2.02 - 2.12 (m, 1 H) 1.71 - 1.94 (m, 5 H) 1.60 (s, 3 H) 1.09 (s, 3 H) 0.92 (s, 2 H) 0.84 - 0.90 (m, 9 H) 0.56 (s, 3 H) -0.05 - 0.02 (m, 6 H) ppm.

24b: (5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-11-[4-(2,2-Dimethyl-1,3-dioxolan-4-yl)phenyl]-5',5',13-trimethyl-17-(pentafluoroethyl)-1,2,6,7,8,11,12,13,14,15,16,17-dodecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxane]-5,17(4*H*)-diol
^{1}H NMR (600 MHz, $CDCl_3$): δ= 7,23 d (*J*=9 Hz, 2H, aryl); 7,20 d (*J*=9 Hz, 2H); 5,03 dd (*J*=9; 8,4 Hz, 1H); 4,46 s (1H); 4,33 dbr (*J*=6,5 Hz, 1H); 4,27 dd (*J*=9; 8,4 Hz, 1H); 3,68 dd (*J*=9; 9 Hz, 1H); 1,56 s (3H); 1,49 s (3H); 1,07 s (3H); 0,86 s (3H); 0,50 s (3H) ppm.

24c: (5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-5',5',13-Trimethyl-17-(pentafluoroethyl)-11-phenyl-1,2,6,7,8,11,12,13,14,15,16,17-dodecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxane]-5,17(4*H*)-diol
^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.22 (d, *J*=2.26 Hz, 4 H) 7.09 - 7.16 (m, 1 H) 4.42 - 4.46 (m, 1 H) 4.31 - 4.36 (m, 1 H) 4.07 - 4.17 (m, 1 H) 3.54 (s, 4 H) 2.15 - 2.51 (m, 9 H) 2.04 (s, 2 H) 1.87 - 1.91 (m, 1 H) 1.68 - 1.85 (m, 4 H) 1.56 (s, 5 H) 1.05 (s, 3 H) 0.86 (s, 3 H) 0.53 (s, 3 H) ppm.

24d: (5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-5',5',13-Trimethyl-17-(pentafluoroethyl)-11-(4-vinylphenyl)-1,2,6,7,8,11,12,13,14,15,16,17-dodecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxane]-5,17(4*H*)-diol
^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.28 - 7.35 (m, 2 H) 7.14 - 7.23 (m, 2 H) 6.59 - 6.75 (m, 1 H) 5.65 - 5.78 (m, 1 H) 5.14 - 5.25 (m, 1 H) 4.40 - 4.48 (m, 1 H) 4.26 - 4.35 (m, 1 H) 3.54 (s, 4 H) 2.14 - 2.52 (m, 8 H) 1.93 (s, 2 H) 1.67 - 1.86 (m, 4 H) 1.51 - 1.65 (m, 4 H) 1.05 (s, 3 H) 0.86 (s, 3 H) 0.55 (s, 3 H) ppm.

24e: (5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-5',5',13-Trimethyl-17-(pentafluoroethyl)-11-[4-(prop-1-en-2-yl)phenyl]-1,2,6,7,8,11,12,13,14,15,16,17-dodecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxane]-5,17(4*H*)-diol
^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.37 (d, *J*=8.48 Hz, 2 H) 7.17 (br d, *J*=8.29 Hz, 2 H) 5.35 - 5.41 (m, 1 H) 5.00 - 5.09 (m, 1 H) 4.44 (s, 1 H) 4.27 - 4.36 (m, 1 H) 3.39 - 3.56 (m, 4 H) 2.09 - 2.50 (m, 13 H) 2.04 (s, 2 H) 1.90 (s, 1 H) 1.67 - 1.85 (m, 5 H) 1.36 - 1.63 (m, 7 H) 1.05 (s, 3 H) 0.86 (s, 3 H) 0.55 (s, 3 H) ppm.

24f: (5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-11-[4-(Dimethoxymethyl)phenyl]-5',5',13-trimethyl-17-(pentafluoroethyl)-1,2,6,7,8,11,12,13,14,15,16,17-dodecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxane]-5,17(4*H*)-diol

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.33 (d, *J*=8.34 Hz, 2 H) 7.23 (s, 2 H) 5.36 (s, 1 H) 4.43 (s, 1 H) 4.30 - 4.37 (m, 1 H) 4.05 - 4.16 (m, 1 H) 3.40 - 3.60 (m, 4 H) 3.31 (s, 6 H) 2.40 (br s, 9 H) 2.04 (s, 2 H) 1.95 (s, 1 H) 1.67 - 1.85 (m, 5 H) 1.37 - 1.46 (m, 1 H) 1.04 (s, 3 H) 0.86 (s, 3 H) 0.51 (s, 3 H) ppm.

24g: (5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-11-[4-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)phenyl]-5',5',13-trimethyl-17-(pentafluoroethyl)-1,2,6,7,8,11,12,13,14,15,16,17-dodecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxane]-5,17(4*H*)-diol

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.04 - 7.16 (m, 4 H) 4.39 - 4.45 (m, 1 H) 4.27 - 4.34 (m, 1 H) 3.74 - 3.82 (m, 2 H) 3.39 - 3.58 (m, 4 H) 2.71 - 2.81 (m, 2 H) 2.12 - 2.49 (m, 9 H) 1.99 - 2.08 (m, 1 H) 1.89 (s, 1 H) 1.69 - 1.84 (m, 4 H) 1.57 (s, 6 H) 1.37 - 1.48 (m, 1 H) 1.05 (s, 3 H) 0.83 - 0.89 (m, 14 H) 0.53 (s, 3 H) -0.05 (d, *J*=1.77 Hz, 6 H) ppm.

24h: (5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-11-[4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)phenyl]-5',5',13-trimethyl-17-(pentafluoroethyl)-1,2,6,7,8,11,12,13,14,15,16,17-dodecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxane]-5,17(4*H*)-diol

^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.12 - 7.24 (m, 4 H) 4.67 - 4.74 (m, 2 H) 4.42 - 4.45 (m, 1 H) 4.29 - 4.35 (m, 1 H) 3.38 - 3.63 (m, 4 H) 2.14 - 2.51 (m, 8 H) 1.96 - 2.08 (m, 1 H) 1.85 - 1.91 (m, 1 H) 1.64 - 1.82 (m, 4 H) 1.58 - 1.63 (m, 1 H) 1.05 (s, 3 H) 0.93 (s, 9 H) 0.86 (s, 3 H) 0.53 (s, 3 H) 0.08 (s, 6 H) ppm.

24i: (5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-11-[4-(Benzyloxy)phenyl]-5',5',13-trimethyl-17-(pentafluoroethyl)-1,2,6,7,8,11,12,13,14,15,16,17-dodecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxane]-5,17(4*H*)-diol

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.30 - 7.47 (m, 5 H) 7.11 (d, *J*=8.59 Hz, 2 H) 6.87 (d, *J*=8.84 Hz, 2 H) 5.02 (s, 2 H) 4.43 (s, 1 H) 4.25 - 4.31 (m, 1 H) 3.54 (s, 4 H) 2.26 - 2.46 (m, 6 H) 2.15 - 2.25 (m, 2 H) 1.99 - 2.07 (m, 1 H) 1.89 (s, 1 H) 1.69 - 1.84 (m, 4 H) 1.51 - 1.63 (m, 3 H) 1.35 - 1.46 (m, 1 H) 1.05 (s, 3 H) 0.87 (s, 3 H) 0.55 (s, 3 H) ppm.

