Synthesis and Biological Activities of some Mifepristone Derivatives

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GENERAL

All reagents and solvents for syntheses were purchased from Sigma-Aldrich, Fluka or Merck and used without further purification. Reagent-grade solvents were purified and dried using standard methods. DMF was purified by azeotropic distillation and dried over 4Å molecular sieve. Trietylamine and diethylenetriamine were dried over KOH. For preparation of absolute MeOH, 98% MeOH was first treated with fresh calcinated CaO and distilled; subsequently, it was refluxed with magnesium splinters and iodine and distilled again. THF and acetonitrile were dried over sodium wire or P_2O_5 (0.5-1% w/v), respectively. Solvents of analytical and spectroscopic grade as well as deuterated NMR solvents were purchased from Merck and Chemische Fabrik Uetikon, respectively. Purity of compounds was determined by elemental analyses (Mikroanalytisches Laboratorium of the Institute of Physical Chemistry, University of Vienna, Austria) and / or HPLC; purity of key target compounds was ≥ 95 % except otherwise noted.

SPECTROSCOPY

UV spectra were recorded on a Shimadzu UV-160A spectrometer and absorption maxima λ_{max} are given in nm.

IR spectra were taken on a Perkin-Elmer FT-IR 2000 spectrometer. Absorption maxima ν_{max} are given in cm^{-1} and referred to as s (strong), m (medium), w (weak) and br (broad).

NMR spectra were recorded on a Varian Unity Inova 400/600 NMR spectrometer equipped with a tuneable broadband probe. Inverse detected gradient selected 2D experiments (gCOSY, HSQC, HMBC) were done using standard pulse sequence programs. HMBC experiments were optimised for a long range-coupling constant of 8 Hz. Tetramethylsilane (TMS) was used as internal reference standard. Chemical shifts δ are given in ppm, coupling constants (*J* values) are expressed in Hz and multiplicities are referred to as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Assignments marked with * are exchangeable.

Mass spectra. EI-mass spectra were measured with a Finnigan MAT 212 or Varian MAT 312 spectrometer at 70 eV ionizing voltage. GC-MS were measured on a HP-GC 6890-HP-MSD 7890. Intensities are given in % of the base peak. High resolution mass spectra were obtained in the positive and negative mode on an Agilent 1100 Trap SL ion trap in the range of 100-1000 m/z or 100-2000 m/z using electrospray ionisation. Data marked with $^{\#}$ have been recorded with a Bruker Daltonics DataAnalysis 3.0; (ESI 128.3 Volt).

CHROMATOGRAPHY

Thin-layer chromatography (TLC) was run on aluminium-backed silica gel plates (Kieselgel 60 F_{254} of Merck). Spots were visualized under UV light at 254 nm and/or in an iodine chamber. Eluents: E I = EtOAc:cyclohexane (3:2, vol/vol); E II = EtOAc; E III = chloroform : MeOH (4:1, vol/vol); E IV = chloroform : MeOH (99:1, vol/vol); E V = chloroform : MeOH (9:1, vol/vol); E VI = CH_2Cl_2 : acetone (4:1, vol/vol); E VII = toluene : EtOAc : formic acid (5:4:1, vol/vol); E VIII = MeOH; E IX = toluene: acetone (1:1, vol/vol).

Flash chromatography was done by Flash Master Personal, Jones Chromatography.

Column Ø 27 mm, length 150 mm, silica gel Merck 60 (0.063-0.200 mm; 70-230 mesh ATSM).

Column chromatography was carried out on silica gel 60 (0.063-0.200 mm).

Preparative HPLC was done using a Labomatic HD-200 pump equipped with a Labocord-700 UV/VIS detector (absorption recorded at λ = 254 nm); column 1: YMC-Pack™ ODS-A™ (C18), 10 µm, 250 × 20 mm and column 2: Prontosil 120-5-C 18H, 5.0 µm, 250 × 20 mm.

Analytical HPLC was done using a HP 1050 autosampler and pump equipped with an Agilent 1100 G1314A VWD UV/VIS detector (absorption recorded at λ = 300 nm except otherwise noted); column: YMC-Pack™ ODS-A™ (C18), 5 µm, 250 × 4.6 mm; eluent: acetonitrile : H_2O (9:1, vol/vol); flow: 1ml/min.

SYNTHETIC PROCEDURES AND SPECTROSCOPIC DATA

17β-Hydroxy-11β-[4-(methylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (2)

Prepared as described in literature [S1,S2]; purification: preparative HPLC (column 2; acetonitrile : H_2O (84:16, vol/vol); flow: 23 ml/min; t_R = 3.4 min). Educt **1** was recovered (130 mg, 26%, t_R = 4.3 min).

$C_{28}H_{33}NO_2$; (MW: 415.57)

Calc: C 80.93, H 8.00, N 3.37; Found + ½ H_2O: C 79.21, H 8.07, N 3.30

Yield: 28% (colourless lyophilisate)

MS (m/z): 415 (M^+)

TLC: R_f = 0.45 (E I); R_f =0,75 (E II), R_f = 0.71 (E V), R_f = 0.59 (E VI), R_f = 0.05 (E VII)

Analytical HPLC: 96.7 %, t_R = 4.822 min (tracing: 3.3 %, t_R = 4.390 min)

UV/VIS: (MeOH): λ_{max} = 209.0, 250.0, 303.5 nm

IR (KBr): ν = 3387 (m), 2929 (s), 2870 (m) 2250 (w), 1654 (s) cm^{-1}

^{1}H-NMR: ($CDCl_3$) δ = 0.50 (3H, s, CH_3-18), 1.40 (1H, m, H-15), 1.42 (1H, m, H-7), 1.68 (2H, m, H-14, H-15), 1.84 (3H, s, CH_3-21), 1.89 (1H, td, J = 11.4, J = 3.2, H-16), 1.98 (1H, m, H-7), 2.16 (1H, m, H-16), 2.21 (1H, m, H-12), 2.29 (4H, m, H-1, 2x(H-2), H-12), 2,42 (1H, dd, J = 10.4, J = 0.8, H-8), 2.52 (2H, m, H-6), 2.73 (1H, m, H-1), 2.86 (3H, s, N-CH_3), 4.31 (1H, d, J = 6.4, H-11), 5.52 (1H, s, H-4), 6.61 (2H, m, H-3', H-5'), 6.97 (2H, m, H-2', H-6') ppm

^{13}C-NMR: ($CDCl_3$) δ = 3.7 (q, C-21), 13.6 (q, C-18), 23.2 (t, C-15), 25.6 (t, C-1), 27.2 (t, C-7), 31.0 (t, C-6), 36.7 (t, C-2), 38.8 (t, C-16), 38.8 (t, C-12), 39.0 (d, C-8), 39.4 (d, C-11), 40.5 (q, N-CH_3), 46.7 (s, C-13), 49.7 (d, C-14), 79.9 (s, C-17), 82.0 (s, C-20*), 82.4 (s, C-19*), 112.7 (d, C-3', C-5'), 122.5 (d, C-4), 127.3 (d, C-2', C-6'), 128.8 (s, C-10), 132.0 (s, C-1'), 146.8 (s, C-9), 148.4 (s, C-4'), 156.9 (s, C-5), 199.5 (s, C-3) ppm

17β-Hydroxy-11β-[4-hydroxyphenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**3**)

3 was prepared as described in literature[S3,S4,S5] and purified by column chromatography (eluent E VIII).

$C_{27}H_{30}O_3$ (MW 402.30)

Yield: 85% (colourless lyophilisate)

MS (m/z): 402 (M^+)

TLC (E VIII): $R_f = 0.24$

UV/VIS (MeOH): λ_{max} =226.5, 302.5 nm

IR (KBr): ν = 3287 (m), 2968 (s), 2861 (m), 2151 (w), 1642 (s), 1611 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.50 (3H, s, CH_3-18), 1.34 (1H, m, H-15), 1.44 (1H, m, H-7), 1.50 (1H, m, H-14), 1.70 (1H, m, H-15), 1.88 (3H, s, CH_3-21), 1.92 (1H, m, H-16), 2.00 (1H, m, H-7), 2.19 (1H, m, H-16), 2.23 (2H, m, H-12), 2.35 (1H, m, H-8), 2.42 (2H, m, H-2), 2.47 (1H, m, H-1), 2.56 (2H, m, H-6), 2.75 (1H, m, H-1), 4.35 (1H, d, J = 6.5, H-11), 5.03 (1H, s, OH), 5.77 (1H, s, H-4), 6.69 (2H, m, H-3', H-5'), 6.97 (2H, m, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.7 (q, C-18), 23.3 (t, C-15), 25.8 (t, C-1), 27.3 (t, C-7), 31.1 (t, C-6), 36.8 (t, C-2), 38.9 (t, C-12*), 39.1 (d, C-8), 39.1 (t, C-16*), 39.7 (d, C-11), 46.8 (s, C-13), 49.7 (d, C-14), 80.2 (s, C-17), 82.2 (s, C-20), 82.6 (s, C-19), 115.4 (d, C-3', C-5'), 122.9 (d, C-4), 128.0 (d, C-2', C-6'), 129.4 (s, C-10), 136.5 (s, C-1'), 146.2 (s, C-9), 153.5 (s, C-4'), 156.8 (s, C-5), 199.6 (s, C-3) ppm

17β-Hydroxy-11β-[4-methoxyphenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**4**)

After dissolving **3** (20 mg, 0.05mmol) in 2 mL THF a ten fold excess of a diazomethane ether solution (2 mL) was added and the mixture stirred for 1 h at room temperature. Solvent and excess of diazomethane solution were evaporated in vacuo; the residue was purified by column chromatography (eluent E VIII).

$C_{28}H_{32}O_3$ (MW 416.56)

Yield: 89% (colourless lyophilisate)

MS (m/z): 416 (M^+)

TLC (E VIII): $R_f = 0.31$

UV/VIS (MeOH): $\lambda_{max} = 235.0, 299.5$ nm

IR (KBr): $\nu = 3426$ (m), 2944 (s), 2870 (m), 2363 (s), 1660 (s), 1509 (m) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.50 (3H, s, CH_3-18), 1.34 (1H, m, H-15), 1.42 (1H, m, H-7), 1.49 (1H, m, H-14), 1.70 (1H, m, H-15), 1.89 (3H, s, CH_3-21), 1.92 (1H, m, H-16), 2.01 (1H, m, H-7), 2.19 (1H, m, H-16), 2.23 (2H, m, H-12), 2.33 (1H, m, H-8), 2.42 (2H, m, H-2), 2.44 (1H, m, H-1), 2.57 (2H, m, H-6), 2.74 (1H, m, H-1), 3.68 (3H, s, OCH_3), 4.38 (1H, d, J = 5.6, H-11), 5.78 (1H, s, H-4), 6.77 (2H, m, H-3', H-5'), 7.06 (2H, m, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.7 (q, C-18), 23.3 (t, C-15), 25.9 (t, C-1), 27.3 (t, C-7), 31.1 (t, C-6), 36.8 (t, C-2), 38.9 (t, C-12*), 39.1 (d, C-8), 39.1 (t, C-16*), 39.7 (d, C-11), 46.8 (s, C-13), 49.7 (d, C-14), 51.2 (q, OCH_3), 80.1 (s, C-17), 82.2 (s, C-19), 82.6 (s, C-20), 115.4 (d, C-3', C-5'), 122.8 (d, C-4), 128.0 (d, C-2', C-6'), 129.3 (s, C-10), 136.8 (s, C-1'), 146.2 (s, C-9), 154.6 (s, C-4'), 156.8 (s, C-5), 199.6 (s, C-3) ppm

17β-Hydroxy-11β-[4-(9-bromnonoxy)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**5**)

K_2CO_3 (250 mg, 1.09 mmol) and 1,9-dibromononane (237mg, 0.83 mmol) were added to a solution of **3** (200 mg, 0.497mmol) in 10 mL acetone under argon. The mixture was stirred for 20 h at 50 °C. The precipitate was removed, the solvent evaporated in vacuo and the residue purified by column chromatography (eluent E VIII).

$C_{36}H_{47}O_3Br$ (MW: 607.60)

Yield: 55% (colourless lyophilisate)

MS (m/z): 607 (M^+)

TLC (E VIII): $R_f = 0.36$

UV/VIS (MeOH): $\lambda_{max} = 235.5, 297.0$ nm

IR (KBr): $\nu = 3429$(m), 2931 (s), 2855 (m), 1660 (s), 1508 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.50 (3H, s, CH_3-18), 1.30 (6H, m, H-4'', H-5'', H-6''), 1.34 (1H, m, H-15), 1.39 (5H, m, 2x(H-3''), 2x(H-7''), H-7), 1.46 (1H, m, H-14), 1.68 (1H, m, H-15), 1.73 (2H, m, H-2''), 1.81 (2H, m, H-8''), 1.87 (3H, s, CH_3-21), 1.93 (1H, m, H-16), 2.00 (1H, m, H-7), 2.21 (1H, m, H-16), 2.24 (2H, m, H-12), 2.35 (1H, m, H-8), 2.39 (2H, m, H-2), 2.45 (1H, m, H-1), 2.56 (2H, m, H-6), 2.74 (1H, m, H-1), 3.39 (2H, t, H-9''), 3.90 (2H, t, H-1''), 4.36 (1H, d, J = 5.8, H-11), 5.77 (1H, s, H-4), 6.61 (2H, m, H-3', H-5'), 6.97 (2H, m, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.7 (q, C-18), 23.3 (t, C-15), 25.9 (t, C-1), 27.3 (t, C-7), 26.8 – 28.1 (t, C-4'', C-5'', C-6''), 29.2 (t, C-7''), 29.3 (t, C-3''), 29.3 (C-8''), 31.8 (t, C-6), 32.7 (t, C-2''), 34.0 (t, C-9''), 36.8 (t, C-2), 38.8 (t, C-12*), 39.0 (t, C-16*), 39.1 (t, C-8), 39.7 (d, C-11), 46.8 (s, C-13), 49.7 (d, C-14), 67.9 (t, C-1''), 80.1 (s, C-17), 82.2 (s, C-19), 82.5 (s, C-20), 114.4 (d, C-3', C-5'), 122.8 (d, C-4), 127.8 (d, C-2', C-6'), 129.3 (s, C-10), 136.2 (s, C-1'), 146.2 (s, C-9), 156.8 (s, C-4'), 157.0 (s, C-5), 199.5 (s, C-3) ppm

17β-Hydroxy-11β-[4-(N-methylpropylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**6**)

6 was synthesized according to general procedure I reacting **2** (100 mg, 0.24 mmol) with 1-bromopropane (0.72 mmol); the product was purified by flash-chromatography (eluent E I) and preparative HPLC (column 2; acetonitrile : H_2O (84:16, vol/vol), flow: 23 mL/min; t_R = 6 min 4 sec).

$C_{31}H_{39}NO_2$ (MW: 457.65)

Yield: 34% (light yellow lyophilisate)

MS (m/z): 458 $(M+H)^+$

TLC: R_f = 0.82 (E I), R_f = 0.84 (E II)

UV/VIS (CH_2Cl_2): λ_{max} = 270.0, 301.0 nm

IR (KBr): ν = 3422 (m), 2936 (s), 2870 (m), 2363 (w), 2241 (w), 1656 (s) 1612 (m) 1560 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.55 (3H, s, CH_3-18), 0.91 (3H, t, H-3''), 1.34 (1H, m, H-15), 1.45 (1H, m, H-7), 1.58 (2H, m, H-2''), 1.71 (1H, m, H-14), 1.72 (1H, m, H-15), 1.89 (3H, s, CH_3-21), 1.93 (1H, t, H-16), 2.00 (1H, m, H-7), 2.21 (1H, m, H-16), 2.26 (1H, m, H-12), 2.31 (1H, m, H-12), 2.34 (2H, m, H-1, H-2), 2.42 (1H, m, H-2), 2.45 (1H, m, H-8), 2.56 (2H, m, H-6), 2.76 (1H, m, H-1), 2.89 (3H, s, N-CH_3), 3.22 (2H, m, H-1''), 4.34 (1H, d, J = 5.8, H-11), 5.76 (1H, s, H-4), 6.61 (2H, m, H-3', H-5'), 6.99 (2H, m, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.7 (q, C-18), 11.5 (q, C-3''), 20.0 (t, C-2''), 23.3 (t, C-15), 25.9 (t, C-1), 27.4 (t, C-7), 31.1 (t, C-6), 36.9 (t, C-2), 38.3 (q, N-CH_3), 38.8 (t, C-12), 38.9 (t, C-16) 39.2 (d, C-8), 39.6 (d, C-11), 46.9 (s, C-13), 49.9 (d, C-14), 54.8 (t, C-1''), 80.2 (s, C-17), 82.4 (s, C-19*), 82.5 (s, C-20*), 112.2 (d, C-3', C-5'), 122.7 (d, C-4), 127.6 (d, C-2', C-6'), 129.1 (s, C-10), 131.2 (s, C-1'), 147.0 (s, C-9), 147.8 (s, C-4'), 157.0 (s, C-5), 199,6 (s, C-3) ppm

17β-Hydroxy-11β-[4-(N-methylhexylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**7**)

7 was synthesized according to general procedure I reacting **2** (100 mg, 0.24 mmol) with 1-bromohexane (0.72 mmol); the product was purified by flash-chromatography (eluent E I) and preparative HPLC (column 2; acetonitrile : H_2O (84:16, vol/vol), flow: 23 mL/min; t_R = 12 min 10 sec).

