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Abstract: The four possible isomers of each of 3-methoxy- and 3-benzyloxyestra-1,3,5(10)-trien-17-ols (5-8 and 9-12) were converted through 16-p-tosyloxymethyl- or 16-bromomethyl derivatives into their 3-methoxy- and 3-benzyloxy-16-azidomethylestra(1,3,5(10)-triene derivatives (13-16 and 17-20). The regioselective Cu(I)-catalyzed 1,3-dipolar cycloaddition of these compounds with different terminal alkynes afforded novel 1,4-disubstituted diastereomers (21a-f, 22a-f, 23a-f, 24a-f and 25a-f, 26a-f, 27a-f, 28a–f). The antiproliferative activities of the structurally related triazoles were determined in vitro with the microculture tetrazolium assay on four malignant human cell lines of gynecological origin (Hela, SiHa, MCF-7 and MDA-MB-231).

**Detailed Response to Reviewers**

Response to Reviewer's comments:

Reviewer 1:

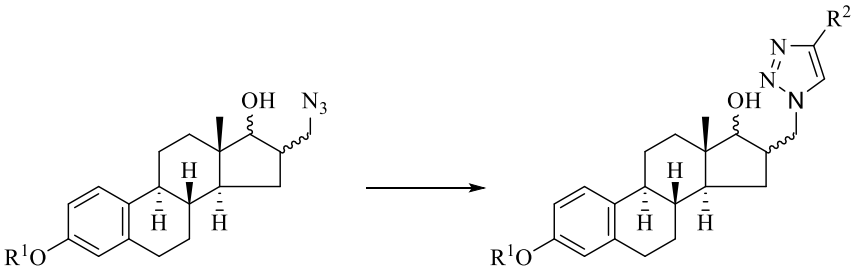
1. Graphical abstract have been uploaded.
2. Absolute configuration of compounds **5** and **8** has been unambigously discussed in Ref. 5 and 6, and in the Figure 1. of the present manuscript.
3. Corrected.
4. Corrected.

Reviewer 2:

1. Graphical abstract have been uploaded.
2. Corrected.
3. Copies of NMR spectra have been uploaded.
4. Corrected, and highlighted in yellow.

Thank you for your reviews.

**Graphical Abstract (for review)**




| | C-16 | C-17 | $R^1$ |
|---|---|---|---|
| **13** | β | β | Me |
| **14** | α | β | |
| **15** | β | α | |
| **16** | α | α | |
| **17** | β | β | Bn |
| **18** | α | β | |
| **19** | β | α | |
| **20** | α | α | |

| | C-16 | C-17 | $R^1$ |
|---|---|---|---|
| **21** | β | β | Me |
| **22** | α | β | |
| **23** | β | α | |
| **24** | α | α | |
| **25** | β | β | Bn |
| **26** | α | β | |
| **27** | β | α | |
| **28** | α | α | |

| | $IC_{50}$ (μM) MDA-MB-231 |
|---|---|
| **25b** | 3.33 |
| **25c** | 5.91 |
| **26e** | 5.69 |
| **27c** | 6.74 |

| **21–28** | $R^2$ |
|---|---|
| a | cyclopropyl |
| b | cyclopentyl |
| c | cyclohexyl |
| d | phenyl |
| e | $CH_2$-OCO-*p*-$NO_2$-phenyl |
| f | $CH_2OH$ |

Highlights

1. Synthesis of 3-methoxy- and 3-benzyloxy-16-azidomethylestra(1,3,5(10)-trienes.

2. CuAAC reaction of 16-azidomethyl steroidal compounds with different terminal alkynes.

3. Substantial antiproliferative activity for 3-benzyl-16-triazolylmethylene derivatives.

# Stereocontrolled Synthesis of the Four Possible 3-Methoxy and 3-Benzyloxy-16-Triazolyl-methyl-estra-17-ol Hybrids and their Antiproliferative Activities

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ABSTRACT The four possible isomers of each of 3-methoxy- and 3-benzyloxyestra-1,3,5(10)-trien-17-ols (**5**–**8** and **9**–**12**) were converted through 16-*p*-tosyloxymethyl- or 16-bromomethyl derivatives into their 3-methoxy- and 3-benzyloxy-16-azidomethylestra(1,3,5(10)-triene derivatives (**13**–**16** and **17**–**20**). The regioselective Cu(I)-catalyzed 1,3-dipolar cycloaddition of these compounds with different terminal alkynes afforded novel 1,4-disubstituted diastereomers (**21a–f, 22a–f, 23a–f, 24a–f** and **25a–f, 26a–f, 27a–f, 28a–f**). The antiproliferative activities of the structurally related triazoles were determined *in vitro* with the microculture tetrazolium assay on four malignant human cell lines of gynecological origin (Hela, SiHa, MCF-7 and MDA-MB-231).

*Keywords:* 3-methoxy- and 3-benzyloxy-16-azidomethylestra-1,3,5(10)-triene-17-ols; 1,3-dipolar cycloaddition, 4′substituted-steroid triazoles; cytotoxic activity

## 1. Introduction

Among the hybrid natural products, hybrids of steroid frameworks have attracted great attention due to significant biological properties and numerous therapeutic effects of the basic compound. Steroids have become ideal synthons for the development of diverse conjugates due to their rigid framework and potential for varying levels of functionalization, broad biological activity profile and their ability to penetrate the cell membranes and bind to specific hormonal receptors [1-3].