24j: (5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-11-[4-(Dimethylamino)phenyl]-5',5',13-trimethyl-17-(pentafluoroethyl)-1,2,6,7,8,11,12,13,14,15,16,17-dodecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxane]-5,17(4*H*)-diol

Intermediate **24j** was used as crude material for the preparation of compound **14**. No analytical data were measured for this intermediate.

24k: (5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-5',5',13-Trimethyl-11-[4-(methylsulfanyl)phenyl]-17-(pentafluoroethyl)-1,2,6,7,8,11,12,13,14,15,16,17-dodecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxane]-5,17(4*H*)-diol

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.14 (s, 4 H) 4.42 - 4.47 (m, 1 H) 4.26 - 4.32 (m, 1 H) 3.54 (s, 4 H) 2.47 (s, 3 H) 2.14 - 2.45 (m, 8 H) 1.98 - 2.07 (m, 1 H) 1.91 - 1.96 (m, 1 H) 1.69 - 1.83 (m, 4 H) 1.52 - 1.62 (m, 4 H) 1.05 (s, 3 H) 0.86 (s, 3 H) 0.54 (s, 3 H).

24l: (5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-5',5',13-Trimethyl-11-[4-(3-methyloxetan-3-yl)phenyl]-17-(pentafluoroethyl)-1,2,6,7,8,11,12,13,14,15,16,17-dodecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxane]-5,17(4*H*)-diol

A solution of butyllithium in hexane (11.13 mL, 2.5 M, 27.82 mmol) was added to a solution of isopropylmagnesium chloride in THF (6.95 mL, 2 M, 13.91 mmol, diluted with 7 mL THF), at 0°C. After stirring for 30 minutes at 0°C, a solution of 3-(4-bromophenyl)-3-methyloxetane (1.579 g, 6.96 mmol) in THF (7 mL) was added and the mixture was stirred for another 2 h at 0°C. Afterwards, copper(I) chloride (21 mg, 0.21 mmol) was added and it was stirred for another 5 minutes at 0°C. Then, a solution of compound **23** (685 mg, 1.39 mmol) in THF (7 mL) was added. The reaction mixture was allowed to warm up to 25°C within 3 h. Afterwards, the reaction mixture was diluted with ethyl acetate and poured into saturated aqueous ammonium chloride solution. The mixture was diluted with that much ammonium hydroxide solution that a basic pH was measured. It was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and evaporated. The crude product was purified by chromatography over silica gel using hexane/ethyl acetate to yield the title compound (393 mg, 44%).

^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.16 - 7.24 (m, 2 H) 7.07 - 7.15 (m, 2 H) 4.93 (d, *J*=5.27 Hz, 2 H) 4.62 (d, *J*=5.46 Hz, 2 H) 4.42 (s, 1 H) 4.31 (br d, *J*=6.40 Hz, 1 H) 4.12 (d, *J*=7.16 Hz, 1 H) 3.39 - 3.62 (m, 4 H) 2.13 - 2.53 (m, 9 H) 1.97 - 2.10 (m, 4 H) 1.65 - 1.85 (m, 8 H) 1.59 (s, 4 H) 1.26 (t, *J*=7.16 Hz, 2 H) 1.04 (s, 3 H) 0.87 (s, 3 H) 0.53 (s, 3 H) ppm.

LC-MS (ESI+): m/z 641 $[M+H]^+$.

Synthesis of compound **7**:

25: (5*R*,8*S*,13*S*,14*S*,17*S*)-11-(4-Cyclopropylphenyl)-5',5',13-trimethyl-17-(pentafluoroethyl)-1,2,6,7,8,11,12,13,14,15,16,17-dodecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxane]-5,17(4*H*)-diol

Preparation of diazomethane solution: A mixture of 40% aqueous potassium hydroxide solution (26 mL) and diethyl ether (75 mL) was cooled to 0°C. Nitrosomethylurea (8.25 g) was slowly added so that the reaction temperature did not rise above 5°C. The organic layer was separated and dried over solid potassium hydroxide at 0°C. The formed diazomethane solution was directly used for the next step:

Compound **24d** (100 mg, 0.17 mmol) was dissolved in 10 mL diethyl ether. The freshly prepared diazomethane solution was added at 0°C. Afterwards, palladium(II) acetate (44 mg, 0.195 mmol) was added in portions (exothermic reaction). Stirring was continued for 15 minutes. Then, the reaction mixture was filtered through silica gel, evaporated and used without purification for the next step.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.11 (s, 2 H) 6.99 (d, J=8.29 Hz, 2 H) 4.47 (s, 1 H) 4.28 - 4.38 (m, 1 H) 3.41 - 3.65 (m, 4 H) 2.14 - 2.56 (m, 9 H) 2.09 (s, 2 H) 1.70 - 1.98 (m, 6 H) 1.38 - 1.66 (m, 5 H) 1.09 (s, 3 H) 0.94 - 1.06 (m, 3 H) 0.91 (s, 3 H) 0.66 - 0.74 (m, 2 H) 0.58 (s, 3 H) ppm.

7: (17α)-11-(4-Cyclopropylphenyl)-20,20,21,21,21-pentafluoro-17-hydroxy-19-norpregna-4,9-dien-3-one

The protecting groups were cleaved according to general procedure a): Starting with compound **25** (85 mg, 0.14 mmol), the title compound was obtained (49.8 mg, 70.6 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.02 (d, *J*=4.71 Hz, 4 H) 5.67 - 5.76 (m, 1 H) 3.72 - 3.95 (m, 1 H) 2.02 - 2.63 (m, 13 H) 1.49 - 1.99 (m, 7 H) 1.21 (s, 3 H) 0.88 - 1.02 (m, 2 H) 0.61 - 0.73 (m, 2 H) ppm.

LC-MS (ESI+): *R*t=1.71 min, m/z 507 $[M+H]^+$.

Synthesis of compounds **9** and **13**:

26: 4-[(17α)-20,20,21,21,21-Pentafluoro-17-hydroxy-3-oxo-19-norpregna-4,9-dien-11-yl]benzaldehyde

The protecting groups were cleaved according to general procedure c): Starting with compound **24f** (5.85 g, 9.07 mmol), the title compound was obtained (4.17 g, 92.9 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.97 (s, 1 H) 7.75 - 7.86 (m, 2 H) 7.34 - 7.40 (m, 2 H) 5.79 - 5.84 (m, 1 H) 4.44 - 4.57 (m, 1 H) 2.01 - 2.81 (m, 15 H) 1.72 - 1.92 (m, 4 H) 1.38 - 1.65 (m, 4 H) 1.13 (d, *J*=6.22 Hz, 10 H) 0.57 (s, 3 H) ppm.

LC-MS (ESI+): *R*t=1.37 min, m/z 495 $[M+H]^+$.