$C_{34}H_{45}NO_2$ (MW: 499.73)

Yield: 49% (light yellow lyophilisate)

MS (m/z): 522 (M^+ + Na)

TLC: R_f = 0.83 (E I), R_f = 0.89 (E II), R_f = 0.93 (E V)

Analytical HPLC: 99.1 %, t_R = 5.888 min (tracing: 0.9%, t_R = 4.889 min)

UV/VIS (CH_2Cl_2): λ_{max} = 206.0, 265.0, 302.0 nm

IR (KBr): ν = 3424 (m), 2931 (s), 2868 (m), 2241 (w), 1661 (s) 1612 (m) 1516 (s) cm^{-1}

^{1}H-NMR: ($CDCl_3$) δ = 0.52 (3H, s, CH_3-18), 0.85 (3H, t, H-6''), 1.25 (4H, m, H-4'', H-5''), 1.34 (1H, m, H-15), 1.46 (1H, m, H-7), 1.50 (4H, m, H-2'', H-3''), 1.71 (1H, m, H-14), 1.72 (1H, m, H-15), 1.90 (3H, s, CH_3-21), 1.94 (1H, t, H-16), 2.01 (1H, m, H-7), 2.22 (1H, m, H-16), 2.24 (1H, m, H-12), 2.30 (1H, m, H-2), 2.36 (1H, m, H-12), 2.44 (2H, m, H-2, H-8), 2.75 (1H, m, H-1), 2.57 (2H, m, H-6), 2.75 (1H, m, H-1), 2.87 (3H, s, N-CH_3), 3.22 (2H, m, H-1''), 4.36 (1H, d, J = 5.8, H-11), 5.76 (1H, s, H-4), 6.67 (2H, m, H-3', H-5'), 7.05 (2H, m, H-2', H-6') ppm

^{13}C-NMR: ($CDCl_3$) δ = 3.8 (q, C-21), 13.7 (q, C-18), 14.0 (q, C-6''), 22.6 (t, C-5''), 23.3 (t, C-15), 25.8 (t, C-1), 26.6 (t, C2''), 26.8 (t, C-3''), 27.3 (t, C-7), 31.1 (t, C-6), 31.7 (t, C-4''), 36.9 (t, C-2), 38.2 (q, N-CH_3), 38.8 (t, C-16), 38.9 (t, C-12), 39.1 (d, C-8), 39.5 (d, C-11), 46.8 (s, C-13), 49.8 (d, C-14), 53.0 (t, C-1''), 80.2 (s, C-17), 82.3 (s, C-19*), 82.4 (s, C-20*), 112.2 (d, C-3', C-5'), 122.6 (d, C-4), 127.5 (d, C-2', C-6'), 129.0 (s, C-10), 131.1 (s, C-1'), 146.9 (s, C-9), 147.4 (s, C-4'), 157.0 (s, C-5), 199,6 (s, C-3) ppm

17β-Hydroxy-11β-[4-(N-methynonylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (8)

8 was synthesized according to general procedure I reacting **2** (100 mg, 0.24 mmol) with 1-bromo-nonane (0.72 mmol); the product was purified by flash-chromatography (eluent E I) and preparative HPLC (column 2; acetonitrile : H_2O (84:16, vol/vol), flow: 23 mL/min; t_R = 24 min 6 sec).

$C_{37}H_{51}NO_2$ (MW: 541.81)

Yield: 53% (light yellow lyophilisate)

MS (m/z): 542 $(M+H)^+$

TLC: R_f = 0.89 (E I), R_f = 0.92 (E II), R_f = 0.97 (E IV)

UV/VIS (CH_2Cl_2): λ_{max} = 269.5, 300.0 nm

IR (KBr): ν = 3421 (m), 2926 (s), 2854 (m), 2241 (w), 1656 (s) 1612 (m) 1517 (s) cm^{-1}

^{1}H-NMR: ($CDCl_3$) δ = 0.53 (3H, s, CH_3-18), 0.88 (3H, t, H-9''), 1.24 (2H, m, H-7''), 1.28 (2H, m H-8''), 1.29 (8H, m, H-3'', H-4'', H-5'', H-6''), 1.34 (1H, m, H-15), 1.46 (1H, m, H-7), 1.53 (2H, m, H-2''), 1.72 (1H, m, H-14), 1.73 (1H, m, H-15), 1.90 (3H, s, CH_3-21), 1.93 (1H, t, H-16), 2.01 (1H, m, H-7), 2.22 (1H, m, H-16), 2.27 (1H, m, H-12), 2.33 (1H, m, H-12), 2.35 (1H, m, H-2), 2.44 (1H, m, H-2), 2.45 (1H, m, H-8), 2.77 (1H, m, H-1), 2.58 (2H, m, H-6), 2.77 (1H, m, H-1), 2.89 (3H, s, N-CH_3), 3.24 (2H, m, H-1''), 4.36 (1H, d, J = 5.8, H-11), 5.76 (1H, s, H-4), 6.59 (2H, m, H-3', H-5'), 6.99 (2H, m, H-2', H-6') ppm

^{13}C-NMR: ($CDCl_3$) δ = 3.8 (q, C-21), 13.8 (q, C-18), 14.1 (q, C-9''), 22.7 (t, C-8''), 23.3 (t, C-15), 25.8 (t, C-1), 26.8 (t, C2''), 27.3 (t, C-3''), 27.4 (t, C-7), 29.4 (t, C-5), 31.1 (t, C-6), 31.7 (t, C-4''), 31.9 (t, C-7''), 36.9 (t, C-2), 38.3 (q, N-CH_3), 38.9 (t, C-12), 38.9 (t, C-16), 39.1 (d, C-8), 39.8 (d, C-11), 46.9 (s, C-13), 49.9 (d, C-14), 53.2 (t, C-1''), 80.3 (s, C-17), 82.3 (s, C-19*), 82.5 (s, C-20*), 112.3 (d, C-3', C-5'), 122.8 (d, C-4), 127.6 (d, C-2', C-6'), 129.3 (s, C-10), 145.4 (s, C-9), 157.2 (s, C-5), 199,6 (s, C-3) ppm

17β-Hydroxy-11β-[4-(3-hydroxy-N-methypropylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**9**)

9 was synthesized according to general procedure I reacting **2** (100 mg, 0.24 mmol) with 3-bromo-1-propanol (0.72 mmol); the product was purified by flash-chromatography (eluent E I) and preparative HPLC (column 2; acetonitrile : H_2O (56:44, vol/vol), flow: 23 mL/min; t_R = 4 min 36 sec). Byproduct **42** was also obtained and isolated.

$C_{31}H_{39}NO_3$ (MW: 473.65)

Yield: 20% (light yellow lyophilisate)

MS (m/z): 473 (M^+)

TLC: R_f = 0.23 (E I), R_f = 0.34 (E VI), R_f = 0.46 (E VII)

Analytical HPLC: 95.6 %,t_R = 4.387 min (tracing: 4.4 %, t_R = 4.034 min)

UV/VIS (CH_2Cl_2): λ_{max} = 268.0, 299.5 nm

IR (KBr): ν = 3423 (m), 2939 (s), 2870 (m), 2241 (w), 1649 (s), 1611 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0,55 (3H, s, CH_3-18), 1.35 (1H, m, H-15), 1.42 (1H, m, H-7), 1.72 (1H, m, H-14), 1.73 (1H, m, H-15), 1.83 (2H, m, H-2''), 1.89 (3H, s, CH_3-21), 1.94 (1H, t, H-16), 2.01 (1H, m, H-7), 2.23 (1H, m, H-16), 2.25 (1H, m, H-12), 2.32 (1H, m, H-12), 2.34 (1H, m, H-1), 2.35 (1H, m, H-2), 2.44 (1H, m, H-2), 2.45 (1H, m, H-8), 2.57 (2H, m, H-6), 2.77 (1H, m, H-1), 2.89 (3H, s, N-CH_3), 3.41 (2H, m, H-1''), 3.74 (2H, m, H-3''), 4.35 (1H, d, J = 6.6, H-11), 5.76 (1H, s, H-4), 6.68 (2H, m, H-3', H-5'), 7.00 (2H, m, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.7 (q, C-18), 23.3 (t, C-15), 25.9 (t, C-1), 27.4 (t, C-7), 29.7 (t, C-2''), 31.1 (t, C-6), 36.9 (t, C-2), 38.4 (q, N-CH_3), 38.8 (t, C-12), 38.9 (t, C-16), 39.2 (d, C-8), 39.6 (d, C-11), 46.9 (s, C-13), 49.9 (d, C-14), 50.5 (t, C-1''), 61.2 (t, C-3''), 80.2 (s, C-17), 82.4 (s, C-19), 82.5 (s, C-20), 113.1 (d, C-3', C-5'), 122.7 (d, C-4), 127.6 (d, C-2', C-6'), 129.1 (s, C-10), 132.3 (s, C-1'), 146.8 (s, C-9), 147.7 (s, C-4'), 157.0 (s, C-5), 199.7 (s, C-3) ppm

17β-Hydroxy-11β-[4-(6-hydroxy-N-methylhexylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (10)

10 was synthesized according to general procedure I reacting **2** (100 mg, 0.24 mmol) with 6-bromo-1-hexanol (0.72 mmol); the product was purified by flash-chromatography (eluent E I) and preparative HPLC (column 1; acetonitrile : H_2O (2:3, vol/vol), flow: 12 mL/min; t_R = 9 min 20 sec).

$C_{34}H_{45}NO_3$ (MW: 515.73)

Yield: 54% (colourless lyophilisate)

Calc: C 79.18, H 8.79, N 2.72; Found: C 78.51, H 8.80, N 3.25.

MS (m/z): 515 (M^+)

TLC: R_f = 0.22 (E I), R_f = 0.54 (E II), R_f = 0.41 (E V), R_f = 0.31 (E VI), R_f = 0.00 (E VII)

Analytical HPLC: 95.8 %, t_R = 5.328 min (tracings: 3.3%, t_R = 4.047 min; 0.9%, t_R = 4.612 min)

UV/VIS (MeOH): λ_{max} = 208.5, 263.5, 303.5 nm

IR (KBr): ν = 3421 (m), 2934 (s), 2861 (m), 2250 (w), 1653 (s), 1611 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0,53 (3H, s, CH_3-18), 1.34 (1H, m, H-15), 1.42 (1H, m, H-7), 1.46 (6H, m, H-3'', H-4'', H-5''), 1.55 (2H, m, H-2''), 1.70 (2H, m, H-14, H-15), 1.87 (3H, s, CH_3-21), 1.88 (1H, td, J = 12.0, J = 3.2, H-16), 2.00 (1H, m, H-7), 2.24 (3H, m, 2x(H-12), H-16), 2.39 (4H, m, H-1, 2x(H-2), H-8), 2.55 (2H, m, H-6), 2.75 (1H, m, H-1), 2.86 (3H, s, N-CH_3), 3.24 (2H, m, H-1''), 3.61 (2H, br, H-6''), 4.32 (1H, d, J = 6.8, H-11), 5.73 (1H, s, H-4), 6.57 (2H, m, H-3', H-5'), 6.97 (2H, m, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.7 (q, C-18), 23.3 (t, C-15), 25.6 (t, C-2''), 25.8 (t, C-1), 26.7 (t, C-3''*) 26.9 (t, C-4''*), 27.4 (t, C-7), 31.1 (t, C-6), 32.7 (t, C-5''), 36.9 (t, C-2), 38.2 (q, N-CH_3), 38.8 (t, C-12**), 38.9 (t, C-16**), 39.1 (d, C-8), 39.5 (d, C-11), 46.8 (s, C-13), 49.8 (d, C-14), 52.9 (t, C-1''), 62.8 (t, C-6''), 80.2 (s, C-17), 82.3 (s, C-19***), 82.5 (s, C-20***), 112.2 (d, C-3', C-5'), 123.6 (d, C-4), 127.6 (d, C-2', C-6'), 129.0 (s, C-10), 131.3 (s, C-1'), 146.8 (s, C-9), 147.3 (s, C-4'), 157.0 (s, C-5), 199.7 (s, C-3) ppm

17β-Hydroxy-11β-{4-[5-(1,3-dioxol-2-yl)-N-methylpentylamino]-phenyl}-17α-(1-propinyl)-estra-4,9-dien-3-one (11)

2 (100 mg, 0.24 mmol) and freshly distilled 6-bromohexanal ethylene glycol acetal[S6,S7,S8] (268 mg, 1.20 mmol) were dissolved in anhydrous DMF (2.0 mL) and stirred under argon in the presence of dry K_2CO_3 (1.4 mg, 1.0 mmol) for 28 h at 60 °C. Precipitated KBr was filtered off and the solvent removed in vacuo; the residue was purified by flash-chromatography (eluent E I) and preparative HPLC (column 1; acetonitrile : H_2O (84:16, vol/vol), flow: 16 mL/min; t_R = 8 min 24 sec).

$C_{36}H_{47}NO_3$ (MW: 557.77)

Yield: 40% yield (colourless lyophilisate)

MS (m/z): 558 (M^+)

TLC: R_f = 0.53 (E I), R_f = 0.77 (E II), R_f = 0.78 (E V), R_f = 0.05 (E VII)

Analytical HPLC: 89.6%, t_R = 6.653 min (tracings: 5.8 %, t_R = 4.569 min; 4.6 %, t_R = 4.035 min)

UV/VIS (MeOH): λ_{max} = 207.5, 263.0, 302.0 nm

IR (KBr): ν = 3442 (m), 2941 (s), 2867 (m), 2241 (w), 1660 (s),1611 (m), 1516 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.51 (3H, s, CH_3-18), 1.32 (2H, m, H-3''), 1.38 (1H, m, H-15), 1.41 (1H, m, H-7), 1.42 (2H, m, H-4''), 1.53 (2H, m, H-2''), 1.62 (2H, m, H-5''), 1.68 (2H, m, H-15, H-14), 1.86 (3H, s, CH_3-21), 1.90 (1H, t, J = 12.4, H-16), 1.98 (1H, m, H-7), 2.20 (1H, m, H-16), 2.24 (2H, m, H-12), 2.32 (1H, m, H-1), 2.37 (2H, m, H-2), 2.42 (1H, m, H-8), 2.53 (2H, m, H-6), 2.72 (1H, m, H-1), 2.84 (3H, s, N-CH_3), 3.22 (2H, m, J = 7.2, H-1''), 3.81 (2H, m, H-1''', H-2'''), 3.91 (2H, m, H-1''', H-2'''), 4.31 (1H, d, J = 6.8, H-11), 4.81 (1H, t, J = 4.8, H-6''), 5.72 (1H, s, H-4), 6.56 (2H, m, H-3', H-5'), 6.95 (2H, m, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.7 (q, C-18), 23.7 (t, C-15), 23.9 (t, C-4''), 25.8 (t, C-1), 26.5 (t, C2''), 27.0 (t, C-3''), 27.3 (t, C-7), 31.1 (t, C-6), 33.8 (t, C-5''), 36.8 (t, C-2), 38.2 (q, N-CH_3), 38.7 (t, C-16*), 38.8 (t, C-12*), 39.1 (d, C-8), 39.5 (d, C-11), 46.8 (s, C-13), 49.8 (d, C-14), 52.8 (t, C-1''), 64.8 (t, C-1''', C-2'''), 80.1 (s, C-17), 82.4 (s, C-19), 82.4 (s, C-20*), 104.4 (q, C-6''), 112.2 (d, C-3', C-5'), 123.6 (d, C-4), 127.5 (d, C-2', C-6'), 129.0 (s, C-10), 131.2 (s, C-1'), 146.9 (s, C-9), 147.3 (s, C-4'), 157.0 (s, C-5), 199,7 (s, C-3) ppm

17β-Hydroxy-11β-[4-(5-formyl-N-methylpentylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (12)

11 (140 mg, 0.25 mmol) was dissolved in 2.85 mL MeOH and 0.23 mL HCl (2 mol/L) were added. The mixture was stirred for 72 h at room temperature (under TLC–monitoring) and thereafter extracted with CH_2Cl_2 and brine (according to ref. S9). The organic layer was washed with $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed in vacuo and the residue purified by preparative HPLC (column 1; acetonitrile : H_2O (84:16, vol/vol), flow: 16 mL/min; / t_R = 7 min 06 sec).