The place, length and orientation of the linkers between the two parts of the hybrids stems unequivocally from the method of their synthesis. The literature provides a large number of methods to introduce the linker onto the sterane skeleton. The effect of the length and character of the linker are very often discussed [4]. However, only limited information is available with respect to the steric effect of the linkers on biological properties. As concerns the 16-substituted estrogenes, usually the 16α-substituted-17β-hydroxy compounds have been studied. The biological activity has generally not been studied for the whole isomer series [5].

In the 16-substituted 17-hydroxysteroids, the two chiral centres permit four stereochemical modifications. Since availability of the complete series of isomers would permit a number of interesting comparative examinations.

We have previously reported the preparation and configurational assignment of the four possible isomers of the 3-methoxy- and 3-benzyloxy-16-hydroxymethyl-estra-1,3,5(10)-trien-17-ol derivatives (**5a**–**8a** and **9a**–**12a**) [6–8]. Treatment of 3-methoxy- and 3-benzyloxyestra-16-hydroxymethylidene-estra-1,3,5(10)-trien-17-ones (**2** and **4**). The C-16 formyl compounds were reduced with $KBH_4$ in methanol yielding a mixture of three (**5a**–**7a** and **9a**–**11a**) of the four possible isomers of each of the 3-methoxy- and 3-benzyloxy-16-hydroxymethylestra-1,3,5(10)-trien-17-ol isomers in a ratio of 50:45:5 in 94% yield [6,8 ]. The fourth isomers (**8a** and **12a**) were prepared from 16α-acetoxymethyl-17β-toluenesulfonate mixed esters **6d** and **10d**, respectively, by neighbouring group participation during solvolysis in aqueous AcOH. The structures of the isomers were confirmed unambiguously by their IR, $^{1}H$ and $^{13}C$ NMR spectra (Scheme 1) [7,8].

**(Scheme 1)**

The four 3-methoxy- and 3-benzyloxy-estra-1,3,5(10)-trien-17-ol isomers (**5a**–**8a** and **9a**–**12a**) are suitable starting materials to prepare 16-triazolyl-methyl derivatives. Triazoles are

attractive units because of their stability against metabolic degradation and their ability to form hydrogen bonds. The Cu(I)-catalysed azide–alkyne cycloaddition (CuAAC) is a facile method of wide applicability for the introduction of a triazole moiety into natural products [9]. In these compounds the triazole heterocycles and their substituted derivatives are connected through a methylene linker to the sterane skeleton. The 16-*p*-tolylsulfonyloxymethyl ester [5,6] and 16-bromomethyl derivatives [10] of the 16-hydroxymethyl starting materials were used for substitution reaction with $NaN_3$ in *N*,*N*-dimethylformamide to have the desired 3-methoxy- and 3-benzyloxy-16-azidomethylestra-1,3,5(10)-trien-17-ols (**13**–**16** and **17**–**20**). From these azido compounds several D-ring-substituted estrane derivatives containing a 1,2,3-triazole ring were synthesized by the reaction of **13**–**16** and **17**–**20** with various terminal alkynes through the use of the "click" chemistry approach to deliver compounds **21a**–**e**, **22a**–**e**, **23a**–**e, 24a**–**e, 25a**–**e, 26a**–**e, 27a**–**e** and **28a**–**e**.

## 2. Experimental

### *2.1. General*

Melting points (Mp) were determined on a Kofler block and are uncorrected. Specific rotations were measured in $CHCl_3$ (*c* 1) at 20 °C with a POLAMAT-A (Zeiss-Jena) polarimeter and are given in units of $10^{-1}$ deg $cm^2$ $g^{-1}$. Elementary analysis data were determined with a Perkin-Elmer CHN analyzer model 2400. The reactions were monitored by TLC on Kieselgel-G (Merck Si 254 F) layers (0.25 mm thick); solvent systems (ss): (A) diisopropyl ether, (B) acetone/toluene/hexane (30:35:35 v/v). The spots were detected by spraying with 5% phosphomolybdic acid in 50% aqueous phosphoric acid. The $R_f$ values were determined for the spots observed by illumination at 254 and 365 nm. Flash chromatography: silica gel 60, 40–63 μm. All solvents were distilled prior to use. NMR spectra were recorded on a Bruker DRX 500 and Bruker Ascend 500 instrument at 500 ($^1$H NMR) or 125 MHz ($^{13}$C NMR). Chemical shifts are reported in ppm (δ scale) and coupling constants (*J*) in Hertz. For the determination of multiplicities, the *J*-MOD pulse sequence was used.

### *2.2. 3-Methoxy- and 3-benzyloxy-16-azidomethylestra-1,3,5(10)-trienes (**13**–**16** and **17**–**20**)*

*General procedure*

Compounds **5b**–**8b** [5,6] (4.70 g, 10 mmol) or **9c**–**12c** [] (4.55 g, 10 mmol) were dissolved in *N*,*N*-dimethylformamide (100 ml) and then $NaN_3$ (2.6 g) was added. The mixture was stirred for 12 h at 80 °C, then poured into water (500 ml). The precipitate separating out was filtered off and subjected to chromatographic separation with $CH_2Cl_2$/hexane in different ratios.