9: 4-[(17α)-20,20,21,21,21-Pentafluoro-17-hydroxy-3-oxo-19-norpregna-4,9-dien-11-yl]benzoic acid

Compound **26** (4.17 g, 8.43 mmol) was dissolved in acetone (150 mL). It was cooled to –5°C and chromosulfuric acid (8 N, Jones reagent) was added in portions (in total, 3.2 mL in three portions; the last addition was 3 hours after the reaction was started). The reaction mixture was stirred for another 2 h after the last addition at 0°C. Afterwards, the yellow reaction mixture was poured into 1 L of ice-water. It was stirred for 20 h. Then, the precipitated product was filtered off and dried in vacuo. The title compound was obtained as light yellow solid (3.22 g, 74.8 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (br d, *J*=8.29 Hz, 2 H) 7.27 - 7.36 (m, 2 H) 5.78 - 5.84 (m, 1 H) 4.40 - 4.56 (m, 1 H) 2.24 - 2.80 (m, 13 H) 2.02 - 2.13 (m, 2 H) 1.81 (br s, 4 H) 1.49 (br s, 3 H) 0.57 (s, 3 H) ppm.

LC-MS (ESI+): *R*t=1.45 min, m/z 511 $[M+H]^+$.

13: *N*,*N*-Dimethyl-4-[(17α)-20,20,21,21,21-pentafluoro-17-hydroxy-3-oxo-19-norpregna-4,9-dien-11-yl]benzamide

Compound **9** (60 mg, 0.12 mmol) was dissolved in *N*,*N*-dimethylformamide (3 mL). Triethylamine (20 µL), dimethylamine (6.9 µL, 0.129 mmol), and 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU, 43 mg, 0.14 mmol) were added. The reaction mixture was stirred for 16 h at 23°C. Afterwards, it was diluted with ethyl acetate (50 mL) and the organic layer was washed with a saturated aqueous solution of sodium bicarbonate and with brine. It was dried over sodium sulfate and evaporated. The crude

product was purified by column chromatography to yield the title compound (48.1 mg, 76.1 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 - 7.43 (m, 2 H) 7.21 - 7.29 (m, 2 H) 5.77 - 5.89 (m, 1 H) 4.47 - 4.54 (m, 1 H) 3.10 - 3.20 (m, 3 H) 2.99 - 3.08 (m, 3 H) 2.22 - 2.82 (m, 12 H) 2.02 - 2.17 (m, 1 H) 1.84 (br s, 3 H) 1.67 (s, 6 H) 0.61 (s, 3 H) ppm.

LC-MS (ESI+): *R*t=1.26 min, m/z 538 $[M+H]^+$.

Synthesis of compound **10**:

27: (17α)-20,20,21,21,21-Pentafluoro-17-hydroxy-11-[4-(2-hydroxyethyl)phenyl]-19-norpregna-4,9-dien-3-one

Compound **24g** (1.000 g, 1.37 mmol) was dissolved in THF. A solution of tetrabutylammonium fluoride in THF (1 M, 1.4 mL) was added and the reaction mixture was stirred for 2 h at 23°C. Afterwards, the reaction mixture was poured into a saturated aqueous solution of sodium bicarbonate. It was extracted with ethyl acetate three times and the combined organic layers were washed with brine. It was dried over sodium sulfate and evaporated. The crude product was used without purification: The protecting groups were cleaved according to general procedure c) to yield the title compound (527 mg, 82.2 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18 (d, *J*=2.26 Hz, 4 H) 5.79 - 5.85 (m, 1 H) 4.42 - 4.53 (m, 1 H) 3.89 (t, *J*=6.50 Hz, 2 H) 2.88 (t, *J*=6.50 Hz, 2 H) 2.72 - 2.84 (m, 1 H) 2.62 (br s, 10 H) 1.84 (br s, 3 H) 1.43 - 1.70 (m, 5 H) 0.64 (s, 3 H) ppm.

10: {4-[(17α)-20,20,21,21,21-Pentafluoro-17-hydroxy-3-oxo-19-norpregna-4,9-dien-11-yl]phenyl}acetic acid

Compound **27** was reacted with chromosulfuric acid (8 N, Jones reagent) in analogy to the procedure described for the synthesis of compound **9**: Compound **10** (144.8 mg, 94.0 %) was obtained from 150 mg (0.29 mmol) of compound **27**.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 - 7.28 (m, 2 H) 7.14 - 7.21 (m, 2 H) 5.78 - 5.85 (m, 1 H) 4.39 - 4.54 (m, 1 H) 3.61 - 3.67 (m, 2 H) 2.70 - 2.80 (m, 1 H) 2.25 - 2.69 (m, 14 H) 2.04 - 2.17 (m, 2 H) 1.75 - 1.93 (m, 7 H) 1.42 - 1.60 (m, 5 H) 0.64 (s, 3 H) ppm.

LC-MS (ESI+): *R*t=0.93 min, m/z 525 $[M+H]^+$.

Synthesis of compound **12**:

28: (5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-11-[4-(Hydroxymethyl)phenyl]-5',5',13-trimethyl-17-(pentafluoroethyl)-1,2,6,7,8,11,12,13,14,15,16,17-dodecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxane]-5,17(4*H*)-diol

Compound **24h** (2.52 g, 3.52 mmol) was dissolved in THF. A solution of tetrabutylammonium fluoride in THF (1 M, 1.28 mL) was added and the reaction mixture was stirred for 2.5 h at 23°C. Afterwards, the reaction mixture was poured into a saturated aqueous solution of sodium bicarbonate. It was extracted with ethyl acetate three times and the combined organic layers were washed with brine. It was dried over sodium sulfate and evaporated. The crude product was purified by column chromatography to give compound **28** (1.43 g, 67.5 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J*=11.12 Hz, 4 H) 4.65 (d, *J*=5.56 Hz, 2 H) 4.44 (d, *J*=1.01 Hz, 1 H) 4.28 - 4.36 (m, 1 H) 3.54 (m, 4 H) 2.19 - 2.51 (m, 8 H) 1.70 - 1.85 (m, 4 H) 1.51 - 1.67 (m, 7 H) 1.05 (s, 3 H) 0.86 (s, 3 H) 0.53 (s, 3 H) ppm.

29: 4-[(5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-5,17-Dihydroxy-5',5',13-trimethyl-17-(pentafluoroethyl)-1,2,4,5,6,7,8,11,12,13,14,15,16,17-tetradecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxan]-11-yl]benzaldehyde

Compound **28** (2.51 g, 4.18 mmol) was dissolved in 50 mL dichloromethane. Molecular sieve (4 Å) was added followed by *N*-methylmorpholine-*N*-oxide (NMO, 734 mg, 6.27 mmol). The reaction mixture was stirred for 15 minutes at 23°C. Then, tetrapropylammonium perruthenate (TPAP, 59 mg, 0.17 mmol) was added and the reaction mixture was stirred for another 3.5 h at 23°C. Afterwards, the black reaction mixture was filtered through silica gel and evaporated. The crude material was purified by column chromatography to yield the title compound (2.35 g, 93.9%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.96 (s, 1 H) 7.79 (d, *J*=8.08 Hz, 2 H) 7.41 (d, *J*=8.08 Hz, 2 H) 4.45 (s, 1 H) 4.36 - 4.42 (m, 1 H) 3.36 - 3.60 (m, 4 H) 2.47 (br d, *J*=2.78 Hz, 4 H) 2.24 (br d, *J*=10.36 Hz, 5 H) 2.03 - 2.12 (m, 1 H) 1.68 - 1.90 (m, 7 H) 1.39 - 1.63 (m, 6 H) 1.05 (s, 3 H) 0.85 (s, 3 H) 0.51 (s, 3 H) ppm.