$C_{34}H_{43}NO_3$ (MW: 513.72)

Yield: 53% (yellow lyophilisate)

Calc: C 79.49, H 8.44, N 2.73; Found: C 78.95, H 8.30, N 2.65

MS (m/z): 514 (M^+)

TLC: R_f = 0.63 (E I), R_f = 0.70 (E V)

Analytical HPLC: 94.1 %, t_R = 5.001 min (tracings: 3.5 %, t_R = 4.573 min; 2.4 %, t_R = 3.908 min)

UV/VIS (MeOH): λ_{max} = 208.5, 259.0, 298.5 nm

IR (KBr): ν = 3421 (m), 2937 (s), 2865 (m), 2241 (w), 1721 (m), 1658 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.51 (3H, s, CH_3-18), 1.31 (2H, m, H-3''), 1.38 (1H, m, H-15), 1.41 (1H, m, H-7), 1.52 (2H, m, J = 7.6, H-2''), 1.64 (2H, m, J = 7.6, H-4''), 1.68 (1H, m, H-14), 1.70 (1H, m, H-15), 1.85 (3H, s, CH_3-21), 1.88 (1H, t, H-16), 1.98 (1H, m, H-7), 2.20 (1H, m, H-16), 2.24 (2H, m, H-12), 2.32 (1H, m, H-1), 2.37 (2H, m, H-2), 2.40 (2H, td, J = 7.0, J = 1.6, H-5''), 2.44 (1H, m, H-8), 2.53 (2H, m, H-6), 2.73 (1H, m, H-1), 2.84 (3H, s, N-CH_3), 3.22 (2H, m, J = 8.3, H-1''), 4.30 (1H, d, J = 6.4, H-11), 5.72 (1H, s, H-4), 6.56 (2H, m, H-3', H-5'), 6.95 (2H, m, H-2', H-6'), 9.72 (1H, t, J = 1.6, H-6'') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.7 (q, C-18), 21.9 (t, C-4''), 23.2 (t, C-15), 25.8 (t, C-1), 26.5 (t, C3''*), 26.6 (t, C-2''*), 27.3 (t, C-7), 31.1 (t, C-6), 36.8 (t, C-2), 38.2 (q, N-CH_3), 38.7 (t, C-16**), 38.8 (t, C-12**), 39.1 (d, C-8), 39.4 (d, C-11), 43.8 (t, C-5''), 46.8 (s, C-13), 49.8 (d, C-14), 52.7 (t, C-1''), 80.1 (s, C-17), 82.3 (s, C-19), 82.3 (s, C-20), 112.2 (d, C-3', C-5'), 122.6 (d, C-4), 127.5 (d, C-2', C-6'), 128.9 (s, C-10), 131.6 (s, C-1'), 146.9 (s, C-9), 147.2 (s, C-4'), 157.0 (s, C-5), 199,7 (s, C-3), 202.5(d, C-6'') ppm

17β-Hydroxy-11β-[4-(2-carboxy-N-methylethylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**13**)

13 was synthesized according to general procedure II reacting **2** (150 mg, 0.361 mmol) with 3-bromopropionic acid (1.80 mmol); the product was purified by flash-chromatography with EtOAc and MeOH and preparative HPLC (column 2; acetonitrile : H_2O (60:16, vol/vol), flow: 23 mL/min; t_R = 4 min 42 sec).

$C_{31}H_{37}NO_4$ (MW: 487.63)

Yield: 55% (yellow lyophilisate)

MS (m/z): 510 (M^+ + Na)

Analytical HPLC: 95.6 %, t_R = 4.161 min (tracing: 4.4%, t_R = 3.877 min)

TLC: R_f = 0.26 (E I), R_f = 0.20 (E II), R_f = 0.45 (E III)

UV/VIS (MeOH): λ_{max} = 263.5, 303.0 nm

IR (KBr): ν = 3424 (m), 2938 (s), 2939 (s), 2870 (m) 2242 (w), 1728 (s), 1656 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.53 (3H, s, CH_3-18), 1.35 (1H, m, H-15), 1.46 (1H, m, H-7), 1.72 (1H, m, H-14), 1.74 (1H, m, H-15), 1.89 (3H, s, CH_3-21), 1.94 (1H, t, H-16), 2.02 (1H, m, H-7), 2.23 (1H, m, H-16), 2.25 (1H, m, H-12), 2.32 (1H, m, H-1), 2.35 (1H, m, H-12), 2.37 (1H, m, H-2), 2.44 (1H, m, H-2), 2.45 (1H, m, H-8), 2.60 (4H, m, 2x(H-6),2x (H-2'')), 2.75 (1H, m, H-1), 2.93 (3H, s, N-CH_3), 3.63 (2H, H-1''), 4.36 (1H, d, J = 6.6, H-11), 5.78 (1H, s, H-4), 6.81 (2H, d, J = 7.2, H-3', H-5'), 7.06 (2H, d, J = 7.2, H-2', H-6') ppm

^{13}C-NMR: ($CDCl_3$) δ = 3.8 (q, C-21), 13.8 (q, C-18), 23.3 (t, C-15), 25.8 (t, C-1), 27.3 (t, C-7), 31.1 (t, C-6), 31.2 (t, C-2''), 36.8 (t, C-2), 39.5 (q, N-CH_3), 38.9 (t, C-12), 38.9 (t, C-16), 39.2 (d, C-8), 39.7 (d, C-11), 46.9 (s, C-13), 49.6 (t, C-1''), 49.8 (d, C-14), 80.2 (s, C-17), 82.3 (s, C-19), 82.5 (s, C-20), 114.6 (d, C-3', C-5'), 122.7 (d, C-4), 128.0 (d, C-2', C-6'), 129.3 (s, C-10), 135.1 (s, C-1'), 145.6 (s, C-4'), 146.7 (s, C-9), 157.3 (s, C-5), 175.9 (s, C-3''), 200.0 (s, C-3) ppm

17β-Hydroxy-11β-[4-(5-carboxy-N-methylpentylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (14)

14 was synthesized according to general procedure II reacting **2** (150 mg, 0.361 mmol) with 6-bromohexanoic acid (1.80 mmol); the product was purified by flash-chromatography with EtOAc and MeOH and preparative HPLC (column 2; acetonitrile : H_2O (56:44, vol/vol), flow: 23 mL/min; t_R = 8 min 30 sec).

$C_{34}H_{43}NO_4$ (MW: 529.71)

Yield: 54% (yellow lyophilisate)

Calc: C 77.09, H 8.18, N 2.64; Found + ¼ H2O: C 76.40, H 8.22, N 2.63

MS (m/z): 530 (M+)

TLC: R_f = 0.03 (EI), R_f = 0.27 (EII), R_f = 0.25 (EV), R_f = 0.21 (EVI), R_f = 0.02 (EVII), R_f = 0.55 (EIX)

Analytical HPLC: 95.9 %, t_R = 4.668 min (tracings: 2.9%, t_R = 4.208 min; 1.2 %, t_R = 3.048 min)

UV/VIS (CH_2Cl_2): λ_{max} = 269.5, 302.0 nm

IR (KBr): ν = 3420 (m), 2938 (s), 2867 (m), 2242 (w), 1730 (s), 1659 (s) 1612 (m) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.55 (3H, s, CH_3-18), 1.36 (1H, m, H-15), 1.38 (2H, m, H-3''), 1.46 (1H, m, H-7), 1.56 (2H, m, H-2''), 1.68 (2H, m, H-4''), 1.72 (1H, m, H-14), 1.73 (1H, m, H-15), 1.89 (3H, s, CH_3-21), 1.94 (1H, t, H-16), 2.02 (1H, m, H-7), 2.22 (1H, m, H-16), 2.28 (1H, m, H-12), 2.28 (2H, t, J = 7.0, H-5''), 2.32 (1H, m, H-1), 2.33 (1H, m, H-12), 2.34 (1H, m, H-2), 2.42 (1H, m, H-2), 2.46 (1H, m, H-8), 2.57 (2H, m, H-6), 2.76 (1H, m, H-1), 2.88 (3H, s, N-CH_3), 3.26 (2H, t, J = 8.0, H-1''), 4.30 (1H, d, J = 6.8, H-11), 5.76 (1H, s, H-4), 6.59 (2H, m, H-3', H-5'), 6.98 (2H, m, H-2', H-6') ppm

^{13}C-NMR: ($CDCl_3$) δ = 3.8 (q, C-21), 13.7 (q, C-18), 23.3 (t, C-15), 24.7 (t, C-4''), 25.8 (t, C-1), 26.4 (t, C2''), 26.7 (t, C-3''), 27.3 (t, C-7), 31.1 (t, C-6), 34.2 (t, C-5''), 36.9 (t, C-2), 38.2 (q, N-CH_3), 38.7 (t, C-16*), 38.8 (t, C-12*), 39.1 (d, C-8), 39.5 (d, C-11), 46.8 (s, C-13), 49.8 (d, C-14), 52.7 (t, C-1''), 80.2 (s, C-17), 82.4 (s, C-19), 82.4 (s, C-20), 112.2 (d, C-3', C-5'), 122.6 (d, C-4), 127.5 (d, C-2', C-6'), 129.0 (s, C-10), 131.1 (s, C-1'), 146.9 (s, C-9), 147.2 (s, C-4'), 157.0 (s, C-5), 173.6 (s, C-6''), 199.6 (s, C-3) ppm

17β-Hydroxy-11β-[4-(7-carboxy-N-methylheptylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (15)

15 was synthesized according to general procedure II reacting **2** (150 mg, 0.361 mmol) with 8-bromooctanoic acid (1.80 mmol); the product was purified by flash-chromatography with EtOAc and MeOH and preparative HPLC (column 2; acetonitrile : H_2O (54:46, vol/vol), flow: 23 mL/min; t_R = 15 min 30 sec).

$C_{36}H_{47}O_4$ (MW: 543.76)

Yield: 30% (yellow lyophilisate)

TLC: R_f = 0.85 (E I), R_f = 0.75 (E II), R_f = 0.89 (E V)

Analytical HPLC: 95.8 %, t_R = 5.629 min (tracings: 1.8 %, t_R = 4.738 min; t_R = 2.4 %, t_R = 4.117 min)

UV/VIS (MeOH): λ_{max} = 289.5, 304.0 nm

IR (KBr): ν = 3424 (m), 2934 (s), 2870 (m), 2242 (w), 1720 (s), 1656 (s) 1647 (m) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.55 (3H, s, CH_3-18), 1.33 (6H, m, H-3'', H-4'', H-5''), 1.34 (1H, m, H-15), 1.46 (1H, m, H-7), 1.60 (2H, m, H-2''), 1.67 (2H, m, H-6''), 1.70 (1H, m, H-14), 1.72 (1H, m, H-15), 1.89 (3H, s, CH_3-21), 1.93 (1H, m, H-16), 2.01 (1H, m, H-7), 2.21 (1H, m, H-16), 2.24 (1H, m, H-12), 2.29 (2H, m, H-7''), 2.30 (1H, m, H-1), 2.33 (1H, m, H-12), 2.36 (1H, m, H-2), 2.43 (1H, m, H-8), 2.44 (1H, m, H-2), 2.57 (2H, m, H-6), 2.74 (1H, m, H-1), 2.93 (3H, s, N-CH_3), 3.49 (2H, m, H-1''), 4.30 (1H, d, H-11), 5.77 (1H, s, H-4), 6.81 (2H, m, H-3', H-5'), 7.06 (2H, m, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.7 (q, C-18), 23.3 (t, C-15), 24.0 (t C-6''), 25.8 (t, C-1), 26.4 (t, C2''), 27.3 (t, C-7), 28.0 (t, C-5''), 28.1 (t, C-3''), 28.1 (t, C-4''), 31.1 (t, C-6), 33.2 (t, C-7''), 36.8 (t, C-2), 38.2 (q, N-CH_3), 38.8 (t, C-12), 38.8 (t, C-16), 39.1 (d, C-8), 39.6 (d, C-11), 46.8 (s, C-13), 49.8 (d, C-14), 52.5 (t, C-1''), 80.3 (s, C-17), 82.3 (s, C-19), 82.5 (s, C-20), 112.4 (d, C-3', C-5'), 122.6 (d, C-4), 127.5 (d, C-2', C-6'), 129.0 (s, C-10), 131.1 (s, C-1'), 147.1 (s, C-9), 147.3 (s, C-4'), 157.3 (s, C-5), 176.9 (s, C-8''), 200.0 (s, C-3) ppm

17β-Hydroxy-11β-[4-(10-carboxy-N-methyldecylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**16**)

16 was synthesized according to general procedure II reacting **2** (150 mg, 0.361 mmol) with 11-bromoundecanoic acid (1.80 mmol); the product was purified by flash-chromatography with EtOAc and MeOH and preparative HPLC (column 2; acetonitrile : H_2O (84:16, vol/vol), flow: 23 mL/min; t_R = 10 min 50 sec).

$C_{39}H_{53}O_4$ (MW: 585.84)

Yield: 33% (yellow lyophilisate)

TLC:, R_f = 0.94 (E I), R_f = 0.80 (E II), R_f = 0.90 (E III)

Analytical HPLC: t_R = 98.7 %, 8.294 min (tracing: 1.3 %, t_R = 6.371 min)

UV/VIS (MeOH): λ_{max} = 289.0, 304.0 nm

IR (KBr): ν = 3424 (m), 2931 (s), 2855 (m), 2242 (w), 1712 (s), 1659 (s), 1647 (m) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.56 (3H, s, CH_3-18), 1.27 (10H, m, H-3'', H-4'', H-5'', H-6'', H-7''), 1.32 (m, 2H, H-8''), 1.36 (1H, m, H-15), 1.46 (1H, m, H-7), 1.54 (2H, m, H-2''), 1.62 (2H, m, H-9''), 1.70 (1H, m, H-14), 1.73 (1H, m, H-15), 1.89 (3H, s, CH_3-21), 1.93 (1H, m, H-16), 2.01 (1H, m, H-7), 2.24 (1H, m, H-16), 2.27 (1H, m, H-12), 2.32 (1H, m, H-12), 2.33 (2H, m, H-10''), 2.36 (2H, m, H-1, H-2), 2.44 (1H, m, H-2), 2.45 (1H, m, H-8), 2.58 (2H, m, H-6), 2.76 (1H, m, H-1), 2.88 (3H, s, N-CH_3), 3.23 (2H, m, H-1''), 4.35 (1H, d, H-11), 5.76 (1H, s, H-4), 6.60 (2H, m, H-3', H-5'), 6.98 (2H, m, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.8 (q, C-18), 23.3 (t, C-15), 24.6 (t C-9''), 25.8 (t, C-1), 26.6 (t, C2''), 27.3 (t, C-7), 28.8 (t, C-8''), 29.3 (t, C-3''), 29.3 (t, C-4''), 29.3 (t, C-5''), 29.3 (t, C-6''), 29.3 (t, C-7''), 31.1 (t, C-6), 33.7 (t, C-10''), 36.8 (t, C-2), 38.1 (q, N-CH_3), 38.8 (t, C-12), 38.9 (t, C-16), 39.1 (d, C-8), 39.6 (d, C-11), 46.8 (s, C-13), 49.8 (d, C-14), 52.9 (t, C-1''), 80.3 (s, C-17), 82.3 (s, C-19), 82.6 (s, C-20), 112.4 (d, C-3', C-5'), 122.7 (d, C-4), 127.5 (d, C-2', C-6'), 129.0 (s, C-10), 131.1 (s, C-1'), 146.9 (s, C-9), 147.4 (s, C-4'), 157.2 (s, C-5), 177.5 (s, C-11''), 199.9 (s, C-3) ppm

17β-Hydroxy-11β-[4-(2-methoxycarbonyl-N-methylethylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**17**)

A mixture of **2** (250 mg, 0.60 mmol), methyl 3-bromopropionate (2.3 g, 13.74 mmol) and dry K_2CO_3 (83.2 mg, 0.60 mmol) was stirred in the absence of moisture for 42 h at 50° C. The product was purified by flash-chromatography (eluent E I) and preparative HPLC (column 2; acetonitrile : H_2O (84:16, vol/vol), flow: 23 mL/min; t_R = 3 min 40 sec).

$C_{32}H_{39}NO_4$ (MW: 501.66)

Yield: 58% (yellow lyophilisate)

MS: +MS: 502 $(M+1)^+$, -MS: 501 $(M-1)^-$

TLC: R_f = 0.67 (E I), R_f = 0.98 (E IV)

Analytical HPLC: 96.5 %, t_R = 5.290 min (tracings: 1.9 %, t_R = 4.316 min; 1.6 %, t_R = 4.639 min)

UV/VIS (CH_2Cl_2): λ_{max} = 265.0, 299.5 nm

IR (KBr): ν = 3436 (m), 2946 (s), 2870 (m), 2241 (w), 1735 (s), 1660 (s), 1611 (s), 1516 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.54 (3H, s, CH_3-18), 1.34 (1H, dt, H-15), 1.46 (1H, m, H-7), 1.71 (1H, m, H-14), 1.73 (1H, m, H-15), 1.88 (3H, s, CH_3-21), 1.94 (1H, t, H-16), 2.01 (1H, m, H-7), 2.21 (1H, m, H-12), 2.26 (1H, m, H-16), 2.33 (3H, m, H-1, H-2, H-12), 2.44 (1H, m, H-2), 2.46 (1H, m, H-8), 2.56 (2H, m, H-2''), 2.57 (2H, m, H-6), 2.76 (1H, m, H-1), 2.90 (3H, s, N-CH_3), 3.63 (2H, m, H-1''), 3.65 (3H, s, O-CH_3), 4.34 (1H, d, J = 5.8, H-11), 5.76 (1H, s, H-4), 6.66 (2H, d, H-3', H-5'), 7.02 (2H, d, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.8 (q, C-18), 23.3 (t, C-15), 25.8 (t, C-1), 27.4 (t, C-7), 31.1 (t, C-6), 31.5 (t, C-2''), 36.9 (t, C-2), 38.2 (q, N-CH_3), 38.9 (t, C-12), 38.9 (t, C-16), 39.1 (d, C-8), 39.6 (d, C-11), 46.7 (s, C-13), 48.8 (t, C-1''), 49.8 (d, C-14), 51.7 (q, O-CH_3), 80.1 (s, C-17), 82.4 (s, C-19*), 82.4 (s, C-20*), 112.7 (d, C-3', C-5'), 122.7 (d, C-4), 127.8 (d, C-2', C-6'), 129.1 (s, C-10), 132.3 (s, C-1'), 146.7 (s, C-4'), 146.7 (s, C-9), 157.0 (s, C-5), 172.7 (s, C-3''), 199.6 (s, C-3) ppm

17β-Hydroxy-11β-[4-(5-ethoxycarbonyl-N-methylpentylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**18**)

18 was synthesized according to general procedure III starting from **14** (20 mg, 0.038 mmol).