*2.2.1. 3-Methoxy-16β-azidomethyl-estra-1,3,5(10)-trien-17β-ol (**13**)*

Compound **5b** (470 mg, 1 mmol) was used for the synthesis as described in Section 2.2. The crude product was chromatographed on silica gel with $CH_2Cl_2$/hexane (1:3 v/v) to yield pure **13** (318 mg, 93%). Mp 134–135 °C; $R_f$ = 0.65 (ss A); $[\alpha]_D^{20}$ = + 80 (*c* 1 in $CHCl_3$). (Found C, 70.23; H, 8.05. $C_{20}H_{27}N_3O_2$ (341.45) requires C, 70.35; H, 7.97%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.82 (s, 3H, 18-$H_3$), 2.87 (m, 2H, 6-$H_2$), 3.32 (dd, 1H, *J* = 12.5 Hz, *J* = 7.5 Hz, 16a-$H_2$), 3.61 (dd, 1H, *J* = 12.5 Hz, *J* = 7.5 Hz, 16a-$H_2$), 3.78 (s, 3H, 3-$OCH_3$), 3.87 (d, 1H, *J* = 10.0 Hz, 17-H), 6.64 (d, 1H, *J* = 2.5 Hz, 4-H), 6.72 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.20 (d, 1H, *J* = 8.5 Hz, 1-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 12.2 (C-18), 26.3, 27.5, 29.7, 30.4, 37.7, 38.2, 40.2, 44.0, 44.3 (C-13), 49.0, 53.4 (C-16a), 55.2 (3-$OCH_3$), 81.5 (C-17), 111.6 (C-2), 113.9 (C-4), 126.2 (C-1), 132.5 (C-10), 137.9 (C-5), 157.7 (C-3).

*2.2.2. 3-Methoxy-16α-azidomethylestra-1,3,5(10)-trien-17β-ol (**14**)*

Compound **6b** (470 mg, 1 mmol) was used for the synthesis as described in Section 2.2. The crude product was chromatographed on silica gel with $CH_2Cl_2$/hexane (1:3 v/v) to yield pure **14** (287 mg, 84%). Mp 85–86 °C; $R_f$ = 0.62 (ss A); $[\alpha]_D^{20}$ = + 48 (*c* 1 in $CHCl_3$). (Found C, 70.42; H, 7.65. $C_{20}H_{27}N_3O_2$ (341.45) requires C, 70.35; H, 7.97%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.84 (s, 3H, 18-$H_3$), 2.86 (m, 2H, 6-$H_2$), 3.43 (d, 1H, *J* = 7.5 Hz, 17-H), 3.48 (dd, 2H, *J* = 6.5 Hz, J = 3.5 Hz, 16a-$H_2$), 3.78 (s, 3H, 3-$OCH_3$), 6.63 (s, 1H, 4-H), 6.72 (dd, 1H, *J* = 6.5 Hz, *J* = 2.0 Hz, 2-H), 7.20 (d, 1H, *J* = 8.5 Hz, 1-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 11.8 (C-18), 26.1, 27.2, 28.0, 29.7, 36.6, 38.5, 43.6, 43.9, 44.2 (C-13), 48.5, 55.2 (3-$OCH_3$), 55.6 (C-16a), 85.1 (C-17), 111.5 (C-2), 113.8 (C-4), 126.3 (C-1), 132.4 (C-10), 137.8 (C-5), 157.5 (C-3).

*2.2.3. 3-Methoxy-16β-azidomethylestra-1,3,5(10)-trien-17α-ol (**15**)*

Compound **7b** (470 mg, 1 mmol) were used for the synthesis as described in Section 2.2. The

crude porduct was chromatographed on silica gel with $CH_2Cl_2$/hexane (1:3 v/v) to yield pure **15** (275 mg, 80%). Mp 96–98; °C; $R_f$ = 0.60 (ss A); $[\alpha]_D^{20}$ = + 68 (*c* 1 in $CHCl_3$). (Found C, 70.26; H, 8.15. $C_{20}H_{27}N_3O_2$ (341.45) requires C, 70.35; H, 7.97%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.76 (s, 3H, 18-$H_3$), 2.86 (m, 2H, 6-$H_2$), 3.43 (dd, 2H, *J* = 7.5 Hz, J = 3.0 Hz, 16a-$H_2$), 3.61 (s, 1H, 17-H), 3.78 (s, 3H, 3-$OCH_3$), 6.64 (d, 1H, *J* = 2.5 Hz, 4-H), 6.72 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.22 (d, 1H, *J* = 8.5 Hz, 1-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 17.7 (C-18), 25.9, 27.9, 29.8, 30.3, 31.9, 38.6, 43.3, 45.0 (C-13), 48.9, 55.2 (3-$OCH_3$), 55.6 (C-16a), 83.0 (C-17), 111.5 (C-2), 113.8 (C-4), 126.3 (C-1), 132.4 (C-10), 137.9 (C-5), 157.5 (C-3).