30: 4-[(5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-5,17-Dihydroxy-5',5',13-trimethyl-17-(pentafluoroethyl)-1,2,4,5,6,7,8,11,12,13,14,15,16,17-tetradecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxan]-11-yl]benzoic acid

Compound **29** (1.090 g, 1.82 mmol) was dissolved in a mixture of 2-methyl-2-butene / THF (1:1, 20 mL). At 0°C water (13 mL), sodium chlorite (1.021 g, 11.3 mmol) and sodium dihydrogen phosphate (754 mg, 6.28 mmol) were added. The reaction mixture was stirred for 3.5 h at 0°C. Afterwards, the reaction mixture was added slowly to a saturated aqueous sodium thiosulfate solution. It was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over sodium sulfate and evaporated. After purification of the crude material, compound **30** was obtained (839 mg, 75.0%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, *J*=8.48 Hz, 2 H) 7.35 (d, *J*=8.48 Hz, 2 H) 4.38 (br d, *J*=4.71 Hz, 1 H) 3.36 - 3.62 (m, 4 H) 2.47 (br s, 4 H) 2.14 - 2.34 (m, 4 H) 2.05 (s, 2 H) 1.33 - 1.84 (m, 10 H) 1.05 (s, 3 H) 0.91 - 0.99 (m, 2 H) 0.86 (s, 3 H) 0.52 (s, 3 H) ppm.

31: Methyl 4-[(5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-5,17-dihydroxy-5',5',13-trimethyl-17-(pentafluoroethyl)-1,2,4,5,6,7,8,11,12,13,14,15,16,17-tetradecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxan]-11-yl]benzoate

Compound **30** (833 mg, 1.36 mmol) was dissolved in a mixture of 15 mL THF and 3.5 mL methanol. A solution of (trimethylsilyl)diazomethane (2 M in hexane, 0.78 mL, 1.56 mmol) was added. It was stirred for 1.5 h at 23°C. Afterwards, the reaction mixture was evaporated. The crude product was purified by column chromatography to yield compound **31** (720 mg, 84.5 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J*=8.59 Hz, 2 H) 7.30 (d, *J*=8.59, 2 H) 4.43 - 4.47 (m, 1 H) 4.33 - 4.41 (m, 1 H) 3.90 (s, 3 H) 3.36 - 3.57 (m, 4 H) 2.35 - 2.51 (m, 4 H) 2.14 - 2.33 (m, 4 H) 2.04 (s, 1 H) 1.94 (s, 1 H) 1.69 - 1.85 (m, 4 H) 1.52 - 1.65 (m, 5 H) 1.35 - 1.46 (m, 1 H) 1.05 (s, 3 H) 0.88 - 0.97 (m, 1 H) 0.85 (s, 3 H) 0.51 (s, 3 H) ppm.

32: 4-[(5R,8S,11R,13S,14S,17S)-5,17-Dihydroxy-5',5',13-trimethyl-17-(pentafluoroethyl)-1,2,4,5,6,7,8,11,12,13,14,15,16,17-tetradecahydrospiro[cyclopenta[a]phenanthrene-3,2'-[1,3]dioxan]-11-yl]benzamide

Compound 31 (554 mg, 0.88 mmol) was dissolved in a solution of ammonia in methanol (7 M, 9 mL). The reaction mixture was heated in a sealed tube at 85°C for 96 h. Afterwards, it was evaporated. The crude material was purified by column chromatography to yield compound 32 (270 mg, 50.1 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, *J*=8.10 Hz, 2 H) 7.32 (d, *J*=8.10 Hz, 1 H) 4.45 (s, 1 H) 4.33 - 4.40 (m, 1 H) 3.34 - 3.57 (m, 4 H) 2.20 - 2.50 (m, 7 H) 1.98 - 2.09 (m, 1 H) 1.68 - 1.87 (m, 4 H) 1.55 - 1.63 (m, 5 H) 1.05 (s, 3 H) 0.85 (s, 3 H) 0.51 (s, 3 H) ppm.

12: 4-[(11β,17α)-20,20,21,21,21-Pentafluoro-17-hydroxy-3-oxo-19-norpregna-4,9-dien-11-yl]benzamide

The protecting groups were cleaved according to general procedure b): Starting with compound **32** (263 mg, 0.43 mmol), the title compound was obtained (186 mg, 85 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J*=8.34 Hz, 2 H) 7.28 (d, *J*=8.34 Hz, 2 H) 6.13 - 6.25 (m, 1 H) 5.79 (s, 1 H) 5.67 - 5.77 (m, 1 H) 4.44 - 4.51 (m, 1 H) 2.62 (br s, 4 H) 2.25 - 2.56 (m, 6 H) 2.07 (br dd, *J*=12.88, 4.29 Hz, 1 H) 1.81 (br s, 3 H) 1.39 - 1.55 (m, 2 H) 0.55 (s, 3 H) ppm.

LC-MS (ESI+): 510 $[M+H]^+$.

Synthesis of compounds **15** and **16**:

15: (11β,17α)-11-{4-[(Dimethylamino)methyl]phenyl}-20,20,21,21,21-pentafluoro-17-hydroxy-19-norpregna-4,9-dien-3-one

Compound **26** (200 mg, 0.4 mmol) was dissolved in dichloromethane (3 mL). A solution of dimethylamine in THF (2 M, 0.4 mL, 0.8 mmol) was added. It was stirred for 15 minutes. Afterwards, sodium triacetoxyborohydride (171 mg, 0.81 mmol) was added. Then, stirring was continued for 20 h at 23°C. Afterwards, the reaction mixture was poured into a saturated aqueous solution of sodium bicarbonate. It was extracted with dichloromethane twice and the combined organic layers were washed with brine. It was dried over sodium sulfate and evaporated. The crude product was purified by column chromatography to give compound **15** (131 mg, 62.6 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J*=8.34 Hz, 2 H) 7.12 (d, *J*=8.34 Hz, 2 H) 5.75 - 5.80 (m, 1 H) 4.39 - 4.47 (m, 1 H) 3.30 - 3.45 (m, 2 H) 2.50 - 2.63 (m, 4 H) 2.30 - 2.48 (m, 5 H) 2.21 (s, 6 H) 2.04 (s, 2 H) 1.79 (br s, 8 H) 1.41 - 1.54 (m, 2 H) 0.57 (s, 3 H) ppm.

LC-MS (ESI+): m/z 524 $[M+H]^+$.

16: (11β,17α)-20,20,21,21,21-Pentafluoro-17-hydroxy-11-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-19-norpregna-4,9-dien-3-one

Compound **16** (64 mg, 54.5 %) was prepared in analogy to the procedure described for compound **15** from compound **26** (100 mg, 0.2 mmol) and *N*-methylpiperazine.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20 (d, *J*=8.34 Hz, 2 H) 7.11 (d, *J*=8.34 Hz, 2 H) 5.76 - 5.80 (m, 1 H) 4.40 - 4.48 (m, 1 H) 3.47 (s, 2 H) 2.68 - 2.79 (m, 1 H) 2.31 - 2.64 (m, 19 H) 2.27 (s, 3 H) 2.04 (s, 2 H) 1.67 - 1.86 (m, 9 H) 1.41 - 1.53 (m, 2 H) 0.59 (s, 3 H) ppm

LC-MS (ESI+): m/z 579 $[M+H]^+$.