$C_{32}H_{39}NO$ (MW: 501.66)

Yield: 78% (yellow lyophilisate)

Calc: C 77.31, H 8.34, N 2.58; Found: C 77.22, H 8.37, N 2.27

MS(m/z): 524 (M^+ + Na)

TLC: R_f = 0.63 (E I), R_f = 0.85 (E II), R_f = 0.72 (E V), R_f = 0.81 (E VI), R_f = 0.05 (E VII)

Analytical HPLC: 93.5 %, t_R = 7.060 min (tracings: 3.7%, t_R = 3.957 min; 2.8 %; t_R = 5.706 min)

UV/VIS (MeOH): λ_{max} = 263.5, 304.5 nm

IR (KBr): ν = 3385 (m), 2937 (s), 2866 (m), 2242 (w), 1731 (s), 1639 (s), 1611 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.55 (3H, s, CH_3-18), 1.36 (1H, m, H-15), 1.38 (2H, m, H-3''), 1.46 (1H, m, H-7), 1.56 (2H, m, H-2''), 1.68 (2H, m, H-4''), 1.72 (1H, m, H-14), 1.73 (1H, m, H-15), 1.89 (3H, s, CH_3-21), 1.94 (1H, t, H-16), 2.02 (1H, m, H-7), 2.22 (1H, m, H-16), 2.28 (3H, m, 2x (H-12), J = 7.0, H-5''), 2.32 (1H, m, H-1), 2.40 (2H, m, H-2), 2.46 (1H, m, H-8), 2.57 (2H, m, H-6), 2.73 (1H, m, H-1), 2.88 (3H, s, N-CH_3), 3.26 (1H, t, J = 8.0, H-1''), 3.67 (3H, s, OCH_3), 3.63 (1H, m, H-1''), 4.34 (1H, d, J = 6.8, H-11), 5.76 (1H, s, H-4), 6.59 (2H, m, H-3', H-5'), 6.68 (2H, m, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.7 (q, C-18), 23.3 (t, C-15), 24.7 (t, C-4''), 25.8 (t, C-1), 26.4 (t, C-2''), 26.7 (t, C-3''), 27.3 (t, C-7), 31.1 (t, C-6), 34.2 (t, C-5''), 36.9 (t, C-2), 38.2 (q, N-CH_3), 38.7 (t, C-16*), 38.8 (t, C-12*), 39.1 (d, C-8), 39.5 (d, C-11), 46.8 (s, C-13), 49.8 (d, C-14), 51.7 (q, OCH_3), 52.7 (t, C-1''), 80.1 (s, C-17), 82.4 (s, C-19*), 82.4 (s, C-20*), 112.2 (d, C-3', C-5'), 122.6 (d, C-4), 127.5 (d, C-2', C-6'), 129.0 (s, C-10), 131.3 (s, C-1'), 147.2 (s, C-4'), 146.9 (s, C-9), 157.0 (s, C-5), 173.6 (s, C-6''), 199.6 (s, C-3) ppm

17β-Hydroxy-11β-[4-(7-methoxycarbonyl-N-methylheptylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**19**)

19 was synthesized according to general procedure III starting from **15** (20 mg, 0.037 mmol).

$C_{37}H_{49}O_4$ (MW: 557.79)

Yield: 84% (yellow lyophilisate)

TLC: R_f = 0.74 (E II), R_f = 0.18 (E VII)

Analytical HPLC: 97.8 %, t_R = 8.856 min (tracings: 1 %, t_R = 6.769 min; 1.2 %, t_R = 4.847 min)

UV/VIS (CH_2Cl_2): λ_{max} = 265.5, 300.5 nm

IR (KBr): ν = 3423 (m), 2920 (s), 2851 (m), 2242 (w), 1737 (s), 1661 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.56 (3H, s, CH_3-18), 1.30 (6H, m, H-3'', H-4'', H-5''), 1.35 (1H, m, H-15), 1.46 (1H, m, H-7), 1.55 (2H, m, H-2''), 1.62 (2H, m, H-6''), 1.72 (1H, m, H-14), 1.73 (1H, m, H-15), 1.90 (3H, s, CH_3-21), 1.94 (1H, t, H-16), 2.02 (1H, m, H-7), 2.24 (1H, m, H-16), 2.27 (1H, m, H-12), 2.30 (2H, m, H-7''), 2.32 (1H, m, H-12), 2.36 (1H, m, H-1), 2.38 (1H, m, H-2), 2.45 (1H, m, H-2), 2.47 (1H, m, H-8), 2.58 (2H, m, H-6), 2.78 (1H, m, H-1), 2.89 (3H, s, N-CH_3), 3.25 (2H, m, H-1''), 3.67 (3H, s, OCH_3), 4.35 (1H, d, H-11), 5.75 (1H, s, H-4), 6.60 (2H, m, H-3', H-5'), 6.99 (2H, m, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 4.0 (q, C-21), 13.8 (q, C-18), 23.4 (t, C-15), 25.0 (t, C-6''), 26.0 (t, C-1), 26.9 (t, C-2''), 27.6 (t, C-7), 29,7 (t, C-3'', C-4'', C-5''), 31.2 (t, C-6), 34.1 (t, C-7''), 36.9 (t, C-2), 38.4 (q, N-CH_3), 38.9 (t, C-12), 38.9 (t, C-16), 39.2 (d, C-8), 39.6 (d, C-11), 46.9 (s, C-13), 50.1 (d, C-14), 51,7 (q, O-CH_3), 53.1 (t, C-1''), 80.3 (s, C-17), 82.3 (s, C-19), 82.5 (s, C-20), 112.2 (d, C-3', C-5'), 122.9 (d, C-4), 127.7 (d, C-2', C-6'), 129.0 (s, C-10), 131.2 (s, C-1'), 147.0 (s, C-9), 147.4 (s, C-4'), 157.2 (s, C-5), 174.3 (s, C-8''), 199.7 (s, C-3) ppm

17β-Hydroxy-11β-[4-(10-methoxycarbonyl-N-methyldecylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**20**)

20 was synthesized according to general procedure III starting from **16** (20 mg, 0.034 mmol).

$C_{40}H_{55}O_4$ (MW: 599.87)

Yield: 79% (yellow lyophilisate)

TLC: R_f = 0.76 (E II), R_f = 0.19 (E VII)

Analytical HPLC: 98.2 %, t_R = 15.424 min (tracing: 1.8 %, t_R = 10.609 min)

UV/VIS (CH_2Cl_2): λ_{max} = 265.0, 302.5 nm

IR (KBr): ν = 3421 (m), 2923 (s), 2852 (m), 2242 (w),1733 (s), 1661 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.56 (3H, s, CH_3-18), 1.30 (12H, m, H-3'', H-4'', H-5'', H-6'', H-7'', H-8 ''), 1.35 (1H, m, H-15), 1.46 (1H, m, H-7), 1.54 (2H, m, H-2''), 1.61 (2H, m, H-9''), 1.73 (2H, m, H-14, H-15), 1.90 (3H, s, CH_3-21), 1.94 (1H, t, H-16), 2.01 (1H, m, H-7), 2.24 (1H, m, H-16), 2.27 (1H, m, H-12), 2.31 (2H, m, H-10''), 2.32 (1H, m, H-12), 2.35 (1H, m, H-1), 2.38 (1H, m, H-2), 2.45 (2H, m, H-2, H-8), 2.58 (2H, m, H-6), 2.76 (1H, m, H-1), 2.88 (3H, s, N-CH_3), 3.24 (2H, m, H-1''), 3.67 (3H, s, OCH_3), 4.35 (1H, d, H-11), 5.75 (1H, s, H-4), 6.60 (2H, m, H-3', H-5'), 6.99 (2H, m, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.7 (q, C-18), 23.3 (t, C-15), 25.0 (t, C-9''), 25.9 (t, C-1), 26.8 (t, C-2''), 27.4 (t, C-7), 29.1 – 29.5 (t, C-3'', C-4'', C-5'', C-6'', C-7'', C-8''), 31.1 (t, C-6), 34.1 (t, C-10''), 36.9 (t, C-2), 38.8 (q, N-CH_3), 38.8 (t, C-12), 38.8 (t, C-16), 39.1 (d, C-8), 39.6 (d, C-11), 46.9 (s, C-13), 49.9 (d, C-14), 51,8 (q, O-CH_3), 53.0 (t, C-1''), 80.2 (s, C-17), 82.4 (s, C-19), 82.5 (s, C-20), 112.2 (d, C-3', C-5'), 122.9 (d, C-4), 127.6 (d, C-2', C-6'), 129.0 (s, C-10), 131.2 (s, C-1'), 147.0 (s, C-9), 147.4 (s, C-4'), 157.0 (s, C-5), 174.3 (s, C-11''), 199.7 (s, C-3) ppm

17β-Hydroxy-11β-[4-(5-carbamoyl-N-methylpentylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**21**)

To a cooled (0 °C) mixture of **14** (30,2 mg, 0.057 mmol), triethylamine (5.8 mg, 0.057 mmol) and 0.5 mL dry THF isobutyl chloroformate (7.9 mg, 0.057 mmol) was added and stirred under argon for 40 min. (according to ref. S10). Subsequently, ammonia gas was passed through this solution for 20 min. The reaction mixture was purified by column chromatography (EtOAc). The solvent was removed and the residue purified by preparative HPLC (column 1; acetonitrile : H_2O (67:33, vol/vol), flow: 16 mL/min; t_R = 8 min 24 sec).

$C_{34}H_{44}N_2O_3$ (MW: 528.73)

Yield: 32% (yellow lyophilisate)

TLC: R_f = 0.13 (E II), R_f = 0.69 (E IX)

Analytical HPLC: 96.7 %, t_R = 4.403 min (tracing: 3.3%, t_R = 4.895 min)

UV/VIS (CH_2Cl_2): λ_{max} = 269.0, 300.5 nm

IR (KBr): ν = 3431 (m), 2934 (s), 2867 (m), 2242 (w), 1662 (s), 1640 (s), 1620 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.55 (3H, s, CH_3-18), 1.36 (1H, m, H-15), 1.38 (2H, m, H-3''), 1.46 (1H, m, H-7), 1.56 (2H, m, H-2''), 1.68 (2H, m, H-4''), 1.72 (1H, m, H-14), 1.73 (1H, m, H-15), 1.89 (3H, s, CH_3-21), 1.94 (1H, m, H-16), 2.02 (1H, m, H-7), 2.22 (1H, m, H-16), 2.28 (1H, m, H-12), 2.28 (2H, m, H-5''), 2.32 (1H, m, H-1), 2.33 (1H, m, H-12), 2.40 (2H, m, H-2), 2.46 (1H, m, H-8), 2.57 (2H, m, H-6), 2.76 (1H, m, H-1), 2.88 (3H, s, N-CH_3), 3.26 (2H, m, H-1''), 4.34 (1H, d, H-11), 5.75 (1H, s, H-4), 6.59 (2H, d, H-3', H-5'), 6.98 (2H, d, H-2', H-6') ppm

17β-Hydroxy-11β-[4-(1-methyl-7-oxo-1,8-diaza-dodecyl)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**22**)

To a cooled (0 °C) mixture of **14** (30.2 mg, 0.057 mmol) and 0.5 mL dry THF isobutyl chloroformate (7.9 mg, 0.057 mmol) was added and stirred under argon for 40 min. After adding butylamine (98 %) (4.1 mg, 0.057 mmol) the mixture was stirred for additional 10 min, diluted with CH_2Cl_2 and washed with water. The organic layer was dried over Na_2SO_4 and purified by preparative HPLC (column 1; acetonitrile : H_2O (67:33 vol/vol), flow: 16 mL/min; t_R = 9 min 50 sec).

$C_{38}H_{52}N_2O_3$ (MW: 584.84)

Yield: 38% (yellow lyophilisate)

TLC: R_f = 0.37 (E VII)

UV/VIS (CH_2Cl_2): λ_{max} = 300.0 nm

IR (KBr): ν = 3387 (m, (br)), 2934 (m), 2868 (m), 2242 (w), 1649 (s), 1612 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.55 (3H, s, CH_3-18), 0.92 (3H, t, NH-$CH_2CH_2CH_2CH_3$), 1.34 (4H, m, H-3'', NH-$CH_2CH_2CH_2$), 1.35 (1H, m, H-15), 1.46 (1H, m, H-7), 1.47 (2H, m, NH-CH_2CH_2), 1.58 (2H, m, H-2''), 1.67 (2H, m, H-4''), 1.72 (1H, m, H-14), 1.73 (1H, m, H-15), 1.89 (3H, s, CH_3-21), 1.94 (1H, t, H-16), 2.02 (1H, m, H-7), 2.19 (2H, m, H-5''), 2.22 (1H, m, H-16), 2.28 (1H, m, H-12), 2.32 (1H, m, H-1), 2.33 (1H, m, H-12), 2.38 (1H, m, H-2), 2.45 (1H, m, H-2), 2.46 (1H, m, H-8), 2.58 (2H, m, H-6), 2.76 (1H, m, H-1), 2.88 (3H, s, N-CH_3), 3.24 (2H, m, NH-CH_2), 3.29 (2H, m, H-1''), 4.34 (1H, d, H-11), 5.75 (1H, s, H-4), 6.60 (2H, d, H-3', H-5'), 6.99 (2H, d, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.9 (q, C-21), 13.8 (q, C-18), 13.9 (q, NH-$CH_2CH_2CH_2CH_3$), 20.1 (t, NH-$CH_2CH_2CH_2$), 23.3 (t, C-15), 25.7 (t, C-4''), 25.8 (t, C-1), 26.5 (t, C-2''), 27.0 (t, C-3''), 27.5 (t, C-7), 31.2 (t, C-6), 31.8 (t, NH-CH_2CH_2), 36.8 (t, C-5''), 36.9 (t, C-2), 38.2 (q, N-CH_3), 38.8 (t, C-12), 38.9 (t, C-16), 39.1 (d, C-8), 39.3 (t, NH-CH_2), 39.6 (d, C-11), 46.9 (s, C-13), 50.0 (d, C-14), 52.8 (t, C-1''), 80.2 (s, C-17), 82.3 (s, C-19), 82.5 (s, C-20), 112.3 (d, C-3', C-5'), 122.9 (d, C-4), 127.6 (d, C-2', C-6'), 129.0 (s, C-10), 131.2 (s, C-1'), 147.0 (s, C-9), 147.4 (s, C-4'), 157.1 (s, C-5), 172.7 (s, C-6''), 199.8 (s, C-3) ppm

17β-Hydroxy-11β-[4-(1-oxo-N-methylpentylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**23**)

2 (67 mg, 0.16 mmol) and hexanoyl chloride (130.6 mg, 0.97 mmol) were dissolved in 1.0 mL anhydrous pyridine and stirred under argon for 20 h at 40 °C. The solvent was removed in vacuo and the residue purified by flash chromatography (eluent E II) and preparative HPLC (column 2; acetonitrile : H_2O (56:44, vol/vol), flow: 16 mL/min; t_R = 9 min 50 sec).

$C_{34}H_{43}NO_3$ (MW: 513.72)

Yield: 48% (colourless lyophilisate)

TLC: R_f = 0.44 (E I), R_f = 0.50 (E VII)

Analytical HPLC: 98.8 %, t_R = 5.439 min (tracing: 1.2 %, t_R = 5.020 min)

UV/VIS (MeOH): λ_{max} = 206.5, 301.5 nm

IR (KBr): ν = 3423 (m), 2950 (m), 2869 (m), 2241 (w), 1659 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.50 (3H, s, CH_3-18), 0.80 (3H, m, H-6''), 1.13 (2H, m, H-4''), 1.18 (2H, m, H-5''), 1.36 (1H, m, H-15), 1.50 (1H, m, H-7), 1.54 (2H, m, H-3''), 1.74 (1H, m, H-14), 1.76 (1H, m, H-15), 1.90 (3H, s, CH_3-21), 1.96 (1H, m, H-16), 2.03 (2H, m, H-2''), 2.05 (1H, m, H-7), 2.25 (1H, m, H-16), 2.31 (1H, m, H-12), 2.33 (1H, m, H-1), 2.39 (1H, m, H-2), 2.42 (1H, m, H-12), 2.48 (1H, m, H-2), 2.49 (1H, m, H-8), 2.61 (2H, m, H-6), 2.81 (1H, m, H-1), 3.24 (3H, s, N-CH_3), 4.46 (1H, d, H-11), 5.79 (1H, s, H-4), 7.14 (2H, d, H-3', H-5'), 7.23 (2H, d, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.9 (q, C-21), 13.9 (q, C-18), 13.9 (q, C-6''), 22.8 (t, C-5''), 23.5 (t, C-15), 25.2 (t, C-3''), 26.0 (t, C-1), 27.4 (t, C-7), 31.1 (t, C-6), 31.5 (t, C-4''), 34.0 (t, C-2''), 36.8 (t, C-2), 37.3 (q, N-CH_3), 39.0 (t, C-16), 39.1 (t, C-12), 39.1 (d, C-8), 40.1 (d, C-11), 46.9 (s, C-13), 49.8 (d, C-14), 80.0 (s, C-17), 82.1 (s, C-19), 82.5 (s, C-20), 123.3 (d, C-4), 127.3 (d, C-3', C-5'), 128.5 (d, C-2', C-6'), 129.8 (s, C-10), 143.9 (s, C-1'), 142.0 (s, C-4'), 145.1 (s, C-9), 156.4 (s, C-5), 173.5 (s, C-1''), 199.3 (s, C-3) ppm

17β-Hydroxy-11β-[4-(1-oxo-4-carboxy-N-methylbutylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (24)

2 (100 mg, 0.24 mmol) and glutaric anhydride (41.2 mg, 0.36 mmol) were dissolved in 1.5 mL anhydrous pyridine and stirred under argon for 12 h at 70 °C. The solvent was removed in vacuo and the residue purified by flash chromatography (eluent E II) and preparative HPLC (column 2; acetonitrile : H_2O (60:40, vol/vol), flow: 23 mL/min; t_R = 3 min 04 sec).