*2.2.4. 3-Methoxy-16α-azidomethylestra-1,3,5(10)-trien-17α-ol (**16**)*

Compound **8b** (470 mg, 1 mmol) was used for the synthesis as described in Section 2.2. The crude product was chromatographed on silica gel with $CH_2Cl_2$/hexane (1:3 v/v) to yield pure **16** (283 mg, 86%). Mp 118–120 °C; $R_f$ = 0.65 (ss A); $[\alpha]_D^{20}$ = + 34 (*c* 1 in $CHCl_3$). (Found C, 70.55; H, 7.78. $C_{20}H_{27}N_3O_2$ (341.45) requires C, 70.35; H, 7.97%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.80 (s, 3H, 18-$H_3$), 2.87 (m, 2H, 6-$H_2$), 3.35 (dd, 1H, *J* = 12.0 Hz, *J* = 6.0 Hz, 16a-$H_2$), 3.53 (dd, 1H, *J* = 12.0 Hz, *J* = 9.5 Hz, 16a-$H_2$), 3.78 (s, 3H, 3-$OCH_3$), 3.84 (d, 1H, *J* = 6.0 Hz, 17-H), 6.63 (d, 1H, *J* = 2.5 Hz, 4-H), 6.72 (dd, 1H, *J* = 8.5 Hz, 2-H), 7.21 (d, 1H, *J* = 8.5 Hz, 1-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 17.3 (C-18), 26.1, 28.0, 29.2, 31.3, 39.1, 40.5, 43.6, 46.4 (C-13), 47.0, 52.4 (C-16a), 55.2 (3-$OCH_3$), 79.9 (C-17), 111.6 (C-2), 114.0 (C-4), 126.3 (C-1), 132.7 (C-10), 137.9 (C-5), 157.6 (C-3).

*2.2.5. 3-Benzyloxy-16β-azidomethylestra-1,3,5(10)-trien-17β-ol (**17**)*

Compound **9c** (455 mg, 1 mmol) was used for the synthesis as described in Section 2.2. The crude product was chromatographed on silica gel with $CH_2Cl_2$/hexane (1:1 v/v) to yield pure **17** (250 mg, 59%). Mp 115–117 °C; $R_f$ = 0.45 (ss A). (Found C, 74.55; H, 7.64. $C_{26}H_{31}N_3O_2$ (417.54) requires C, 74.79; H, 7.48%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.82 (s, 3H, 18-$H_3$), 2.86 (m, 2H, 6-$H_2$), 3.33 (dd, 1H, *J* = 12.0 Hz, *J* = 7.5 Hz, 16a-$H_2$), 3.60 (dd, 1H, *J* = 12.5 Hz, *J* = 7.5 Hz, 16a-$H_2$), 3.87 (d, 1H, *J* = 9.5 Hz, 17-H), 5.04 (s, 2H, Bn-$H_2$), 6.73 (s, 1H, 4-H), 6.79 (d, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz, 2-H), 7.21 (d, 1H, *J* = 8.0 Hz, 1-H), 7.32 (t, 1H, *J* = 7.5 Hz, 4'-H), 7.39 (t, 2H, *J* = 7.5 Hz, 3'-H and 5'-H), 7.44 (d, 2H, *J* = 7.5 Hz, 2'-H and 6'-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 12.2 (C-18), 26.2, 27.5, 29.7, 30.3, 37.6, 38.1, 40.1, 43.9, 44.2 (C-13), 48.8 (C-16), 53.3 (C-16a),

69.9 (Bn-$CH_2$), 81.5 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.3 (C-2' and C-6'), 127.8 (C-4'), 128.5 (C-3' and C-5'), 132.7 (C-10), 137.3 (C-1'), 137.9 (C-5), 156.8 (C-3).

*2.2.6. 3-Benzyloxy-16α-azidomethylestra-1,3,5(10)-trien-17β-ol (**18**)*

Compound **10c** (455 mg, 1 mmol) was used for the synthesis as described in Section 2.2. The crude product was chromatographed on silica gel with $CH_2Cl_2$/hexane (3:1 v/v) to yield pure **18** (254 mg, 61%). Mp 75–77 $^oC$; $R_f$ = 0.40 (ss A). (Found C, 74.87; H, 7.32. $C_{26}H_{31}N_3O_2$ (417.54) requires C, 74.79; H, 7.48%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.84 (s, 3H, 18-$H_3$), 2.85 (m, 2H, 6-$H_2$), 3.44 (t, 1H, *J* = 8.0 Hz, 17-H), 3.48 (m, 2H, 16a-$H_2$), 5.04 (s, 2H, Bn-$H_2$), 6.73 (s, 1H, 4-H), 6.79 (d, 1H, J = 8.5 Hz, 2-H), 7.21 (d, 1H, *J* = 8.5 Hz, 1-H), 7.32 (t, 1H, *J* = 7.0 Hz, 4'-H), 7.39 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.44 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 11.8 (C-18), 26.1, 27.2, 27.9, 29.7, 36.6, 38.5, 43.6, 43.9, 44.2 (C-13), 48.6 (C-16), 55.6 (C-16a), 69.9 (Bn-$CH_2$), 85.1 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-2' and -6'), 127.8 (C-4'), 128.5 (C-3' and -5'), 132.7 (C-10), 137.3 (C-1'), 137.9 (C-5), 156.8 (C-3).