Synthesis of compound **11**:

33: (5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-11-(4-Hydroxyphenyl)-5',5',13-trimethyl-17-(pentafluoroethyl)-1,2,6,7,8,11,12,13,14,15,16,17-dodecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxane]-5,17(4*H*)-diol

To a solution of compound **24i** (9.72 g, 14.36 mmol) in methanol (100 mL) was added ammonium formate (5.53 g, 87.6 mmol) and palladium on activated charcoal (10%, 972 mg). The reaction mixture was stirred for 2 h at 23°C. Then, it was filtered through Celite® and the filtrate was evaporated. The obtained crude product (8.5 g, 100 % crude) was used without purification for the next step.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06 (d, *J*=8.29 Hz, 2 H) 6.72 (d, *J*=8.67 Hz, 2 H) 4.19 - 4.30 (m, 1 H) 3.38 - 3.57 (m, 4 H) 2.10 - 2.47 (m, 9 H) 1.98 - 2.07 (m, 1 H) 1.66 - 1.85 (m, 4 H) 1.56 (br d, *J*=13.94 Hz, 4 H) 1.05 (s, 3 H) 0.92 - 1.01 (m, 1 H) 0.86 (s, 3 H) 0.55 (s, 3 H) ppm.

LC-MS (ESI+): 587 $[M+H]^+$.

34: 4-[(5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-5,17-Dihydroxy-5',5',13-trimethyl-17-(pentafluoroethyl)-1,2,4,5,6,7,8,11,12,13,14,15,16,17-tetradecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxan]-11-yl]phenyl nonafluorobutane-1-sulfonate

Butyllithium (1.6 M in hexane, 14.64 mL, 23.42 mmol) was added to a solution of compound **33** (9.16 g, 15.61 mmol) in THF (100 mL) at 0°C. It was stirred for 30 minutes at 0°C. Then, perfluorobutanesulfonyl fluoride (5.62 mL, 31 mmol) was added. Afterwards, it was stirred for 1.5 h at 0°C. Then, the reaction mixture was poured into a mixture of 300 mL saturated

aqueous solution of sodium bicarbonate and 90 mL aqueous sodium hydroxide (2 N). It was stirred for another 45 minutes. Then, the mixture was extracted with ethyl acetate three times. The combined organic layers were washed with brine and dried over sodium sulfate. The crude product was purified by column chromatography to give compound **34** (10.1 g, 74.5 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 - 7.35 (d, *J*=8.30 Hz, 2 H) 7.13 - 7.22 (d, *J*=8.30 Hz, 2 H) 4.42 - 4.49 (m, 1 H) 4.29 - 4.39 (m, 1 H) 3.54 (s, 5 H) 2.14 - 2.50 (m, 9 H) 1.99 - 2.08 (m, 1 H) 1.68 - 1.90 (m, 6 H) 1.05 (s, 3 H) 0.86 (s, 4 H) 0.50 (s, 3 H) ppm.

LC-MS (ESI+): m/z 869 $[M+H]^+$.

35: Methyl 4'-[(5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-5,17-dihydroxy-5',5',13-trimethyl-17-(pentafluoroethyl)-1,2,4,5,6,7,8,11,12,13,14,15,16,17-tetradecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxan]-11-yl][biphenyl]-4-carboxylate

A solution of compound **34** (10 g, 11.52 mmol) was dissolved in a mixture of toluene (100 mL) and ethanol (50 mL). Aqueous sodium carbonate solution (2 N, 16.7 mL) was added followed by lithium chloride (1.09 g, 25.7 mmol), (4-methoxycarbonylphenyl)boronic acid (2.12 g, 11.78 mmol), and tetrakis(triphenylphosphine)palladium(0) (1.6 g, 1.39 mmol). The reaction mixture was heated under reflux for 2 h. Then, it was allowed to cool down to 23°C. It was diluted with water. The mixture was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over sodium sulfate and evaporated. The crude product was purified by column chromatography followed by crystallization from diisopropyl ether to give compound **35** (5.8 g, 71.4 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 - 8.14 (m, 2 H) 7.61 - 7.70 (m, 2 H) 7.49 - 7.58 (m, 2 H) 7.27 - 7.38 (m, 2 H) 4.43 - 4.48 (m, 1 H) 4.33 - 4.41 (m, 1 H) 3.94 (s, 3 H) 3.39 - 3.58 (m, 4 H) 2.18 - 2.54 (m, 8 H) 2.00 - 2.10 (m, 1 H) 1.68 - 1.88 (m, 4 H) 1.62 (s, 2 H) 1.05 (s, 3 H) 0.86 (s, 3 H) 0.58 (s, 3 H) ppm.

11: 4'-[(11β,17α)-20,20,21,21,21-Pentafluoro-17-hydroxy-3-oxo-19-norpregna-4,9-dien-11-yl][biphenyl]-4-carboxylic acid

Cleavage of the ketal and concomitant elimination of the 5-hydroxy group was achieved according to general procedure c): Starting with compound **35** (5.13 g, 7.28 mmol), crude product (4.37 g, 100 % crude) was obtained, which was used without purification for the next

step: It was dissolved in THF (50 mL) and a solution of lithium hydroxide (1.74 g, 72.74 mmol) in water (32 mL) was added. It was stirred for 3.5 h at 90°C. Afterwards, it was allowed to cool down to 23°C. Then, it was diluted with water (25 mL) and, under cooling using an external ice bath, the mixture was acidified with hydrochloric acid (2 N, 38 mL) to reach pH 2. The mixture was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over sodium sulfate and evaporated. The obtained crude material was filtered through Celite® and crystallized from a mixture of dichloromethane and diisopropyl ether to give compound **11** (3.73 g, 87.3 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J*=8.34 Hz, 2 H) 7.69 (s, 2 H) 7.52 - 7.61 (m, 2 H) 7.30 (s, 3 H) 5.78 - 5.85 (m, 1 H) 4.43 - 4.58 (m, 1 H) 2.72 - 2.83 (m, 1 H) 2.26 - 2.69 (m, 12 H) 2.08 (br s, 2 H) 1.76 - 1.88 (m, 4 H) 1.40 - 1.57 (m, 3 H) 0.65 (s, 3 H) ppm.

LC-MS (ESI+): m/z 587 $[M+H]^+$.