$C_{33}H_{38}NO_5$ (MW: 529.68)

Yield: 35 % (light yellow lyophilisate)

TLC: R_f = 0.04 (E I), R_f = 0.13 (E IV)

Analytical HPLC: 98.6 %, t_R = 3.934 min (tracing: 1.4 %, t_R = 3.484 min)

UV/VIS (CH_2Cl_2): λ_{max} = 233.0, 300.5 nm

IR (KBr): ν = 3424 (m), 2944 (m), 2872 (m), 2242 (w), 1728 (s), 1640 (s), 1600 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.56 (3H, s, CH_3-18), 1.36 (1H, m, H-15), 1.46 (1H, m, H-7), 1.48 (2H, m, H-3''), 1.72 (1H, m, H-14), 1.73 (1H, m, H-15), 1.89 (3H, s, CH_3-21), 1.94 (1H, t, H-16), 1.96 (2H, m, H-4''), 2.02 (1H, m, H-7), 2.20 (2H, t, H-2''), 2.22 (1H, m, H-16), 2.28 (1H, m, H-12), 2.32 (1H, m, H-1), 2.35 (1H, m, H-12), 2.40 (1H, m, H-2), 2.44 (1H, m, H-2), 2.46 (1H, m, H-8), 2.57 (2H, m, H-6), 2.73 (1H, m, H-1), 3.23 (3H, s, N-CH_3), 4.42 (1H, d, J = 6.8, H-11), 5.76 (1H, s, H-4), 7.07 (2H, d, H-3', H-5'), 7.23 (2H, d, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.7 (q, C-18), 20.5 (t, C-3''), 23.3 (t, C-15), 25.8 (t, C-1), 27.3 (t, C-7), 31.1 (t, C-6), 32.8 (t, C-4''*), 33.1 (t, C-2''*), 36.9 (t, C-2), 37.3 (q, N-CH_3), 38.3 (t, C-16**), 38.7 (t, C-12*), 39.1 (d, C-8), 39.5 (d, C-11), 46.8 (s, C-13), 49.8 (d, C-14), 80.1 (s, C-17), 82.4 (s, C-19), 82.4 (s, C-20), 122.6 (d, C-4), 112.2 (d, C-3', C-5'), 127.5 (d, C-2', C-6'), 129.0 (s, C-10), 141.4 (s, C-4'), 145.3 (s, C-1'), 146.9 (s, C-9), 157.0 (s, C-5), 170.4 (s, C-1''), 172.6 (s, C-5''), 200.3 (s, C-3) ppm

17β-Hydroxy-11β-[4-(1-oxo-5-carboxy-N-methylpentylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**25**)

25 was synthesized according to the procedure described for compound **24** reacting **2** (100 mg, 0.24 mmol) with adipic acid anhydride (46.3 mg, 0.36 mmol); the product was purified by flash chromatography (eluent E II) and preparative HPLC (column 2; acetonitrile : H_2O (67:33, vol/vol), flow: 23 mL/min; t_R = 2 min 40 sec).

$C_{34}H_{40}NO_5$ (MW: 542.69)

Yield: 26 % (yellow lyophilisate)

TLC: R_f = 0.05 (E I), R_f = 0.18 (E IV)

Analytical HPLC: 95.3 %, t_R = 4.107 min (tracings: 2.1 %, t_R = 3.514 min; 2.6 %, t_R = 3.767 min)

UV/VIS (CH_2Cl_2): λ_{max} = 236.0, 297.5 nm

IR (KBr): ν = 3424 (m), 2943 (m), 2870 (m), 2241 (w), 1726 (s), 1639 (s), 1600 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.51 (3H, s, CH_3-18), 1.36 (1H, m, H-15), 1.38 (2H, m, H-4''), 1.46 (1H, m, H-7), 1.50 (2H, m, H-3''), 1.72 (1H, m, H-14), 1.73 (1H, m, H-15), 1.90 (3H, s, CH_3-21), 1.94 (1H, t, H-16), 1.98 (2H, m, H-5''), 2.02 (1H, m, H-7), 2.14 (2H, t, H-2''), 2.22 (1H, m, H-16), 2.28 (1H, m, H-12), 2.32 (1H, m, H-1), 2.35 (1H, m, H-12), 2.40 (1H, m, H-2), 2.44 (1H, m, H-2), 2.46 (1H, m, H-8), 2.57 (2H, m, H-6), 2.73 (1H, m, H-1), 3.21 (3H, s, N-CH_3), 4.35 (1H, d, H-11), 5.80 (1H, s, H-4), 7.07 (2H, d, H-3', H-5'), 7.23 (2H, d, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.7 (q, C-18), 23.2 (t, C-15), 24.3 (t, C-3''), 24.7 (t, C-4''), 25.8 (t, C-1), 27.3 (t, C-7), 31.1 (t, C-6), 33.4 (t, C-5''*), 33.6 (t, C-2''*), 36.8 (t, C-2), 37.3 (q, N-CH_3), 38.8 (t, C-16**), 38.8 (t, C-12*), 39.1 (d, C-8), 39.4 (d, C-11), 46.8 (s, C-13), 49.8 (d, C-14), 80.1 (s, C-17), 82.4 (s, C-19), 82.4 (s, C-20), 122.6 (d, C-4), 112.2 (d, C-3', C-5'), 127.5 (d, C-2', C-6'), 129.0 (s, C-10), 141.6 (s, C-4'), 144.6 (s, C-1'), 146.9 (s, C-9), 157.0 (s, C-5), 177.0 (s, C-1''), 172.9 (s, C-6''), 199.5 (s, C-3) ppm

17β-Hydroxy-11β-[4-(1-oxo-4-methoxycarbonyl-N-methylbutylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**26**)

26 was synthesized according to general procedure III starting from **24** (20 mg, 0.037 mmol); the product was additionally purified by preparative HPLC (column 2; acetonitrile : H_2O (67:33, vol/vol), flow: 23 mL/min; t_R = 3 min 25 sec).

$C_{34}H_{40}NO_5$ (MW: 543.70)

Yield: 45 % (yellow lyophilisate)

TLC: R_f = 0.13 (E I), R_f = 0.23 (E II)

Analytical HPLC: 97.3 %, t_R = 4.301 min (tracing: 2.7 %, t_R = 3.582 min)

UV/VIS (CH_2Cl_2): λ_{max} = 235.0, 269.5 nm

IR (KBr): ν = 3423 (m), 2947 (m), 2871 (m), 2242 (w), 1735 (s), 1655 (s), 1603 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.56 (3H, s, CH_3-18), 1.36 (1H, m, H-15), 1.46 (1H, m, H-7), 1.48 (2H, m, H-3''), 1.72 (1H, m, H-14), 1.73 (1H, m, H-15), 1.89 (3H, s, CH_3-21), 1.94 (1H, t, H-16), 1.96 (2H, m, H-4''), 2.02 (1H, m, H-7), 2.20 (2H, t, H-2''), 2.22 (1H, m, H-16), 2.28 (1H, m, H-12), 2.32 (1H, m, H-1), 2.35 (1H, m, H-12), 2.40 (1H, m, H-2), 2.44 (1H, m, H-2), 2.46 (1H, m, H-8), 2.57 (2H, m, H-6), 2.73 (1H, m, H-1), 3.23 (3H, s, N-CH_3), 3.62 (s, OCH_3), 4.42 (1H, d, J = 6.8, H-11), 5.76 (1H, s, H-4), 7.07 (2H, d, H-3', H-5'), 7.23 (2H, d, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.7 (q, C-18), 20.5 (t, C-3''), 23.3 (t, C-15), 25.8 (t, C-1), 27.3 (t, C-7), 31.1 (t, C-6), 32.8 (t, C-4''*), 33.1 (t, C-2''*), 36.9 (t, C-2), 37.3 (q, N-CH_3), 38.3 (t, C-16**), 38.7 (t, C-12*), 39.1 (d, C-8), 39.5 (d, C-11), 46.8 (s, C-13), 49.8 (d, C-14), 51.6 (q, OCH_3), 80.1 (s, C-17), 82.4 (s, C-19), 82.4 (s, C-20), 122.6 (d, C-4), 112.2 (d, C-3', C-5'), 127.5 (d, C-2', C-6'), 129.0 (s, C-10), 141.4 (s, C-4'), 145.3 (s, C-1'), 146.9 (s, C-9), 157.0 (s, C-5), 170.4 (s, C-1''), 172.6 (s, C-5''), 200.3 (s, C-3) ppm

17β-Hydroxy-11β-[4-(1-oxo-5-methoxycarbonyl-N-methylpentylamino)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**27**)

27 was synthesized according to general procedure III starting from **25** (20 mg, 0.037 mmol); the product was additionally purified by preparative HPLC (column 2; acetonitrile : H_2O (67:33, vol/vol), flow: 23 mL/min; t_R = 4 min).

$C_{35}H_{42}NO_5$ (MW: 556.72)

Yield: 53 % (yellow lyophilisate)

TLC: R_f = 0.15 (E I), R_f = 0.21 (E II), R_f = 0.06 (E VII)

Analytical HPLC: 95.3%, t_R = 4.319 min (tracings: 2 %, t_R = 1.606 min; 2.7 %, t_R = 5.120 min)

UV/VIS (CH_2Cl_2): λ_{max} = 236.0, 298.5 nm

IR (KBr): ν = 3421 (m), 2947 (m), 2870 (m), 2241 (w), 1735 (s), 1656 (s), 1600 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.50 (3H, s, CH_3-18), 1.36 (1H, m, H-15), 1.38 (2H, m, H-4''), 1.46 (1H, m, H-7), 1.50 (2H, m, H-3''), 1.72 (1H, m, H-14), 1.73 (1H, m, H-15), 1.90 (3H, s, CH_3-21), 1.94 (1H, t, H-16), 1.98 (2H, m, H-5''), 2.02 (1H, m, H-7), 2.15 (2H, t, H-2''), 2.22 (1H, m, H-16), 2.28 (1H, m, H-12), 2.32 (1H, m, H-1), 2.35 (1H, m, H-12), 2.40 (1H, m, H-2), 2.44 (1H, m, H-2), 2.46 (1H, m, H-8), 2.57 (2H, m, H-6), 2.73 (1H, m, H-1), 3.21 (3H, s, N-CH_3), 3.61 (3H, s, OCH_3), 4.35 (1H, d, H-11), 5.80 (1H, s, H-4), 7.05 (2H, d, H-3', H-5'), 7.22 (2H, d, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.7 (q, C-18), 23.2 (t, C-15), 24.3 (t, C-3''), 24.7 (t, C-4''), 25.8 (t, C-1), 27.3 (t, C-7), 31.1 (t, C-6), 33.4 (t, C-5''*), 33.6 (t, C-2''*), 36.8 (t, C-2), 37.3 (q, N-CH_3), 38.8 (t, C-16**), 38.8 (t, C-12*), 39.1 (d, C-8), 39.4 (d, C-11), 46.8 (s, C-13), 49.8 (d, C-14), 51.5 (q, OCH_3), 80.1 (s, C-17), 82.4 (s, C-19), 82.4 (s, C-20), 122.6 (d, C-4), 112.2 (d, C-3', C-5'), 127.5 (d, C-2', C-6'), 129.0 (s, C-10), 141.6 (s, C-4'), 144.6 (s, C-1'), 146.9 (s, C-9), 157.0 (s, C-5), 177.0 (s, C-1''), 173.0 (s, C-6''), 199.5 (s, C-3) ppm

17β-Hydroxy-11β-[4-(1-methyl-3-butylureido)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**28**)

28 was synthesized according to general procedure IV reacting **2** (116 mg, 0.26 mmol) with n-butyl isocyanate (122 mg, 1.23 mmol); the product was purified by preparative HPLC (column 1; acetonitrile : H_2O (65/35, vol/vol), flow: 12 mL/min; t_R = 8 min).

$C_{33}H_{42}N_2O_3$ (MW: 514.70)

Yield: 35% (colourless lyophilisate)

Calc: C 77.01, H 8.22, N 5.44; Found: C 79.21, H 8.07, N 3.30

MS (m/z): 515 (M^+)

TLC: R_f = 0.07 (E I), R_f = 0.50 (E VII)

Analytical HPLC: 96 %, t_R = 4.795 min (tracing: 4 %, t_R = 4.487 min)

UV/VIS (MeOH): λ_{max} = 209.0, 302.0 nm

IR (KBr): ν = 3445 (m), 3379 (m), 2934 (s), 2870 (m), 2241 (w), 1663 (s, br) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.45 (3H, s, CH_3-18), 0.80 (3H, t, J = 6.8, H-4''), 1.17 (2H, tq, J = 6.8, H-3''), 1.30 (1H, m, H-15), 1.31 (2H, tt, J = 6.8, H-2''), 1.42 (1H, dq, J = 12.8, J = 8.8, H-7), 1.71 (1H, m, H-14), 1.72 (1H, m, H-15), 1.85 (3H, s, CH_3-21), 1.91 (1H, t, J = 12.8, J = 6.6, H-16), 2.02 (1H, dq, J = 12.8, J = 8.8, H-7), 2.20 (1H, m, H-16), 2.27 (1H, m, H-1), 2.30 (1H, m, H-2), 2.42 (3H, m, H-2, H-8, H-12), 2.55 (2H, m, H-6), 2.74 (1H, dt, H-1), 3.09 (2H, dt, J = 6.8, J = 4.8, H-1''), 3.18 (3H, s, N-CH_3), 4.19 (1H, t, b, N-H), 4.40 (1H, d, J = 6.8, H-11), 5.74 (1H, s, H-4), 7.09 (2H, d, H-3', H-5'), 7.18 (2H, d, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.6 (q, C-18*), 13.7 (q, C-4''*), 19.9 (t, C-3''), 23.2 (t, C-15), 25.8 (t, C-1), 27.2 (t, C-7), 31.0 (t, C-6), 32.1 (t, C-2''), 36.7 (t, C-2), 40.0 (q, N-CH_3), 40.5 (t, C-1''), 38.8 (t, C-16), 39.0 (t, C-12), 39.0 (d, C-8), 40.0 (d, C-11), 46.8 (s, C-13), 49.6 (d, C-14), 79.8 (s, C-17), 82.1 (s, C-19), 82.5 (s, C-20), 123.1 (d, C-4), 127.2 (d, C-3', C-5'), 128.4 (d, C-2', C-6'), 129.6 (s, C-10), 141.0 (s, C-4'), 143.7 (s, C-1'), 145.2 (s, C-9), 156.4 (s, C-5), 157.3 (s, CO), 199.3 (s, C-3) ppm

17β-Hydroxy-11β-[4-(1-methyl-3-butylthioureido)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**29**)

29 was synthesized according to general procedure IV reacting **2** (116 mg, 0.26 mmol) with n-butyl isothiocyanate (142 mg, 1.23 mmol); the product was purified by preparative HPLC (column 1; acetonitrile : H_2O (60:40, vol/vol), flow: 12 mL/min; t_R = 8 min).

$C_{33}H_{42}N_2O_2S$ (MW: 530.77)

Yield: 33% yield (colourless lyophilisate)

Calc: C 74.68, H 7.98, N 5.28; Found: C 79.21, H 8.07, N 3.30

MS (m/z): 531 (M^+)

TLC: R_f = 0.33 (E I), R_f = 0.57 (E VII)

Analytical HPLC: 95.6 %, t_R = 5.410 min (tracing: 4.4 %, t_R = 4.785min)

UV/VIS (MeOH): λ_{max} = 212.5, 243.0, 301.0 nm

IR (KBr): ν = 3401 (m), 2934 (s), 2870 (m), 2241 (w), 1662 (s), 1349 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.49 (3H, s, CH_3-18), 0.83 (3H, t, J = 7.2, H-4''), 1.17 (2H, tt, J = 7.6, J = 7.6, H-3''), 1.35 (1H, m, H-15), 1.39 (2H, tt, J = 7.6, J = 7.6, H-2''), 1.50 (1H, m, H-7), 1.73 (1H, m, H-14), 1.77 (1H, m, H-15), 1.90 (3H, s, CH_3-21), 1.96 (1H, td, J = 14.0, J = 4.0, H-16), 2.05 (1H, m, H-7), 2.26 (1H, m, H-16), 2.32 (1H, m, H-1), 2.36 (1H, m, H-2), 2.45 (1H, m, H-12), 2.46 (2H, m, H-2, H-12), 2.50 (1H, m, H-8), 2.61 (2H, m, H-6), 2.80 (1H, dt, H-1), 3.52 (2H, dt, J = 5.2, J = 7.6, H-1''), 3.64 (3H, s, N-CH_3), 5.22 (1H, t, J = 5.2, N-H), 4.47 (1H, d, J = 6.8, H-11), 5.80 (1H, s, H-4), 7.13 (2H, d, H-3', H-5'), 7.31 (2H, d, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.6 (q, C-18*), 13.7 (q, C-4''*), 19.8 (t, C-3''), 23.2 (t, C-15), 25.9 (t, C-1), 27.2 (t, C-7), 30.9 (t, C-2''*), 31.0 (t, C-6*), 36.7 (t, C-2), 38.8 (t, C-16), 39.0 (t, C-12), 39.2 (d, C-8), 40.1 (d, C-11), 43.0 (t, C-1''), 45.4 (q, N-CH_3), 46.8 (s, C-13), 49.6 (d, C-14), 79.9 (s, C-17), 82.0 (s, C-19**), 82.7 (s, C-20**), 123.2 (d, C-4), 127.0 (d, C-3', C-5'), 129.1 (d, C-2', C-6'), 129.8 (s, C-10), 140.3 (s, C-4'), 144.7 (s, C-9), 145.3 (s, C-1'), 156.2 (s, C-5), 181.8 (s, CS), 199.0 (s, C-3) ppm

17β-Hydroxy-11β-{4-[methyl-3-(4-chlorphenyl)-ureido]-phenyl}-17α-(1-propinyl)-estra-4,9-dien-3-one (30)

30 was synthesized according to general procedure IV reacting **2** (116 mg, 0.26 mmol) with 4-chlorophenyl isocyanate (120 mg, 0.78 mmol); the product was purified by preparative HPLC (column 1; acetonitrile : H_2O (65:35, vol/vol), flow: 12 mL/min; t_R = 7 min 30 sec).