*2.2.7. 3-Benzyloxy-16β-azidomethyl-estra-1,3,5(10)-trien-17α-ol (**19**)*

Copound **11c** (455 mg, 1 mmol) was used for the synthesis as described in Section 2.2. The crude product was chromatographed on silica gel with $CH_2Cl_2$/hexane (3:1 v/v) to yield pure **19** (23. mg, 40%). Mp. 134-136 $^oC$. $R_f$ = 0.38 (ss A). (Found C, 74.92; H, 7.37. $C_{26}H_{31}N_3O_2$ (417.54) requires C, 74.79; H, 7.48%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.84 (s, 3H, 18-$H_3$), 2.85 (m, 2H, 6-$H_2$), 3.43 (d, 2H, *J* = 8.0 Hz, 17-H), 3.48 (t, 2H, J = 6.5 Hz, 16a-$H_2$), 5.04 (s, 2H, Bn-$H_2$), 6.73 (s, 1H, 4-H), 6.79 (d, 1H, *J* = 8.0 Hz, 2-H), 7.22 (d, 1H, *J* = 8.0 Hz 1-H), 7.33 (d, 1H, *J* = 7.0 Hz, 4'-H), 7.39 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.44 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 11.8 (C-18), 26.1, 27.2, 28.0, 29.7, 36.6, 38.4, 43.5, 43.9, 44.1 (C-13), 48.5 (C-16), 55.6 (C-16a), 69.9 (Bn-$CH_2$), 85.1 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-2' and -6'), 127.8 (C-4'), 128.5 (C-3' and -5'), 132.7 (C-10), 137.3 (C-1'), 137.9 (C-5), 156.7 (C-3).

*2.2.8. 3-Benzyloxy-16α-azidomethyl-estra-1,3,5(10)-trien-17α-ol (**20**)*

Compound **12c** (455 mg, 1 mmol) was used for the synthesis as described in Section 2.2. The crude was chromatographed on silica gel with $CH_2Cl_2$/hexane (1:1 v/v) to yield pure **20** (330 mg, 79%). Mp 90–92 $^oC$. $R_f$ = 0.45 (ss A). (Found C, 74.68; H, 7.55. $C_{26}H_{31}N_3O_2$ (417.54) requires C,

74.79; H, 7.48%). $^{1}$H NMR (δ, ppm, $CDCl_3$): 0.79 (s, 3H, 18-$H_3$), 2.71 (m, 2H, 6-$H_2$), 3.35 (dd, 1H, *J* = 12.0 Hz, *J* = 6.5 Hz, 16a-$H_2$), 3.52 (dd, 1H, *J* = 12.0 Hz, *J* = 6.5 Hz, 16a-$H_2$), 3.84 (d, 1H, *J* = 5.0 Hz, 17-H), 5.04 (s, 2H, Bn-$H_2$), 6.73 (s, 1H, 4-H), 6.79 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.22 (d, 1H, *J* = 8.5 Hz, 1-H), 7.33 (t, 1H, *J* = 7.5 Hz, 4'-H), 7.39 (t, 2H, *J* = 7.5 Hz, 3'- and 5'-H), 7.44 (d, 2H, *J* = 7.5 Hz, 2'- and 6'-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 17.2 (C-18), 26.0, 27.9, 29.0, 29.7, 31.2, 38.9, 40.4, 43.5, 46.3 (C-13), 46.8 (C-16), 52.2 (C-16a), 69.9 (Bn-$CH_2$), 79.7 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-2' and -6'), 127.8 (C-4'), 128.5 (C-3' and -5'), 132.8 (C-10), 137.3 (C-1'), 138.0 (C-5), 156.7 (C-3).

*2.3. General procedure for the synthesis of triazoles (**21a–e**, **22a–e**, **23a–e, 24a–e**, **25a–e**, **26a–e**, **27a–e**, and **28a–e**)*

3-Methoxy-16-azidomethylestra-1,3,5(10)-trien-17-ol isomers (**13**–**16**) (342 mg, 1 mmol) or 3-benzyloxy-16-azidomethylestra-1,3,5(10)-trien-17-ol isomers (**17**–**20**) 418 mg, 1 mmol) were dissolved in $CH_2Cl_2$ (20 ml), then CuI (19 mg, 0.10 mmol), $Et_3N$ (0.2 ml, 2 mmol) and the appropriate terminal alkynes (2 mmol) were added. The mixtures were stirred under reflux for 24 h, then diluted with water (30 ml) and extracted with $CH_2Cl_2$ (2 × 30 ml). The combined organic phases were dried over $Na_2SO_4$ and evaporated *in vacuo*. The crude products were purified by flash chromatography using $CH_2Cl_2$/ethyl acetate in different ratios.