Synthesis of compound **19**:

36: *N*-[{4-[(5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-5,17-Dihydroxy-5',5',13-trimethyl-17-(pentafluoroethyl)-1,2,4,5,6,7,8,11,12,13,14,15,16,17-tetradecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-[1,3]dioxan]-11-yl]phenyl}(methyl)- λ^4-sulfanylidene]-4-methylbenzenesulfonamide

Compound **24k** (3 g, 4.86 mmol) was suspended in acetonitrile (80 mL). Chloramine T trihydrate® (1.64 g, 5.82 mmol) was added. It was stirred for 20 h at 23°C. Then, it was diluted with dichloromethane (70 mL). The precipitated sodium chloride was filtered off and the filtrate was evaporated. The crude material was purified by column chromatography to yield compound **36** (3.16 g, 82.7 %) as mixture of diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 - 7.79 (m, 2 H) 7.55 - 7.63 (m, 2 H) 7.35 - 7.41 (m, 2 H) 7.15 - 7.21 (m, 2 H) 4.40 (s, 1 H) 4.30 - 4.38 (m, 1 H) 3.39 - 3.59 (m, 4 H) 2.81 (s, 3 H) 2.40 - 2.48 (m, 4 H) 2.36 (s, 3 H) 2.12 - 2.31 (m, 4 H) 2.04 (s, 3 H) 1.69 - 1.86 (m, 4 H) 1.49 - 1.58 (m, 3 H) 1.05 (d, *J*=2.53 Hz, 3 H) 0.87 (s, 3 H) 0.44 (s, 3H) ppm. (mixture of diastereomers)

37: *N*-[{4-[(5*R*,8*S*,11*R*,13*S*,14*S*,17*S*)-5,17-Dihydroxy-5',5',13-trimethyl-17-(pentafluoroethyl)-1,2,4,5,6,7,8,11,12,13,14,15,16,17-

tetradecahydrospiro[cyclopenta[a]phenanthrene-3,2'-[1,3]dioxan]-11-yl]phenyl}(methyl)oxido-λ^6-sulfanylidene]-4-methylbenzenesulfonamide

Compound **36** (3.16 g, 4.02 mmol) was dissolved in a mixture of acetonitrile (2.5 mL) and methanol (1.6 mL). Sodium carbonate (1.22 g, 11.5 mmol) was added, followed by a 30% hydrogen peroxide solution (30% in water, 2.34 mL, 76 mmol). It was stirred for 2.5 h at 23°C. Then, the reaction mixture was poured into water. It was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate and evaporated. The crude material was purified by column chromatography to yield compound **37** (2.72 g, 82.72 %) as mixture of diastereomers.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.90 (s, 4 H) 7.44 - 7.53 (m, 2 H) 7.26 (s, 2 H) 4.43 - 4.46 (m, 1 H) 4.37 - 4.41 (m, 1 H) 3.46 (s, 5 H) 2.45 - 2.48 (m, 2 H) 2.40 (s, 3H) 2.16 - 2.32 (m, 4 H) 1.70 (s, 3 H) 1.51 - 1.56 (m, 1 H) 1.37 - 1.46 (m, 1 H) 1.05 (s, 3 H) 0.89 - 0.97 (m, 1 H) 0.87 (s, 3 H) 0.51 (s, 3 H) ppm. (mixture of diastereomers)

38: 4-Methyl-*N*-[methyl(oxido){4-[(11β,17α)-20,20,21,21,21-pentafluoro-17-hydroxy-3-oxo-19-norpregna-4,9-dien-11-yl]phenyl}-λ^6-sulfanylidene]benzenesulfonamide

Cleavage of the ketal and concomitant elimination of the 5-hydroxy group was achieved according to general procedure b): Starting with compound **37** (2.72 g, 3.33 mmol), compound **38** (2.2 g, 94.7 %) was obtained as mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 - 7.98 (m, 2 H) 7.82 - 7.89 (m, 2 H) 7.40 - 7.47 (m, 2 H) 7.26 (s, 2 H) 5.80 - 5.84 (m, 1 H) 4.47 - 4.55 (m, 1 H) 3.43 (d, *J*=3.01 Hz, 3 H) 2.46 - 2.73 (m, 8 H) 2.40 (s, 4 H) 2.12 - 2.22 (m, 2 H) 1.72 - 1.87 (m, 4 H) 1.18 - 1.31 (m, 2 H) 0.55 (s, 3 H) ppm. (mixture of diastereomers)

LC-MS (ESI+): m/z 698 $[M+H]^+$.

19: (11β,17α)-20,20,21,21,21-Pentafluoro-17-hydroxy-11-[4-(*S*methylsulfonimidoyl)phenyl]-19-norpregna-4,9-dien-3-one

Compound **38** (500 mg, 0.72 mmol) was dissolved in chloroform (10 mL). Concentrated sulfuric acid (1.15 mL) was added at 0°C. The mixture was stirred for 7 h at 0°C. Afterwards, the reaction mixture was slowly poured into a saturated aqueous solution of sodium bicarbonate. Afterwards, 5% sodium hydroxide solution was added to reach a pH of 8–9. Then, the mixture was extracted with dichloromethane three times. The combined organic layers were washed with brine, dried over sodium sulfate and evaporated. The crude material

was purified by column chromatography to obtain compound **19** (306 mg, 78.2 %) as a mixture of diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (dd, *J*=8.59, 3.28 Hz, 2 H) 7.35 - 7.44 (m, 2 H) 5.81 (d, *J*=2.53 Hz, 1 H) 4.51 (s, 1 H) 3.11 (s, 3 H) 2.23 - 2.78 (m, 12 H) 2.02 - 2.15 (m, 1 H) 1.71 - 1.94 (m, 4 H) 1.33 - 1.65 (m, 4 H) 0.56 and 0.40 (s, 3 H) ppm. (mixture of diastereomers)

LC-MS (ESI+): *R*t=1.23 min, m/z 544 $[M+H]^+$.

DMPK

DMPK – metabolic stability assay

The *in vitro* metabolic stability of test compounds was determined by incubating them at 0.3–3 µM in a suspension of liver microsomes in 100 mM phosphate buffer, pH 7.4 (NaH_2PO_4 x H_2O + Na_2HPO_4 x $2H_2O$) and at a protein concentration of 0.5 mg/mL at 37°C. The microsomes were activated by adding a co-factor mix containing 8 mM glucose-6-phosphate, 4 mM $MgCl_2$; 0.5 mM NADP and 1 IU/mL glucose-6-phosphate dehydrogenase in phosphate buffer, pH 7.4. The metabolic assay was started shortly afterwards by adding the test compound to the incubation. Organic solvent in the incubations was limited to ≤0.01% dimethylsulfoxide (DMSO) and ≤1% acetonitrile. During incubation, the microsomal suspensions were continuously shaken at 580 rpm and incubations were stopped at 0, 30, and 60 min by immediately adding equal volumes of cold methanol. Samples were frozen at –20°C overnight, subsequently centrifuged for 15 minutes at 3000 rpm and the supernatant was analyzed with an Agilent 1200 HPLC-system with MS/MS or UV detection.

The rate of degradation of a test compound was determined and the intrinsic clearances (CL_{int}) were calculated according to Lau [Y. Lau, E. Sapidou, X. Cui, R. White, K.-C. Cheng, Drug Metab. Disp., 2002, 30, 1446–1454] considering amount of microsomal protein and specific liver weight. The predicted hepatic *in vivo* blood clearance (CL_H) was then calculated based on the 'well stirred' liver model using the CL_{int} and liver blood flow (Q_H) resulting in the hepatic extraction ratio E_H according to $E_H = CL_H / Q_H$. Maximum bioavailability (F_{max} [%]) was calculated from the calculated extraction ratio according to: F_{max} [%] = 1-E_H assuming 100% absorption. The following parameter values were used: Liver blood flow –

1.3 L/h/kg (human), 4 L/h/kg (rat); specific liver weight – 21 g/kg (human), 40 g/kg (rat); microsomal protein content – 45 mg/g (human, rat).