$C_{35}H_{37}ClN_2O_3$ (MW: 569.14)

Yield: 30% (colourless lyophilisate)

Calc: C 73.86, H 6.55, N 4.92; Found: C 73.21, H 6.47, N 4.80

MS (m/z): 569 (M^+)

TLC: R_f = 0.20 (E I), R_f = 0.57 (E VII)

Analytical HPLC: 96.5 %, t_R = 5.050 min (tracing: 3.5 %, t_R = 4.640 min)

UV/VIS (MeOH): λ_{max} = 208.5, 249.5, 302.0 nm

IR (KBr): ν = 3424 (m), 2943 (s), 2871 (m), 2241 (w), 1663 (s, br) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.50 (3H, s, CH_3-18), 1.34 (1H, m, H-15), 1.46 (1H, m, H-7), 1.68 (1H, m, H-14), 1.74 (1H, m, H-15), 1.87 (3H, s, CH_3-21), 1.93 (1H, td, J = 14.8, J = 4.8, H-16), 2.02 (1H, m, H-7), 2.20 (1H, m, H-16), 2.27 (1H, m, H-12), 2.29 (1H, m, H-1), 2.34 (1H, m, H-2), 2.44 (2H, m, H-8, H-12), 2.45 (1H, m, H-2), 2.56 (2H, m, H-6), 2.78 (1H, dt, H-1), 3.27 (3H, s, N-CH_3), 4.45 (1H, d, J = 6.8, H-11), 5.77 (1H, s, H-4), 6.14 (1H, s, NH), 7.14 (4H, m, H-2'', H-3'', H-5'', H-6''), 7.20 (2H, d, H-3', H-5'), 7.27 (2H, d, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.8 (q, C-18), 23.3 (t, C-15), 25.9 (t, C-1), 27.3 (t, C-7), 31.0 (t, C-6), 36.7 (t, C-2), 38.2 (q, N-CH_3), 38.9 (t, C-16), 39.0 (t, C-12), 39.2 (d, C-8), 40.1 (d, C-11), 46.9 (s, C-13), 49.7 (d, C-14), 80.0 (s, C-17), 82.1 (s, C-19), 82.7 (s, C-20), 120.1 (d, C-2'', C-6''), 123.3 (d, C-4), 127.4 (d, C-3', C-5'), 127.6 (s, C-4''), 128.7 (d, C-3'', C-5''), 128.9 (d, C-2', C-6'), 129.8 (s, C-10), 137.4 (s, C-1''), 141.2 (s, C-4'), 144.8 (s, C-1'), 144.8 (s, C-9), 156.3 (s, C-5), 154.1 (s, CO), 199.2 (s, C-3) ppm

17β-Hydroxy-11β-{4-[methyl-3-(4-chlorphenyl)-thioureido]-phenyl}-17α-(1-propinyl)-estra-4,9-dien-3-one (**31**)

31 was synthesized according to general procedure IV reacting **2** (116 mg, 0.26 mmol) with 4-chlorophenyl isothiocyanate (132 mg, 0.78 mmol); the product was purified by preparative HPLC (column 1; acetonitrile : H_2O (65:35, vol/vol), flow: 12 mL/min; t_R = 9 min 50 sec).

$C_{35}H_{37}ClN_2O_2S$ (MW: 585.21)

Yield: 34% (colourless lyophilisate)

Calc: C 71.84, H 6.37, N 4.92; Found: C 71.61, H 6.07, N 4.70

MS (m/z): 585 (M^+)

TLC: R_f = 0.31 (E I), R_f = 0.59 (E VII)

Analytical HPLC: 95.8 %, t_R = 5.109 min (tracings: 2.7 %, t_R = 4.564 min; 1.5 %, t_R = 6.533 min)

UV/VIS (MeOH): λ_{max} = 285.0 nm

IR (KBr): ν = 3376 (m), 2941 (s), 2870 (m), 2241 (w), 1657 (s), 1340 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.48 (3H, s, CH_3-18), 1.34 (1H, m, H-15), 1.48 (1H, m, H-7), 1.68 (1H, m, H-14), 1.75 (1H, m, H-15), 1.89 (3H, s, CH_3-21), 1.93 (1H, t, H-16), 2.04 (1H, m, H-7), 2.21 (1H, m, H-16), 2.28 (1H, m, H-12), 2.30 (1H, m, H-1), 2.36 (1H, m, H-2), 2.45 (2H, m, H-8, H-12), 2.46 (1H, m, H-2), 2.60 (2H, m, H-6), 2.78 (1H, m, H-1), 3.70 (3H, s, N-CH_3), 4.47 (1H, d, J = 7.2, H-11), 5.79 (1H, s, H-4), 6.90 (1H, s, NH), 7.22 (6H, m, H-3', H-5', H-2'', H-3'', H-5'', H-6''), 7.33 (2H, d, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 13.9 (q, C-18), 23.3 (t, C-15), 25.9 (t, C-1), 27.2 (t, C-7), 31.0 (t, C-6), 36.7 (t, C-2), 38.9 (t, C-16), 39.0 (t, C-12*), 39.1 (d, C-8), 40.1 (d, C-11), 43.6 (q, N-CH_3), 46.9 (s, C-13), 49.7 (d, C-14), 79.9 (s, C-17), 82.0 (s, C-19), 82.8 (s, C-20), 123.3 (d, C-4), 126.5 (d, C-2'', C-6''), 126.8 (d, C-3', C-5'), 128.6 (d, C-3'', C-5''), 129.3 (d, C-2', C-6'), 130.0 (s, C-10), 131.2 (s, C-4''), 137.7 (s, C-1''), 140.3 (s, C-4'), 144.5 (s, C-9*), 145.8 (s, C-1'*), 156.2 (s, C-5), 181.2 (s, CS), 199.1 (s, C-3) ppm

17β-Hydroxy-11β-{4-[1-methyl-3-(5-carboxypentyl)-ureido]-phenyl}-17α-(1-propinyl)-estra-4,9-dien-3-one (32)

33 (350 mg, 0.596 mmol) was dissolved in 5 mL THF and the solution adjusted to p_H = 1 with 2 mol/L H_2SO_4. The solvent was removed in vacuo and the residue purified by flash chromatography with EtOAc and by preparative HPLC (column 2; acetonitrile : H_2O (54:46, vol/vol), flow: 23 mL/min; t_R = 4 min 30 sec).

$C_{35}H_{44}N_2O_5$ (MW: 572.74)

Yield: 47% (colourless lyophilisate)

MS (m/z): 573 (M^+)

TLC: R_f = 0.00 (E I), R_f = 0.20 (E II), R_f = 0.20 (E V), R_f = 0.34 (E VI), R_f = 0.35 (E VII)

Analytical HPLC: 100%, t_R = 3.734 min

UV/VIS (MeOH): λ_{max} = 209.0, 243.0, 302.0 nm

IR (KBr): ν = 3442 (m), 2937 (m), 2868 (m), 2241 (w), 1727 (s), 1650 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.50 (3H, s, CH_3-18), 1.22 (1H, m, H-3''), 1.25 (1H, m, H-2''), 1.35 (1H, m, H-15), 1.38 (1H, m, H-3''), 1.39 (1H, m, H-2''), 1.48 (1H, m, H-7), 1.59 (2H, m, H-4''), 1.74 (1H, m, H-14), 1.76 (1H, m, H-15), 1.91 (3H, s, CH_3-21), 1.96 (1H, m, H-16), 2.04 (1H, m, H-7), 2.24 (1H, m, H-16), 2.29 (2H, m, H-5''), 2.31 (1H, m, H-12), 2.33 (1H, m, H-1), 2.37 (1H, m, H-2), 2.41 (1H, m, H-12), 2.47 (2H, m, H-2, H-8), 2.61 (2H, m, H-6), 2.79 (1H, m, H-1), 3.14 (1H, m, H-1''), 3.22 (3H, s, N-CH_3), 3.23 (1H, m, H-1''), 4.25 (1H, t, NH), 4.45 (1H, d, H-11), 5.80 (1H, s, H-4), 7.15 (2H, d, H-3', H-5'), 7.24 (2H, d, H-2', H-6') ppm

^{13}C-NMR: ($CDCl_3$) δ = 3.8 (q, C-21), 13.8 (q, C-18), 23.4 (t, C-15), 24.3 (t, C-4''), 25.9 (t, C-1), 26.2 (t, C-3''), 27.3 (t, C-7), 29.7 (t, C-2''), 31.0 (t, C-6), 33.7 (t, C-5''), 36.7 (t, C-2), 37.1 (q, N-CH_3), 38.9 (t, C-16), 39.2 (d, C-8), 39.3 (t, C-12), 40.1 (d, C-11), 40.5 (t, C-1''), 46.9 (s, C-13), 49.6 (d, C-14), 80.3 (s, C-17), 81.9 (s, C-19), 82.8 (s, C-20), 123.2 (d, C-4), 127.3 (d, C-3', C-5'), 128.6 (d, C-2', C-6'), 129.8 (s, C-10), 141.0 (s, C-4'), 144.0 (s, C-1'), 145.1 (s, C-9), 156.6 (s, C-5), 157.5 (s, CO), 176.9 (s, C-6''), 199.6 (s, C-3) ppm

17β-Hydroxy-11β-{4-[1-methyl-3-(5-methoxycarbonylpentyl)-ureido]-phenyl}-17α-(1-propinyl)-estra-4,9-dien-3-one (**33**)

33 was synthesized according to general procedure IV reacting **2** (150 mg, 0.36 mmol) with methyl 6-isocyanato caproate[S11,S12] (247 mg, 1.44 mmol); the product was purified by preparative HPLC (column 2; acetonitrile : H_2O (67:33, vol/vol), flow: 23 mL/min; t_R = 3 min 55 sec).

$C_{36}H_{46}N_2O_5$ (MW: 586.77)

Yield: 87 % (colourless lyophilisate)

Calc: C 73.69, H 7.90, N 4.77; Found: C 73.21, H 7.67, N 4.61

MS (m/z): 587 (M^+)

TLC: R_f = 0.27 (E I), R_f = 0.48 (E II), R_f = 0.39 (E VII)

Analytical HPLC: 95.2 %, t_R = 4.229 min (tracings: 2.8 %, t_R = 4.007 min; 2 %, t_R = 3.778 min)

UV/VIS (MeOH): λ_{max} = 208.0, 242.0, 302.0 nm

IR (KBr): ν = 3385 (m), 2942 (m), 2866 (m), 2241 (w), 1736 (s), 1662 (s, br) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.50 (3H, s, CH_3-18), 1.24 (1H, m, H-3''), 1.36 (2H, m, H-15, H-3''), 1.41 (1H, m, H-2''), 1.50 (2H, m, H-7, H-2''), 1.58 (2H, m, H-4''), 1.74 (1H, m, H-14), 1.76 (1H, m, H-15), 1.90 (3H, s, CH_3-21), 1.96 (1H, m, H-16), 2.05 (1H, m, H-7), 2.25 (1H, m, H-16), 2.28 (2H, m, H-5''), 2.31 (1H, m, H-12), 2.33 (1H, m, H-1), 2.39 (1H, m, H-2), 2.42 (1H, m, H-12), 2.48 (1H, m, H-2), 2.49 (1H, m, H-8), 2.61 (2H, m, H-6), 2.81 (1H, m, H-1), 3.15 (2H, t, H-1''), 3.23 (3H, s, N-CH_3), 3.65 (3H, s, OCH_3), 4.25 (1H, t, NH), 4.46 (1H, d, H-11), 5.79 (1H, s, H-4), 7.14 (2H, d, H-3', H-5'), 7.23 (2H, d, H-2', H-6') ppm

^{13}C-NMR ($CDCl_3$): δ = 3.9 (q, C-21), 13.9 (q, C-18), 23.5 (t, C-15), 24.7 (t, C-4''), 26.0 (t, C-1), 26.4 (t, C-3''), 27.4 (t, C-7), 29.9 (t, C-2''), 31.1 (t, C-6), 34.0 (t, C-5''), 36.8 (t, C-2), 37.1 (q, N-CH_3), 39.0 (t, C-16), 39.1 (d, C-8), 39.1 (t, C-12), 40.1 (d, C-11), 40.7 (t, C-1''), 46.9 (s, C-13), 49.8 (d, C-14), 51.5 (q, OCH_3), 80.0 (s, C-17), 82.1 (s, C-19), 82.5 (s, C-20), 123.2 (d, C-4), 127.3 (d, C-3', C-5'), 128.5 (d, C-2', C-6'), 129.8 (s, C-10), 141.1 (s, C-4'), 143.9 (s, C-1'), 145.1 (s, C-9), 156.4 (s, C-5), 157.3 (s, CO), 174.2 (s, C-6''), 199.3 (s, C-3) ppm

17β-Hydroxy-11β-{4-[1,14,14-trimethyl-11-(2-methylpropyl)-2,9,12-trioxo-1,3,10-triaza-13-oxa-pentadecyl]-phenyl}-17α-(1-propinyl)-estra-4,9-dien-3-one (**34**)

32 (115 mg, 0.2 mmol) and an equimolar amount of triethylamine (20.2 mg, 0.2 mmol) were dissolved in 3 mL THF under argon at 0 °C (according to ref. S8). Isobutyl chloroformate (27.3 mg, 0.2 mmol) was added and the mixture was stirred for 40 min at 0°C. Subsequently, a solution of leucine-t-butyrate in 0.2 mL THF [the free base was extracted from leucine-t-butyrate·x HCl (37 mg, 0.2 mmol) with NaOH 2 mol/L] was added and the mixture stirred for additional 1.5 h. The product was purified by flash chromatography with EtOAc and by preparative HPLC (column 2; acetonitrile : H_2O (67:33, vol/vol), flow: 23 mL/min; t_R = 6 min 50 sec).

$C_{45}H_{63}N_3O_6$ (MW: 742.01)

Yield: 56 % (colourless lyophilisate)

MS (m/z): 744 $(MH_2)^+$

TLC: R_f = 0.00 (E I), R_f = 0.00 (E II), R_f = 0.25 (E V), R_f = 0.00 (E VI), R_f = 0.24 (E VII)

Analytical HPLC: 100%, t_R = 4.105 min

UV/VIS (MeOH): λ_{max} = 205.5, 301.5 nm

IR (KBr): ν = 3341 (m), 2934 (m), 2870 (m), 2241 (w), 1734 (s), 1647 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.49 (3H, s, CH_3-18), 0.91 (3H, m, 5’’’), 0.92 (3H, m, 6’’’), 1.17 (2H, m, H-3’’), 1.34 (1H, m, H-15), 1.38 (2H, m, H-2’’), 1.45 (3H, m, H-2’’’’), 1.47 (1H, m, H-3’’’), 1.48 (1H, m, H-7), 1.58 (1H, m, H-4’’), 1.58 (2H, m, H-3’’’, H-4’’), 1.62 (1H, m, H-4’’’), 1.72 (1H, m, H-14), 1.75 (1H, m, H-15), 1.89 (3H, s, CH_3-21), 1.94 (1H, m, H-16), 2.04 (1H, m, H-7), 2.24 (1H, m, H-16), 2.25 (2H, m, H-5’’), 2.30 (1H, m, H-12), 2.32 (1H, m, H-1), 2.37 (1H, m, H-2), 2.42 (1H, m, H-12), 2.47 (2H, m, H-2, H-8), 2.60 (2H, m, H-6), 2.79 (1H, m, H-1), 3.09 (1H, t, H-1’’), 3.19 (1H, t, H-1’’), 3.22 (3H, s, N-CH_3), 4.45 (1H, d, H-11), 4.49 (1H, m, H-2’’’), 5.79 (1H, s, H-4), 7.14 (2H, d, H-3’, H-5’), 7.23 (2H, d, H-2’, H-6’) ppm

^{13}C-NMR ($CDCl_3$): δ = 3.8 (q, C-21), 14.0 (q, C-18), 22.2 (q, C-5’’’), 22.8 (q, C-6’’’), 23.4 (t, C-15), 25.0 (d, C-4’’’), 25.3 (t, C-4’’), 26.0 (t, C-1), 26.6 (t, C-3’’), 27.4 (t, C-7), 28.0 (q, C-2’’’’), 29.9 (t, C-2’’), 31.1 (t, C-6), 36.4 (t, C-5’’), 36.8 (t, C-2), 37.0 (q, N-CH_3), 39.0 (t, C-16), 39.2 (d, C-8), 39.4 (t, C-12), 40.2 (d, C-11), 40.5 (t, C-1’’), 42.0 (t, C-3’’’), 46.9 (s, C-13), 49.7 (d, C-14), 51.2 (d, C-2’’’), 80.0 (s, C-17), 81.9 (s, C-1’’’’*), 82.2 (s, C-19*), 82.7 (s, C-20*), 123.2 (d, C-4), 127.4 (d, C-3’, C-5’), 128.6 (d, C-2’, C-6’), 129.8 (s, C-10), 141.1 (s, C-4’), 144.1 (s, C-1’), 145.1 (s, C-9), 156.4 (s, C-5), 157.4 (s, CO), 172.6 (s, C-6’’), 172.7 (s, C-1’’’), 199.3 (s, C-3) ppm

17β-Hydroxy-11β-{4-[11-carboxy-1,13-dimethyl-2,9-dioxo-1,3,10-triaza-tetradecyl]-phenyl}-17α-(1-propinyl)-estra-4,9-dien-3-one (**35**)

34 (44 mg, 0.066 mmol) was dissolved in 1.5 mL dry propionic acid at 0° C and 0.9 mL 30% HBr in propionic acid was added. After 1 min of stirring at 0 °C, the reaction mixture was poured into ice water and extracted with EtOAc. The organic layer was washed with water and dried over Na_2SO_4. The solvent and the excess of propionic acid were distilled off in high vacuo at room temperature and the residue was purified by preparative HPLC (column 2; acetonitrile : H_2O (67:33, vol/vol, flow: 23 mL/min; t_R = 4 min 30 sec).