*2.3.1. 3-Methoxy-16β-(4'-cyclopropyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**21a**)*

Compound **13** (342 mg, 1 mmol) and cyclopropylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with $CH_2Cl_2$/hexane (3:1 v/v) to yield pure **21a** (210 mg, 51%) as a white solid. Mp: 189–191 $^{o}$C; $R_f$ = 0.44 (ss B). (Found C, 73.84; H, 7.98. $C_{25}H_{33}N_3O_2$ (407.55) requires C, 73.68; H, 8.16%). $^{1}$H NMR (δ, ppm, $CDCl_3$): 0.80 (s, 3H, 18-$H_3$), 0.83 (s, 2H, cyclopropyl-$H_2$), 0.94 (s, 2H, cyclopropyl-$H_2$), 2.72 (d, 1H, *J* = 7.0 Hz, 1"-H), 2.84 (m, 2H, 6-$H_2$), 3.77 (s, 3H, 3-$OCH_3$), 3.93 (d, 1H, *J* = 9.5 Hz, 17-H), 4.21 (dd, 1H, *J* = 13.0 Hz, *J* = 6.0 Hz, 16a-$H_2$), 4.62 (t, 1H, *J* = 8.0 Hz, 16a-$H_2$), 6.62 (s, 1H, 4-H), 6.71 (d, 1H, *J* = 8.5 Hz, 2-H), 7.20 (d, 1H, *J* = 8.5 Hz, 1-H), 7.29 (s, 1H, 5'-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 6.7 (C-1"), 7.68 (C-2" and -3"),12.3 (C-18), 26.2, 27.4,

29.7, 30.8, 37.5, 38.0, 41.4, 43.8, 44.3 (C-16a), 48.7, 51.7 (C-13), 55.2 (3-$OCH_3$), 80.7 (C-17), 111.5 (C-2), 113.8 (C-4), 126.3 (C-1), 132.4 (C-10), 137.8 (C-5), 157.5 (C-3).

*2.3.2. 3-Methoxy-16β-(4'-cyclopentyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**21b**)*

Compound **13** (342 mg, 1 mmol) and cyclopentylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with $CH_2Cl_2$ to yield pure **21b** (370 mg, 85%) as a white solid. Mp: 191–192 $^oC$; $R_f$= 0.46 (ss B). (Found C, 74.62; H, 8.42. $C_{27}H_{37}N_3O_2$ (435.60) requires C, 74.45; H, 8.56%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.79 (s, 3H, 18-$H_3$), 2.85 (m, 2H, 6-$H_2$), 3.19 (s, 1H, 1"-H), 3.77 (s, 3H, 3-$OCH_3$), 3.94 (d, 1H, *J* = 9.5 Hz, 17-H), 4.24 (d, 1H, *J* = 8.0 Hz, 16a-$H_2$), 4.65 (s, 1H, 16a-$H_2$), 6.62 (s, 1H, 4-H), 6.71 (d, 1H, *J* = 8.5 Hz, 2-H), 7.20 (d, 1H, *J* = 8.5 Hz, 1-H), 7.34 (s, 1H, 5'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 12.3 (C-18), 25.1 (C-3" and -4"), 26.2, 27.4, 29.7 (C-2" and 5"), 30.8, 33.2, 36.7, 37.5, 38.0, 42.4 (C-16a), 43.8, 44.3 (C-13), 48.7, 51.8, 55.2 (3-$OCH_3$), 62.1 (C-16), 80.7 (C-17), 111.5 (C-2), 113.7 (C-4), 126.3 (C-1), 132.4 (C-10), 137.8 (C-5), 157.4 (C-3).

*2.3.3. 3-Methoxy-16β-(4'-cyclohexyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**21c**)*

Compound **13** (342 mg, 1 mmol) and cyclohexylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **21c** (370 mg, 82%) as a white solid. Mp: 189–190 $^oC$; $R_f$= 0,40 (ss B). (Found C, 74.92; H, 8.55. $C_{28}H_{41}N_3O_2$ (449.63) requires C, 74.80; H, 8.74%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.79 (s, 3H, 18-$H_3$), 2.84 (m, 2H, 6-$H_2$), 3.77 (s, 3H, 3-$OCH_3$), 3.94 (d, 1H, *J* = 9.5 Hz, 17-H), 4.24 (m, 1H, 16a-$H_2$), 4.65 (m, 1H, 16a-$H_2$), 6.62 (s, 1H, 4-H), 6.71 (d, 1H, *J* = 8.5 Hz, 2-H), 7.20 (d, 1H, *J* = 8.5 Hz, 1-H), 7.32 (s, 1H, 5'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 12.3 (C-18), 26.0, 26.1 (C-2" and -6"), 26.2, 27.4, 29.7, 30.8, 33.0, 37.5, 38.0, 41.4 (C-1"), 43.8, 44.3 (C-13), 48.3, 55.2 (3-$OCH_3$), 62.1, 80.7 (C-17), 111.5 (C-2), 113.7 (C-4), 126.3 (C-1), 132.4 (C-10), 137.8 (C-5), 157.4 (C-3).