Plasma protein binding

Determination of plasma protein binding of test compounds in human and animal plasma was performed according to Schuhmacher et. al.[27]

DMPK – Determination of metabolites of lonaprisan in human plasma

Human serum samples were generated in the clinical study ME301781. Serum samples were selected from volunteers after single oral administration of 200 mg/volunteer lonaprisan in the first treatment period. Seven human serum pool samples were prepared from six individuals at different time points. The concentration–time profiles and then AUC of the three metabolites (compounds 1, 2, and 3), as well as for the drug substance lonaprisan, were determined by an LC-MS/MS method with external calibration using reference compounds for compound 1, 2, 3, and lonaprisan.

Instruments and materials

Instruments and materials	**Manufacturer**
Mass Spectrometer QTOF Ultima Global	Waters, Eschborn, Germany
HPLC Pump 1100	Agilent, Waldbronn, Germany
UV Detector 1100	Agilent, Waldbronn, Germany
Autosampler HTS PAL	CTC Analytics, Zwingen, Switzerland
Rotor Heidolph	Heidolph, Kehlheim, Germany
Zentrifuge Minifuge RF	Heraeus, Osterode, Germany
HPLC column 50 x 2.1 mm, 2.5 µm, Xterra MS, C18	Waters, Eschborn, Germany
Balance Mettler AT250	Mettler Toledo, Duesseldorf, Germany

Drug and reference standards for determination of metabolites: detected positive $[M+H]^+$ molecular ion, origin

Substance	$[M+H]^+$ [Dalton]	Lot number	Purity [%]
Lonaprisan	509	82300149	98.8
Compound 1	527	CL 414K1	100
Compound 2	525	HA 6565-2	95.8
Compound 3	511	Sand 28K 1 + K2	93.9

Chemicals used for analysis

Chemical	Grade	Manufacturer
Acetonitrile	HPLC Gradient Grade	Promochem, Wesel, Germany
Ethanol	p.a.	Merck, Darmstadt, Germany
Ammonium acetate	p.a.	Merck, Darmstadt, Germany
NaCl, physiologic solution		Fresenius, Taunusstein, Germany
Water	>18 MΩ	ELGA, Labwater, USF, Ransbach-Baumbach, Germany
Toluene	Picograde	Promochem, Wesel, Germany
2-Propanol	p.a.	Merck, Darmstadt, Germany
Acetic acid	p.a.	Merck, Darmstadt, Germany

Preparation of the sample pools

Individual serum samples from the subjects were thawed at room temperature and vortexed. From each serum sample at a time point, 0.5 mL serum was combined in a glass vial (Packard Bioscience, 25 mL) to a total volume of 3.5 mL. The resulting mixture was vortexed again and stored at approx. –20°C in the freezer until analysis.

Preparation of calibration standards and quality control samples

The quantification was performed using an external calibration. The calibration standards and QC samples were prepared by adding an appropriate volume of a mixed working solution to 300 µL of blank human serum.

Sample preparation for human serum samples, calibration standards and quality control samples

To 300 µL of serum sample, 700 µL of physiologic saline solution was added followed by vortex mixing. The serum samples were extracted with 2.5 mL toluene/2-propanol (98:2) in a Heidolph rotor at ambient temperature for 30 min. Phase separation was achieved by centrifugation at 1500 g and 6°C for 15 min. The organic layer was then transferred into autosampler vials. The solvent was evaporated under a gentle stream of nitrogen and the residues were re-dissolved in 50 µL methanol followed by vortex mixing and centrifugation at 2500 g for 10 min. An aliquot of 10 µL was injected into the LC-MS/MS system.

HPLC conditions for LC-MS/MS

LC column	150 x 2.1 mm, 2.5 µm, Xterra MS C_{18}
Guard column	N/A
Column temperature	45°C
Flow rate	0.350 mL/min
Solvent A	0.1% CH_3COOH
Solvent B	Acetonitrile
Gradient	0.00 min 100% A 30.00 min 100% B 31.00 min 100% B 31.10 min 100% A 35.00 min 100% A

Mass spectrometric conditions

The measurement of the molecular masses and MS^2 fragment spectra of the metabolites was performed using the QTOF Ultima Global mass spectrometer in positive electrospray ionization mode.

System relevant parameters for analysis with the QTOF-Global mass spectrometer:

Mass spectrometer type	**Quadrupole - time of flight**
Interface	ESI
Ionization mode	positive
Capillary voltage	4.5 kV
Cone voltage	60 V
Source temperature	80°C
Nebulizing gas	Nitrogen
Cone gas flow	50 L/h
Desolvation gas flow	550 L/h
Desolvation temp	450°C
RF Lens 1 energy	25 V
Collision gas	argon
Collision energy	20–35 V

Data evaluation for the quantitative determination of metabolites (quantitative data) with the LC-MS method

Chromatographic and mass spectrometric data for the semi-quantitation were evaluated with the QuanLynx software of MassLynx 4.0 software (Micromass, Almere, The Netherlands).

Analyte concentrations for the semi-quantitative determination were calculated using the external standard method. The standard curve was calculated from peak areas of the calibration standards using second-order regression. The measured peak areas of the study and the quality control samples were converted into concentrations by using equation (1):

$$\text{(1)} \qquad \text{Analyte concentration} = \frac{\text{Peak area (analyte) - intercept}}{\text{slope}}$$

intercept: intercept of the corresponding standard curve
slope: slope of the corresponding standard curve

For the calculation of the bias (labeled as deviation in the raw data), the equation (2) was used, respectively:

$$\text{(2)} \qquad \text{bias [\%]} = \frac{\text{mean x 100}}{\text{nominal content}} - 100$$

The *AUC* was calculated using the following validated Microsoft Excel Function:

AUC0_t: Calculates the area under the concentration versus time curve for data using the linear trapezoidal rule. The *AUC* is calculated between the time points in the **time_data** range. In pharmacokinetic calculations, the time points usually begin at time 0 and finish at the last quantifiable point.

Standard curves and lower limit of quantitation (LLOQ) for the determination of lonaprisan and its metabolites in human serum

	Lonaprisan	**Compound 1**	**Compound 2**	**Compound 3**
Calibrated range [ng/mL]	5–300	5–300	5–300	5–300

Concentrations and AUC of lonaprisan and its metabolites identified by LC-MS/MS in pools of human serum from clinical study ME301781 after oral administration of 200 mg lonaprisan

Human serum pool	**Compound 1**	**Compound 2**	**Compound 3**	**Lonaprisan**
	Concentration [ng/mL]			
Day 1, 0 h	<LLOQ	<LLOQ	<LLOQ	5.70
Day 1, 0.5 h	<LLOQ	7.50	9.10	9.50
Day 1, 1.5 h	21.1	40.6	60.8	20.8
Day 1, 2 h	36.3	52.4	79.9	24.2
Day 1, 4 h	60.5	37.3	41.6	12.4
Day 1, 8 h	65.8	20.6	18.8	9.40
Day 1, 24 h	152	29.6	31.6	5.60
Day 1, 48 h	102	15.2	15.0	<LLOQ
AUC (0–24h) [ng x h/mL]	2117	656	718	230
% of *AUC* of lonaprisan	920	285	312	N/A
Relative contribution to sum of *AUC* [%]	57	18	19	6
AUC (0–24h) of drug-related compounds [ng x h/mL]: 3721				

DMPK – Determination of metabolites of vilaprisan in human plasma

The exposure of metabolites of BAY 1002670 in human plasma was investigated by an explorative LC-MS method after single and multiple oral administration of 5 mg BAY 1002670 to healthy volunteers (study #14721).