$C_{41}H_{55}N_3O_6$ (MW: 685.90)

Yield: 77 % (colourless lyophilisate)

MS (m/z): 709 (M^+ + Na)

TLC: R_f = 0.00 (E IV), R_f = 0.22 (E II), R_f = 0.70 (E V), R_f = 0.14 (E VI), R_f = 0.44 (E VII)

Analytical HPLC: 92.5%, t_R = 5.527 min (tracings: 4.2 %, t_R = 4.947; 3.3 %, t_R = 6.475 min)

UV/VIS (MeOH): λ_{max} = 225.0, 299.0 nm

IR (KBr): ν = 3422 (m), 2937 (m), 2869 (m), 2241 (w), 1732 (s), 1717 (s), 1699 (s), 1649 (s) cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 0.51 (3H, s, CH_3-18), 0.94 (3H, m, 5’’’), 0.96 (3H, m, 6’’’), 1.23 (2H, m, H-3’’), 1.36 (1H, m, H-15), 1.38 (2H, m, H-2’’), 1.49 (1H, m, H-7), 1.60 (1H, m, H-4’’), 1.61 (1H, m, H-3’’’) 1.64 (1H, m, H-4’’), 1.72 (1H, m, H-4’’’), 1.73 (1H, m, H-3’’’), 1.74 (1H, m, H-14), 1.77 (1H, m, H-15), 1.91 (3H, s, CH_3-21), 1.97 (1H, m, H-16), 2.05 (1H, m, H-7), 2.23 (2H, m, H-5’’), 2.25 (1H, m, H-16), 2.30 (1H, m, H-12), 2.33 (1H, m, H-1), 2.38 (1H, m, H-2), 2.44 (1H, m, H-12), 2.48 (2H, m, H-2, H-8), 2.61 (2H, m, H-6), 2.80 (1H, m, H-1), 3.14 (1H, t, H-1’’), 3.16 (1H, t, H-1’’), 3.25 (3H, s, N-CH_3), 4.46 (1H, d, H-11), 4.61 (1H, m, H-2’’’), 5.81 (1H, s, H-4), 7.17 (2H, d, H-3’, H-5’), 7.25 (2H, d, H-2’, H-6’) ppm

^{13}C-NMR ($CDCl_3$): δ = 3.9 (q, C-21), 14.1 (q, C-18), 22.0 (q, C-5’’’), 23.1 (q, C-6’’’), 23.7 (t, C-15), 25.1 (d, C-4’’’), 25.5 (t, C-4’’), 26.2 (t, C-1), 26.2 (t, C-3’’), 27.5 (t, C-7), 29.9 (t, C-2’’), 31.2 (t, C-6), 32.0 (t, C-2), 36.2 (t, C-5’’), 37.5 (q, N-CH_3), 39.1 (t, C-16), 39.5 (d, C-8), 39.5 (t, C-12), 40.5 (d, C-11), 40.8 (t, C-1’’), 41.0 (t, C-3’’’), 47.0 (s, C-13), 49.9 (d, C-14), 51.3 (d, C-2’’’), 80.3 (s, C-17), 82.1 (s, C-19), 82.8 (s, C-20), 123.5 (d, C-4), 127.7 (d, C-3’, C-5’), 129.0 (d, C-2’, C-6’), 130.0 (s, C-10), 140.9 (s, C-4’), 144.5 (s, C-1’), 145.5 (s, C-9), 156.9 (s, C-5), 157.9 (s, CO), 199.9 (s, C-3) ppm

17β-Hydroxy-11β-{4-[1-methyl-4-oxo-5-(4-carbamoyl-3-hydroxyphenyl)-1,5-diazapentyl]-phenyl}-17α-(1-propinyl)-estra-4,9-dien-3-one (36)

13 (80 mg, 0.164 mmol) and an excess of triethylamine (33.2 mg, 0.328 mmol) were dissolved in 0.7 mL THF under argon at 0 °C. After adding isobutyl chloroformate (22.4 mg, 0.164 mmol) and stirring of the mixture for 40 min at 0 °C (according to ref. S8) a solution of 4-amino-2-hydroxy-benzamid[S13] (25 mg, 0.164 mmol) in 0.3 mL THF was added and stirring was continued for 1.5 h. The product was purified by flash chromatography with EtOAc and by preparative HPLC (column 2; acetonitrile : H_2O (67:33, vol/vol), flow: 20 mL/min; t_R = 2 min 24 sec) as well as finally by column chromatography with Sephadex LH-20® in EtOAc.

$C_{38}H_{43}N_3O_5$ (MW: 621.77)

Yield: 15 % (yellow lyophilisate)

MS (m/z): 644 (M^+ + Na)

TLC: R_f = 0.04 (E I), R_f = 0.40 (E II), R_f = 0.23 (E V), R_f = 0.10 (E VI)

Analytical HPLC: 95.0 %, t_R = 4.130 min (tracing: 5 %, t_R = 3.473)

UV/VIS (MeOH): λ_{max} = 209.5, 264.0 nm

IR (KBr): ν = 3330 (m), 2938 (m), 2871 (m), 2241 (w), 1653 (s), 1608 (s) cm^{-1}

^{1}H-NMR (CD_3OD): δ = 0.48 (3H, s, CH_3-18), 1.35 (1H, m, H-15), 1.38 (1H, m, H-7), 1.58 (2H, m, H-2''), 1.69 (1H, m, H-14), 1.73 (1H, m, H-15), 1.85 (3H, s, CH_3-21), 1.89 (1H, m, H-16), 2.03 (1H, m, H-7), 2.13 (1H, m, H-16), 2.24 (1H, m, H-1), 2.28 (1H, m, H-2), 2.29 (1H, m, H-12), 2.36 (1H, m, H-12), 2.40 (1H, m, H-2), 2.45 (1H, m, H-8), 2.59 (2H, m, H-6), 2.79 (1H, m, H-1), 2.92 (3H, s, N-CH_3), 3.69 (1H, m, H-1''), 3.74 (1H, m, H-1''), 4.36 (1H, d, H-11), 5.77 (1H, s, H-4), 6.73 (2H, m, H-3', H-5'), 6.98 (1H, m, H-9''), 7.02 (2H, m, H-2', H-6'), 7.20 (1H, m ; H-5''), 7.66 (1H, m ; H-8'') ppm

^{13}C-NMR (CD_3OD): δ = 3.3 (q, C-21), 14.5 (q, C-18), 24.2 (t, C-15), 26.8 (t, C-1), 28.8 (t, C-7), 32.2 (t, C-6), 35.8 (t, C-2''), 37.7 (t, C-2), 38.7 (q, N-CH_3), 39.7 (t, C-16), 40.0 (t, C-12), 40.1 (d, C-11), 40.7 (d, C-8), 48.2 (s, C-13), 50.4 (t, C-1''), 51.3 (d, C-14), 80.8 (s, C-17), 82.5 (s, C-20), 83.7 (s, C-19), 108.6 (d, C-5''), 111.5 (d, C-9''), 114.2 (d, C-3', C-5'), 122.8 (d, C-4), 128.9 (d, C-2', C-6'), 130.0 (d, C-8''), 130.1 (s, C-10), 134.0 (s, C-1'), 145.2 (s, C-7''), 145.2 (s, C-4''), 148.3 (s, C-4'), 150.0 (s, C-9), 153.5 (s, C-3''), 160.6 (s, C-5), 163.0 (s, C-6''), 173.6 (s, C-10''), 202.5 (s, C-3) ppm

17β-Hydroxy-11β-{4-[1-methyl-6-(4-carbamoyl-3-hydroxyphenyl)-1-aza-5-oxa-hexyl]-phenyl}-17α-(1-propinyl)-estra-4,9-dien-3-one (**37**)

2 (112.2 mg, 0.27 mmol), 4-(3'-bromopropoxymethyl)-2-hydroxybenzamide[S14,S15] (83.6 mg, 0.29 mmol) and triethylamine (72.9 mg, 0.72 mmol) were dissolved in 3 mL THF and the mixture was refluxed under argon for 20 h. The precipitate was filtered off, the solvent removed in vacuo and the residue purified by flash chromatography (EtOAc:cyclohexane = 3:2, vol/vol).

$C_{39}H_{46}N_2O_5$ (MW: 622.80)

Yield: 29% (colourless lyophilisate)

TLC: R_f = 0.16 (E I), R_f = 0.31 (E VI), R_f = 0.00 (E VII)

UV/VIS (MeOH): λ_{max} = 209.5 nm

IR (KBr): ν = 3430 (m), 2938 (m), 2871 (m), 2241 (w), 1653 (s), 1608 (s) cm^{-1}

^{1}H-NMR $(CD_3)_2CO$): δ = 0.56 (3H, s, CH_3-18), 1.38 (1H, m, H-15), 1.42 (1H, m, H-7), 1.71 (1H, m, H-15), 1.76 (1H, m, H-14), 1.82 (2H, m, H-2''), 1.82 (3H, s, CH_3-21), 1.92 (1H, m, H-16), 2.05 (1H, m, H-7), 2.12 (1H, m, H-16), 2.24 (1H, m, H-2), 2.25 (1H, m, H-1), 2.27 (1H, m, H-12), 2.33 (1H, m, H-2), 2.35 (1H, m, H-12), 2.52 (1H, m, H-8), 2.59 (1H, H-6), 2.64 (1H, m, H-6), 2.81 (1H, m, H-1), 2.92 (3H, s, N-CH_3), 3.41 (2H, m, H-1''), 3.49 (2H, m, H-3''), 4.39 (1H, d, H-11), 4.39 (2H, m, H-4''), 5.64 (1H, s, H-4), 6.67 (2H, m, H-3', H-5'), 6.89 (1H, m, H-9''), 7.02 (2H, m, H-2', H-6'), 7.44 (1H, m, H-10''), 7.81 (1H, m, H-6'') ppm

^{13}C-NMR $(CD_3)_2CO$): δ = 3.5 (q, C-21), 14.3 (q, C-18), 24.0 (t, C-15), 26.6 (t, C-1), 27.9 (t, C-2''), 28.5 (t, C-7), 31.7 (t, C-6), 37.5 (t, C-2), 38.7 (q, N-CH_3), 39.7 (t, C-16), 39.9 (t, C-12), 40.2 (d, C-8), 40.4 (d, C-11), 47.8 (s, C-13), 50.3 (t, C-1''), 50.8 (d, C-14), 68.2 (t, C-3''), 72.8 (t, C-4''), 80.1 (s, C-17), 81.5 (s, C-20), 84.3 (s, C-19), 113.1 (d, C-3', C-5'), 114.5 (s, C-5''), 116.5 (d, C-9''), 123.0 (d, C-4), 127.9 (d, C-6''), 128.4 (d, C-2', C-6'), 129.7 (s, C-7''), 129.8 (s, C-10), 132.9 (s, C-1'), 135.0 (d, C-10''), 147.8 (s, C-9), 148.3 (s, C-4'), 157.0 (s, C-5), 162.7 (s, C-8''), 173.7 (s, C-11''), 198.2 (s, C-3) ppm

17β-Hydroxy-11β-[4-(9-hydroxy-1-methyl-6,9-dioxo-1-aza-5-oxa-nonyl)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**38**)

9 (47 mg, 0.1 mmol), succinic anhydride (10 mg, 0.1 mmol), 4-(dimethylamino)pyridine[S16] (7.3 mg, 0.06 mmol) and an excess of triethylamine (20.2 mg, 0.2 mmol) were dissolved in 4 mL CH_2Cl_2 and refluxed for 5 h. The solvent was removed in vacuo, the residue suspended in EtOAc and the reaction mixture adjusted to p_H = 4.0 by adding HCl (2 mol/L) in MeOH; the residue was purified by flash chromatography with EtOAc as eluent.

$C_{35}H_{43}NO_6$ (MW: 573.72)

Yield: 41 % (yellow lyophilisate)

TLC: R_f = 0.47 (E II), R_f = 0.30 (E VII)

Analytical HPLC: 100 %, t_R = 4.350 min

UV/VIS (CH_2Cl_2): λ_{max} = 266.5, 301.5

IR (KBr): ν = 3434 (m), 2936 (m), 2863 (m), 2241 (w), 1734 (s), 1655 (s), 1612 (s), 1517 (m) cm^{-1}

^{1}H-NMR ($(CD_3)_2CO$): δ = 0.57 (3H, s, CH_3-18), 1.38 (1H, m, H-15), 1.41 (1H, m, H-7,), 1.71 (1H, m, H-15), 1.75 (1H, m, H-14), 1.83 (3H, s, CH_3-21), 1.90 (2H, m, H-2''), 1.92 (1H, m, H-16), 2.06 (1H, m, H-7), 2.12 (1H, m, H-16), 2.24 (1H, m, H-2), 2.25 (1H, m, H-1), 2.28 (1H, m, H-12), 2.33 (1H, m, H-2), 2.36 (1H, m, H-12), 2.53 (1H, m, H-8), 2.58 (1H, m, H-6), 2.62 (4H, m, H-2''', H-3'''), 2.65 (1H, m, H-6), 2.82 (1H, m, H-1), 2.90 (3H, s, N-CH_3), 3.42 (2H, m, H-1''), 4.12 (2H, m, H-3''), 4.40 (1H, d, H-11), 5.64 (1H, s, H-4), 6.69 (2H, m, H-3', H-5'), 7.06 (2H, m, H-2', H-6') ppm

^{13}C-NMR ($(CD_3)_2CO$): δ = 3.5 (q, C-21), 14.3 (q, C-18), 24.0 (t, C-15), 24.6 (t, C-4''), 26.6 (t, C-1), 26.8 (t, C-2''), 28.5 (t, C-7), 29.5 (t, C-2'''), 29.5 (t, C-3'''), 31.7 (t, C-6), 37.6 (t, C-2), 38.4 (q, N-CH_3), 39.7 (t, C-16), 39.9 (t, C-12), 40.2 (d, C-8), 40.4 (d, C-11), 47.8 (s, C-13), 49.9 (t, C-1''), 50.8 (d, C-14), 62.9 (t, C-3''), 80.1 (s, C-17), 81.5 (s, C-20), 84.3 (s, C-19), 113.2 (d, C-3', C-5'), 123.0 (d, C-4), 128.5 (d, C-2', C-6'), 129.8 (s, C-10), 133.3 (s, C-1'), 147.6 (s, C-9), 148.3 (s, C-4'), 157.0 (s, C-5), 172.7 (s, C-1'''), 173.3 (s, C-4'''), 198.2 (s, C-3) ppm

17β-Hydroxy-11β-[4-(12-hydroxy-1-methyl-9,12-dioxo-1-aza-8-oxa-dodecyl)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**39**)

39 was synthesized according to the procedure described for compound **38** reacting **10** (51.6 mg, 0.1 mmol) with succinic anhydride (10 mg, 0.1 mmol); the residue was purified by flash chromatography with EtOAc as eluent.