*2.3.4. 3-Methoxy-16β-(4'-phenyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**21d**)*

Compound **13** (342 mg, 1 mmol) and phenylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **21d** (368 mg, 83%) as a white solid. Mp: 232–234 $^oC$; $R_f$= 0.35 (ss B). (Found C, 75.98; H, 7.36. $C_{28}H_{33}N_3O_2$ (443.58) requires C, 75.81; H, 7.50%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.79 (s, 3H, 18-$H_3$), 2.73 (m, 2H, 6-$H_2$), 3.68 (s, 3H, 3-$OCH_3$), 3.79 (d, 1H, *J* = 10.0 Hz, 17-H), 4.20 (t, 1H, *J* = 13.5 Hz, 16a-$H_2$), 4.63 (dd, 1H, *J* = 13.5 Hz, *J* = 4.5 Hz, 16a-$H_2$), 6.59 (s, 1H, 4-H), 6.67 (d, 1H, *J* = 8.5 Hz, 2-H), 7.16 (d, 1H, *J* = 8.5 Hz, 1-H), 7.32 (t, 1H, *J* = 7.5 Hz, 4”-H), 7.44 (t, 2H, *J* = 7.5 Hz, 3”- and 5”-H), 7.85 (d, 2H, *J* = 7.5 Hz, 2”- and 6”-H), 8.60 (s, 1H, 5’-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 12.4 (C-18), 25.8, 26.9, 29.1, 30.0, 36.9, 37.8, 40.4, 43.3, 43.7 (C-13), 47.8, 52.3 (C-16a), 54.8 (3-$OCH_3$), 79.5 (C-17), 111.4 (C-2), 113.3 (C-4), 121.5 (C-5’), 124.5 (C-2” and -6”), 126.0 (C-1), 127.6 (C-4”), 127.8 (C-3” and -5”), 130.9 (C-1”), 132.0 (C-10), 137.3 (C-5), 146.0 (C-4’), 156.9 (C-3).

*2.3.5. 3-Methoxy-16β-(4’-nitro-benzoyloxymethyl-1’H-1’,2,’3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17β-ol (**21e**)*

Compound **13** (342 mg, 1 mmol) and propargyl 4-nitrobenzoate (2 mmol, 410 mg) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **21e** (475 mg, 86%) as a yellow solid. Mp: 134–135.5 $^oC$; $R_f$= 30 (ss B). (Found C, 66.12; H, 6.08. $C_{30}H_{34}N_4O_6$ (546.61) requires C, 65.92; H, 6.27%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.73 (s, 3H, 18-$H_3$), 2.70 (m, 2H, 6-$H_2$), 3.66 (s, 3H, 3-$OCH_3$), 4.18 (dd, 1H, *J* = 13.5 Hz, *J* = 11.5 Hz, 16a-H2), 4.58 (dd, 1H, *J* = 13.5 Hz, *J* = 4.5 Hz, 16a-$H_2$), 5.02 (d, 1H, *J* = 4.5 Hz, 17-H), 5.44 (s, 2H, 4’-$H_2$), 6.55 (d, 1H, *J* = 1.5 Hz, 4-H), 6.63 (dd, 1H, *J* = 8.5 Hz, *J* = 2.0 Hz, 2-H), 7.12 (d, 1H, *J* = 8.5 Hz, 1-H), 8.16 (d, 2H, *J* = 8.5 Hz, 3”- and 5”-H), 8.31 (t, 3H, *J* = 8.5 Hz, 2”- and 6”-H, 5’-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 12.3 (C-18), 25.8, 26.9, 29.1, 30.0, 36.9, 37.8, 40.4, 43.3, 43.7 (C-13), 47.8, 52.2 (C-16a), 54.7 (3-$OCH_3$), 58.7 (4’-$CH_2$), 79.5 (C-17), 111.3 (C-2), 113.3 (C-4), 123.8 (C-2” and -6”), 125.1 (C-5’), 126.0 (C-1), 130.6 (C-3” and -5”), 131.9 (C-10), 134.7 (C-1”), 137.2 (C-5), 141.0 (C-4”), 150.2 (C-4’), 156.9 (C-3), 163.9 (C=O).

*2.3.6. 3-Methoxy-16β-(4’-hydroxymethyl-1’H-1’,2’,3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17β-ol (**21f**)*

Compound **13** (274 mg, 0.5 mmol) was dissolved in methanol (10 ml) containing $NaOCH_3$ (14 mg, 0.25 mmol), and the solution was allowed to stand for 24 h. It was then diluted with water, and the precipitate separating out was filtered off and recrystallized from a mixture of ethyl acetate/hexane to afford **21f** (171 mg, 86%) as a white crystalline material. Mp: 194–195 $^{o}$C; $R_f$= 0.25 (ss B). (Found C, 69.23; H, 8.04. $C_{23}H_{31}N_3O_3$ (397.51) requires C, 69.49; H, 7.86%). $^1$H NMR (δ, ppm, DMSO-$d_6$): 0.76 (s, 3H, 18-$H_3$), 2.71 (m, 2H, 6-$H_2$), 3.68 (s, 3H, 3-$OCH_3$), 3.76 (d, 1H, *J* = 5.5 Hz, 17-H), 4.14 (t, 1H, *J* = 12.5 Hz, 16a-$H_2$), 4.49 (m, 3H, 4'-$H_2$ and 16a-$H_2$), 5.03 (d, 1H, *J* = 3.5 Hz, 17-OH), 5.15 (brs, 1H, $CH_2$-OH), 6.59 (s, 1H, 4-H), 6.66 (d, 1H, *J* = 8.5 Hz, 2-H), 7.16 (d, 1H, *J* = 8.5 Hz, 1-H), 7.99 (s, 1H, 5'-H). $^{13}$C NMR (δ, ppm, DMSO-$d_6$): 12.4 (C-18), 25.9, 26.9, 29.2, 30.0, 36.9, 37.9, 40.5, 43.4, 43.8 (C-13), 47.8, 52.0 (C-16a), 54.8 (3-$OCH_3$), 55.0 (4'-$CH_2$), 79.5 (C-17), 111.4 (C-2), 113.4 (C-4), 122.8 (C-5'), 126.1 (C-1), 132.0 (C-10), 137.3 (C-5), 147.6 (C-4'), 157.0 (C-3).