Reference compounds

	[M] [Dalton]	**Batch No.**	**Purity**
Vilaprisan (BAY 1002670)	544	BXR4D8H	16 Jul 2009
Compound 20	546	GARK1821-2-1	01 Jul 2011
Compound 21	562	PRS78357-0-0	21 Dec 2011

Chemicals

Chemicals	**Grade**	**Manufacturer**
Acetonitrile	99.9%	Merck, Darmstadt, Germany
Atomlight	N/A	Perkin Elmer, Weiterstadt, Germany
Ammonium formate	>99%	Fluka, Taufkirchen, Germany
tert-Butyl-methyl ether	per analysis	Merck, Darmstadt, Germany
Formic acid	98–100%	Merck, Darmstadt, Germany
Water	LC-MS	Millipore, Schwalbach, Germany

Equipment

Sartorius ME36S – OCE
(Sartorius, Göttingen, Germany)

LSC Tricarb2900TR
TopCount NXT
(Camberra Packard, Rüsselsheim, Germany)

Biofuge Heraeus – Fresco
(Heraeus, Osterode, Germany)

Sorvall RT 6000D Centrifuge
(Thermo, Dreieich, Germany)

Pipette tips and Combitips
Pipette research + Multipipette
Sample Tubes 1.5, 2 mL
(Eppendorf, Hamburg, Germany)

HPLC Glass Vials, e.g. 1.5 mL

(Agilent Technologies, Waldbronn, Germany)

Snap-Caps
(Wicom, Heppenheim, Germany)

RIA-Extraction-vials (Glass), 75 x 1 mm, 4.0 mL
M&M Glass Company, Los Angeles, USA

Fraction collector FC204
(Gilson, Middleton, USA)

HPLC column Accucore RP-MS Fluoro 150 x 3.0 mm, 2.5 µm
QExactive mass spectrometer
(Thermo, Bremen, Germany)

UPLC pump Acquity
UPLC autosampler Acquity
UPLC column oven Acquity
(Waters, Eschborn, Germany)

Preparation of plasma samples, calibration standards and quality control samples

To 200 µL aliquots of each plasma sample, calibration standards and quality control samples of 200 µL of water (containing 25 ng/mL internal standard [$^{13}C_6$]BAY 1002670) were added to extract the samples with methyl *tert*-butyl ether (pH 7) in the "End by End" rotor at room temperature for 10 minutes. To achieve phase separation, all samples were centrifuged at 3000 rpm for 5 minutes at approx. 10°C. The aqueous phase was frozen out in dry ice/ethanol mixture. The organic phase was decanted in an LC vial, concentrated and re-dissolved in 100 µL eluent. A 45 µL aliquot of the extract was injected into the LC/MS system.

The concentrations of vilaprisan and metabolites compounds **20** and **21** were calculated by comparison with a calibration curve prepared from authentic reference standards for vilaprisan, compounds **20** and **21**.

Calibration range

Analyte	[µg/L]
Vilaprisan	0.05–20
Compound 20	0.25–20
Compound 21	0.10–20

Method

HPLC column	Accucore RP-MS, 150 x 3 mm, 2.6 µm		
Guard column	N/A		
Column temperature	40°C		
Flow rate	0.4 mL / min		
Solvent A	10 mM ammonium acetate		
Solvent B	acetonitrile		
Injection volume	45 µL		
Gradient	Time [min.]	A [%]	B [%]
	0.0	100	0
	30.0	60	40
	50.0	40	60
	55.0	5	95
	55.1	100	0
	59.0	100	0
Split to MS	10%[a]		
Sampling rate during HPLC run	9.6 sec[a]		
Measuring time TopCount NXT per well	5 min[a]		
Background determination	by reference plate[a]		
Detection (MS)	QExactive mass spectrometer		
Interface	Electrospray ionization		
Ionization mode	positive	negative	
Heated capillary temperature	250°C	250°C	
Source voltage	3.5 kV	3.5 kV	
Capillary voltage	23 V	–49 V	
RF lens	85 V	–134 V	
Sheat gas flow (Nitrogen)	20 units	20 units	
Auxiliary gas flow (Nitrogen)	10 units	10 units	
Sweep gas flow (Nitrogen)	50 units	50 units	
Cooling gas	Nitrogen	Nitrogen	
Collision energy	25–30%	25–30%	
Data handling:	Xcalibure®, Thermo Fischer, Dreieich, Germany		

Pharmacokinetic data evaluation

Pharmacokinetic parameters were calculated from the pool plasma concentration–time profiles using the software Toxkin, version 2.6.1 (Entimo, Berlin, Germany) according to the following table:

Pharmacokinetic parameters

Parameter	Symbol	Way of calculation
Maximum concentration	C_{max}	Taken as directly determined from the concentration–time profiles
Half-life associated with the terminal slope of the concentration time curve	$t_{1/2}$	$t_{1/2} = \ln 2/\lambda_Z$
Area under the concentration–time curve from zero to 24 h	$AUC(0\text{-}24h)_{ss}$	Non-compartmental analysis applying the mixed linear/logarithmic trapezoidal rule; extrapolation of the area from the first data point to the time of administration by linear connection of the first data point with the origin $C_0 = C_1$ for i.v. route

Results of exploratory determination of vilaprisan and its metabolites compound 20 and 21 in the human plasma pool following multiple (day 28) peroral administration of 5 mg vilaprisan (study No. 14721)

Time [day]	Time [h]	Vilaprisan [µg/L]	Compound 20 [µg/L]	Compound 21 [µg/L]
28	0	11.704	3.21	3.02
	0.5	13.120	3.43	3.02
	1	22.544	6.04	3.32
	1.5	27.574	7.33	3.50
	2	29.955	8.75	3.68
	2.5	28.379	8.44	3.60
	3	26.991	8.42	3.68
	4	23.504	7.07	3.44
	6	22.144	4.53	3.26
	8	18.938	3.69	3.07
	12	15.614	3.01	3.30
	16	13.611	3.11	3.04
	24	12.182	3.13	3.17
	48	7.523	2.18	2.78
	72	5.844	0.94	2.38
	96	4.046	0.86	2.17
	168	1.521	0.37	1.49
	240	0.594	<LOQ	0.93
	312	0.188	<LOQ	0.489

Summary of estimated PK parameters of vilaprisan and its metabolites in human plasma following multiple (day 28) peroral administration of 5 mg vilaprisan

Dose [mg]	**Time [day]**	**Analyte**	***C_{max}*** **[nmol/L]**	***$t_{1/2}$*** **[h]**	***AUC (0–24)*** [a] **[µg/L x h]**
5	28	Vilaprisan	30.0	51.7	413
		Compound 20	8.75	68.1	97.8
		Compound 21	3.68	124	77.1

[a] = if t_{last} <24 h, *AUC (0-t_{last})* was reported.