$C_{38}O_{49}NO_6$ (MW: 615.81)

Yield: 45 % (yellow lyophilisate)

TLC: R_f = 0.20 (E II), R_f = 0.18 (E VII)

Analytical HPLC: 95.4 %, t_R = 5.087 min (tracings: 3.1 %, t_R = 3.874 min; 1.5 %, t_R = 4.449 min)

UV/VIS (CH_2Cl_2): λ_{max} = 301.5 nm

IR (KBr): ν = 3434 (m), 2936 (m), 2863 (m), 2241 (w), 1734 (s), 1655 (s), 1612 (s), 1517 (m) cm^{-1}

^{1}H-NMR ($(CD_3)_2CO$): δ = 0.57 (3H, s, CH_3-18), 1.37 (2H, m, H-3''), 1.39 (1H, m, H-15), 1.41 (2H, m, H-4''), 1.43 (1H, m, H-7), 1.58 (2H, m, H-2''), 1.62 (2H, m, H-5''), 1.72 (1H, m, H-15), 1.75 (1H, m, H-14), 1.82 (3H, s, CH_3-21), 1.92 (1H, m, H-16), 2.06 (1H, m, H-7), 2.12 (1H, m, H-16), 2.23 (1H, m, H-2), 2.25 (1H, m, H-1), 2.28 (1H, m, H-12), 2.32 (1H, m, H-2), 2.36 (1H, m, H-12), 2.52 (1H, m, H-8), 2.57 (1H, m, H-6), 2.58 (4H, m, H-2''', H-3'''), 2.65 (1H, m, H-6), 2.82 (1H, m, H-1), 2.89 (3H, s, N-CH_3), 3.30 (1H, m, H-1''), 3.40 (1H, m, H-1''), 4.05 (2H, m, H-6''), 4.39 (1H, d, H-11), 5.64 (1H, s, H-4), 6.65 (2H, m, H-3', H-5'), 7.04 (2H, m, H-2', H-6') ppm

^{13}C-NMR ($(CD_3)_2CO$): δ = 3.5 (q, C-21), 14.3 (q, C-18), 24.0 (t, C-15), 24.6 (t, C-4''), 26.6 (t, C-1), 27.3 (t, C-2''), 27.3 (t, C-3''), 28.5 (t, C-7), 29.4 (t, C-5''), 29.4 (t, C-2'''), 29.4 (t, C-3'''), 31.6 (t, C-6), 37.5 (t, C-2), 38.4 (q, N-CH_3), 39.8 (t, C-16), 39.9 (t, C-12), 40.2 (d, C-8), 40.4 (d, C-11), 47.8 (s, C-13), 50.8 (d, C-14), 53.2 (t, C-1''), 64.8 (t, C-6''), 80.1 (s, C-17), 81.5 (s, C-20), 84.3 (s, C-19), 113.0 (d, C-3', C-5'), 123.0 (d, C-4), 128.4 (d, C-2', C-6'), 129.7 (s, C-10), 132.1 (s, C-1'), 147.7 (s, C-9), 148.4 (s, C-4'), 157.1 (s, C-5), 172.7 (s, C-1'''), 173.1 (s, C-4'''), 198.3 (s, C-3) ppm

17β-Hydroxy-11β-[4-(1-methyl-6,9-dioxo-1-aza-5,10-dioxa-undecyl)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**40**)

40 was synthesized according to general procedure III starting from **38** (20 mg, 0.035 mmol).

$C_{36}O_{45}NO_6$ (MW: 587.75)

Yield: 90 % (light yellow lyophilisate)

TLC: R_f = 0.76 (E II)

Analytical HPLC: 98.6%, t_R = 5.095 min (tracing: 1.4 %, t_R = 4.506 min)

UV/VIS (CH_2Cl_2): λ_{max} = 267.0, 300.0 nm

IR (KBr): ν = 3434 (m), 2947 (m), 2870 (m), 2241 (w), 1736 (s), 1658 (s), 1611 (s), 1517 (m) cm^{-1}

^{1}H-NMR $(CD_3)_2CO$): δ = 0.58 (3H, s, CH_3-18), 1.38 (1H, m, H-15), 1.42 (1H, m, H-7,), 1.72 (1H, m, H-15), 1.76 (1H, m, H-14), 1.83 (3H, s, CH_3-21), 1.90 (2H, m, H-2''), 1.92 (1H, m, H-16), 2.05 (1H, m, H-7), 2.12 (1H, m, H-16), 2.23 (1H, m, H-2), 2.25 (1H, m, H-1), 2.28 (1H, m, H-12), 2.33 (1H, m, H-2), 2.36 (1H, m, H-12), 2.53 (1H, m, H-8), 2.58 (1H, m, H-6), 2.62 (4H, m, H-2''', H-3'''), 2.64 (1H, m, H-6), 2.82 (1H, m, H-1), 2.90 (3H, s, N-CH_3), 3.42 (2H, m, H-1''), 3.63 (3H, s, OCH_3), 4.12 (2H, m, H-3''), 4.39 (1H, d, H-11), 5.65 (1H, s, H-4), 6.69 (2H, m, H-3', H-5'), 7.05 (2H, m, H-2', H-6') ppm

^{13}C-NMR $(CD_3)_2CO$): δ = 3.5 (q, C-21), 14.2 (q, C-18), 24.0 (t, C-15), 24.6 (t, C-4''), 26.6 (t, C-1), 26.7 (t, C-2''), 28.5 (t, C-7), 29.5 (t, C-2'''), 29.5 (t, C-3'''), 31.7 (t, C-6), 37.6 (t, C-2), 38.4 (q, N-CH_3), 39.7 (t, C-16), 39.9 (t, C-12), 40.1 (d, C-8), 40.4 (d, C-11), 47.8 (s, C-13), 49.9 (t, C-1''), 50.8 (d, C-14), 51.8 (q, OCH_3), 62.9 (t, C-3''), 80.2 (s, C-17), 81.5 (s, C-20), 84.3 (s, C-19), 113.2 (d, C-3', C-5'), 123.0 (d, C-4), 128.5 (d, C-2', C-6'), 129.8 (s, C-10), 133.3 (s, C-1'), 147.5 (s, C-9), 148.3 (s, C-4'), 157.0 (s, C-5), 172.7 (s, C-1'''), 173.3 (s, C-4'''), 198.2 (s, C-3) ppm

17β-Hydroxy-11β-[4-(1-methyl-9,12-dioxo-1-aza-8,13-dioxa-tetradecyl)-phenyl]-17α-(1-propinyl)-estra-4,9-dien-3-one (**41**)

41 was synthesized according to general procedure III starting from **39** (20 mg, 0.032 mmol).

$C_{39}O_{51}NO_6$ (MW: 629.83)

Yield: 90 % (light yellow lyophilisate)

TLC: R_f = 0.5 (E II)

UV/VIS (CH_2Cl_2): λ_{max} = 299.5 nm

IR (KBr): ν = 3434 (m), 2934 (m), 2858 (m), 2242 (w), 1736 (s), 1656 (s), 1612 (s), 1516 (m) cm^{-1}

^{1}H-NMR $(CD_3)_2CO$): δ = 0.58 (3H, s, CH_3-18), 1.37 (2H, m, H-3''), 1.39 (1H, m, H-15), 1.41 (3H, m, 2x(H-4''), H-7), 1.57 (2H, m, H-2''), 1.63 (2H, m, H-5''), 1.72 (1H, m, H-15), 1.74 (1H, m, H-14), 1.82 (3H, s, CH_3-21), 1.90 (1H, m, H-16), 2.03 (1H, m, H-7), 2.12 (1H, m, H-16), 2.23 (1H, m, H-2), 2.25 (1H, m, H-1), 2.28 (1H, m, H-12), 2.32 (1H, m, H-2), 2.36 (1H, m, H-12), 2.52 (1H, m, H-8), 2.57 (1H, m, H-6), 2.57 (4H, m, H-2''', H-3'''), 2.65 (1H, m, H-6), 2.82 (1H, m, H-1), 2.89 (3H, s, N-CH_3), 3.30 (1H, m, H-1''), 3.40 (1H, m, H-1''), 3.62 (3H, s, OCH_3), 4.05 (2H, m, H-6''), 4.39 (1H, d, H-11), 5.64 (1H, s, H-4), 6.65 (2H, m, H-3', H-5'), 7.04 (2H, m, H-2', H-6') ppm

^{13}C-NMR $(CD_3)_2CO$): δ = 3.5 (q, C-21), 14.3 (q, C-18), 24.0 (t, C-15), 24.6 (t, C-4''), 26.6 (t, C-1), 27.3 (t, C-2''), 27.3 (t, C-3''), 28.5 (t, C-7), 29.3 (t, C-5''), 29.4 (t, C-2'''), 29.4 (t, C-3'''), 31.6 (t, C-6), 37.5 (t, C-2), 38.4 (q, N-CH_3), 39.8 (t, C-16), 39.9 (t, C-12), 40.2 (d, C-8), 40.4 (d, C-11), 47.8 (s, C-13), 50.8 (d, C-14), 51.7 (q, OCH_3), 53.2 (t, C-1''), 64.8 (t, C-6''), 80.1 (s, C-17), 81.5 (s, C-20), 84.3 (s, C-19), 113.0 (d, C-3', C-5'), 123.0 (d, C-4), 128.5 (d, C-2', C-6'), 129.7 (s, C-10), 132.1 (s, C-1'), 147.7 (s, C-9), 148.4 (s, C-4'), 157.2 (s, C-5), 172.7 (s, C-1'''), 173.1 (s, C-4'''), 198.3 (s, C-3) ppm

17β-Hydroxy-11β-[4-(10-hydroxy-1-methyl-6-oxo-1-aza-5,7-dioxa-decyl)-phenyl]-

17α-(1-propinyl)-estra-4,9-dien-3-one (**42**)

42 was obtained as byproduct of the synthesis of **9** and purified by HPLC (column 2; acetonitrile : H_2O (60:40, vol/vol), flow: 23 mL/min; t_R = 6 min 35 sec).

$C_{35}H_{45}NO_3$ (MW: 575.74)

Yield: 5% (light yellow lyophilisate)

TLC: R_f = 0.23 (E I), R_f = 0.33 (E VI), R_f = 0.53 (E VII)

^{1}H-NMR ($CDCl_3$): 0.55 (3H, s, CH_3-18), 1.34 (1H, m, H-15), 1.45 (1H, m, H-7), 1.72 (1H, m, H-14), 1.73 (1H, m, H-15), 1.90 (3H, s, CH_3-21), 1.93 (2H, m, H-5''), 1.94 (3H, m, 2 × (H-2''), t, H-16), 2.01 (1H, m, H-7), 2.23 (1H, m, H-16), 2.25 (1H, H-12), 2.32 (1H, m, H-12), 2.35 (1H, m, H-2), 2.36 (1H, m, H-1), 2.44 (1H, m, H-2), 2.45 (1H, m, H-8), 2.57 (2H, m, H-6), 2.77 (1H, m, H-1), 2.90 (3H, s, N-CH_3), 3.41 (2H, m, H-1''), 3.74 (2H, m, H-6''), 4.17 (2H, m, H-3''), 4.29 (2H, m, H-4''), 4.34 (1H, d, J = 6.0, H-11), 5.76 (1H, s, H-4), 6.62 (2H, m, H-3', H-5'), 7.00 (2H, m, H-2', H-6')

^{13}C-NMR ($CDCl_3$): 3.8 (q, C-21), 13.7 (q, C-18), 23.3 (t, C-15), 25.8 (t, C-1), 26.2 (t, C-2''), 27.4 (t, C-7), 31.1 (t, C-6), 31.7 (t, C-5''), 36.9 (t, C-2), 38.3 (q, N-CH_3), 38.8 (t, C-12), 39.5 (d, C-11), 38.9 (t, C-16), 42.9 (t, C-1''), 46.9 (s, C-13), 49.2 (d, C-8), 49.9 (d, C-14), 59.1 (t, C-6''), 65. (t, C-4''), 65.9 (t, C-3''), 80.2 (s, C-17), 80.2 (s, C-19), 82.5 (s, C-20), 112.5 (d, C-3', C-5'), 122.7 (d, C-4), 127.7 (d, C-2', C-6'), 129.1 (s, C-10), 131.9 (s, C-1'), 146.8 (s, C-9), 147.1 (s, C-4'), 155,5 (s, C=O), 157.0 (s, C-5), 199.7 (s, C-3)

BIOLOGICAL TESTS

Alkaline Phosphatase Assay. T47-D breast cancer cells were coincubated with increasing concentrations of test compound (**2** – **41**, typically 10^{-11} to 10^{-7} mol/L) and progesterone (10^{-9} mol/L). The alkaline phosphatase assay was done as reported previously[S17, S18] with some minor modifications. After 48 h incubation cells were washed with 0.9% saline and stored at –80˚C for at least 30 min.. After thawing cells were incubated with 50µl *p*-nitrophenyl phosphate (5 mmol, Fluka) dissolved in aqueous diethanol amine (1M, supplemented with 0.5 mmol magnesium chloride and 20 µM zinc sulfate and adjusted to p_H 9.8) for 2-5 h in the dark at room temperature. Absorbance of *p*-nitrophenolate was measured in a Lucy 1 multimode plate reader (anthos labtec instruments) at 405 nm (vs. 690 nm as reference). For each compound, at least four independent experiments (with six data points each) were carried out. After background subtraction (absorbance of cells without hormonal treatment), absorbance was normalized to the absorbance resulting from the progesterone incubation. Median (central tendency) $\pm$ median absolute deviation (variability) were calculated. IC_{50} values were determined from dose-response curves and are given in nmol/L. Additionally, the relative potency was calculated as the ratio of the IC_{50} value of the reference antagonist (mifepristone, **1**) to the IC_{50} value of the test compound multiplied by 100 (see Tab 1).

Reporter Gene Assay. T47-D-Cl24 cells, i.e. T47-D cells stably transfected with the luciferase gene linked to the steroid hormone responsive MMTV promoter, were coincubated with increasing concentrations of test compound (**2** and **6** – **11**, 10^{-12} – 10^{-8} mol/L) and progesterone (10^{-9} mol/L). After 24 h incubation luciferase activities were measured by the Reporter Gene Luciferase Assay, Constant Light Signal (Roche Diagnostics) as recommended by the supplier in the Lucy 1 reader. For each compound, four independent experiments (with six data points each) were carried out using white 96-well plates. Luciferase activity is given as normalized response value relative to the luciferase activity induced by progesterone incubation. Median (central tendency) ± median absolute deviation

(variability) were calculated. IC_{50} values were determined from dose-response curves and are given in nmol/L. Again, the relative potency was calculated as the ratio of the IC_{50} value of the reference antagonist (mifepristone, **1**) to the IC_{50} value of the test compound multiplied by 100 (see Tab 1).

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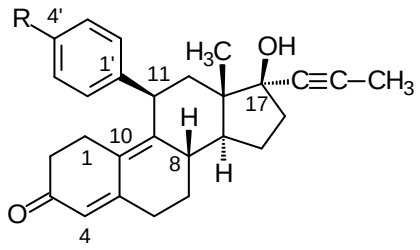
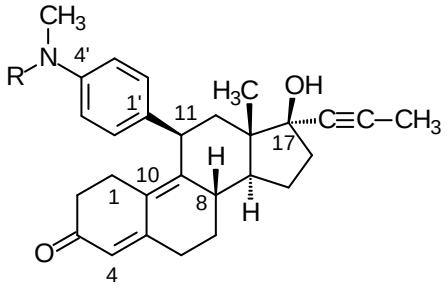
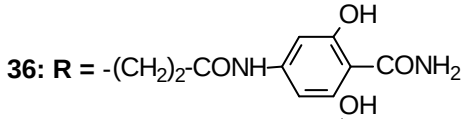
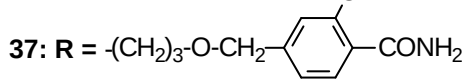


3: R = -OH
4: R = -OCH_3
5: R = -O-$(CH_2)_9$-Br



1: R = -CH_3
2: R = -H
6: R = -$(CH_2)_2$-CH_3
7: R = -$(CH_2)_5$-CH_3
8: R = -$(CH_2)_8$-CH_3
9: R = -$(CH_2)_2$-CH_2OH
10: R = -$(CH_2)_5$-CH_2OH
11: R = -$(CH_2)_5$- 
12: R = -$(CH_2)_5$-CHO
13: R = -$(CH_2)_2$-COOH
14: R = -$(CH_2)_5$-COOH
15: R = -$(CH_2)_7$-COOH
16: R = -$(CH_2)_{10}$-COOH
17: R = -$(CH_2)_2$-$COOCH_3$
18: R = -$(CH_2)_5$-$COOCH_3$
19: R = -$(CH_2)_7$-$COOCH_3$
20: R = -$(CH_2)_{10}$-$COOCH_3$
21: R = -$(CH_2)_5$-$CONH_2$
22: R = -$(CH_2)_5$-$CONHC_4H_9$
23: R = -CO-$(CH_2)_4$-CH_3
24: R = -CO-$(CH_2)_3$-COOH
25: R = -CO-$(CH_2)_4$-COOH
26: R = -CO-$(CH_2)_3$-$COOCH_3$
27: R = -CO-$(CH_2)_4$-$COOCH_3$
28: R = -CO-NH-C_4H_9
29: R = -CS-NH-C_4H_9
30: R = -CO-NH-(4-Cl-C_6H_4)
31: R = -CS-NH-(4-Cl-C_6H_4)
32: R = -CO-NH-$(CH_2)_5$-COOH
33: R = -CO-NH-$(CH_2)_5$-$COOCH_3$
34: R = -CO-NH-$(CH_2)_5$-CO-L-*Leu*-O-*t*-Bu
35: R = -CO-NH-$(CH_2)_5$-CO-L-*Leu*-OH
36: R = 
37: R = 
38: R = -$(CH_2)_2$-CH_2-OCO$(CH_2)_2$COOH
39: R = -$(CH_2)_5$-CH_2-OCO$(CH_2)_2$COOH
40: R = -$(CH_2)_2$-CH_2-OCO$(CH_2)_2$$COOCH_3$
41: R = -$(CH_2)_5$-CH_2-OCO$(CH_2)_2$$COOCH_3$
(**42: R =** -$(CH_2)_3$-OCO-O-$(CH_2)_3$-OH)

Scheme 3. Structures of compounds **1** – **42**.