*2.3.7. 3-Methoxy-16a-(4'-cyclopropyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**22a**)*

Compound **14** (342 mg, 1 mmol) and cyclopropylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **22a** (261 mg, 64%) as a white solid. Mp: 67–69 $^{o}$C; $R_f$= 0.35 (ss B). (Found C, 73.55; H, 7.98. $C_{25}H_{33}N_3O_2$ (407.55) requires C, 73.68; H, 8.16%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.82 (m, 5H, 18-$H_3$ and cyclopropyl-$H_2$), 0.95 (m, 2H, cyclopropyl-$H_2$), 2.83 (m, 2H, 6-$H_2$), 3.53 (d, 1H, *J* = 7.5 Hz, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.35 (t, 1H, *J* = 7.5 Hz, 16a-$H_2$), 4.44 (dd, 1H, *J* = 13.5 Hz, *J* = 7.5 Hz, 16a-$H_2$), 6.62 (d, 1H, *J* = 2.0 Hz, 4-H), 6.70 (dd, 1H, *J* = 8.5 Hz, *J* = 2.0 Hz, 2-H), 7.18 (d, 1H, *J* = 8.5 Hz, 1-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 6.7 (C-1"), 7.7 (C-2" and -3"), 11.8 (C-18), 26.1, 27.2, 28.2, 29.7, 36.6, 38.4, 43.9, 44.3, 44,3 (C-16a), 48.3, 54.5 (C-13), 62.1 (3-$OCH_3$), 85.1 (C-17), 111.5 (C-2), 113.8 (C-4), 126.2 (C-1), 132.3 (C-10), 137.8 (C-5), 157.4 (C-3).

*2.3.8. 3-Methoxy-16a-(4'-cyclopentyl-1'H-1',2',3'-triazol-1-yl)methylestra-1,3,5(10)-trien-17β-ol (**22b**)*

Compound **14** (342 mg, 1 mmol) and cyclopentylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with

ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **22b** (290 mg, 66%) as a white solid. Mp: 163–165 $^oC$; $R_f$= 0.32 (ss B). (Found C, 74.63; H, 8.41. $C_{27}H_{37}N_3O_2$ (435.60) requires C, 74.45; H, 8.56%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.83 (s, 3H, 18-$H_3$), 1.68 (s, 4H, 3”- and 4”-$H_2$), 2.83 (m, 2H, 6-$H_2$), 3.19 (m, 1H, 1”-H), 3.56 (d, 1H, *J* = 7.0 Hz, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.43 (m, 2H, 16a-$H_2$), 6.62 (s, 1H, 4-H), 6.70 (d, 1H, *J* = 8.5 Hz, 2-H), 7.19 (d, 1H, *J* = 8.5 Hz, 1-H), 7.35 (s, 1H, 5’-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 11.9 (C-18), 25.1 (C-3” and -4”), 26.1, 27.2, 28.3, 29.7 (C-2” and -5”), 33.2, 36.6, 38.4, 43.9, 44.2, 44.3 (C-13), 48.4, 55.2 (3-$OCH_3$), 62.1 (C-16a), 85.3 (C-17), 111.5 (C-2), 113.8 (C-4), 126.3 (C-1), 132.3 (C-10), 137.8 (C-5), 157.5 (C-3).

### *2.3.9. 3-Methoxy-16a-(4’-cyclohexyl-1’H-1’,2’,3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17β-ol (**22c**)*

Compound **14** (342 mg, 1 mmol) and cyclohexylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **22c** (345 mg, 76%) as a white solid. Mp: 80–82 $^oC$; $R_f$= 0.34 (ss B). (Found 74.96; H, 8.54. $C_{28}H_{41}N_3O_2$ (449.63) requires C, 74.80; H, 8.74%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.83 (s, 3H, 18-$H_3$), 2.83 (m, 2H, 6-$H_2$), 3.55 (s, 1H, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.46 (s, 2H, 16a-$H_2$), 6.62 (d, 1H, *J* = 2.0 Hz, 4-H), 6.70 (dd, 1H, *J* = 8.5 Hz, *J* = 2.0 Hz, 2-H), 7.19 (d, 1H, *J* = 8.5 Hz, 1-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 11.9 (C-18), 26.0 and 26.1 (C-2” and -6”, C-3” and -5”), 27.2, 28.3, 29.7, 36.6, 38.4, 43.9, 44.3 (C-13), 48.4, 55.2 (3-$OCH_3$), 62.1 (C-1”), 62.1 (C-16a), 85.2 (C-17), 111.5 (C-2), 113.8 (C-4), 126.2 (C-1), 132.3 (C-10), 137.8 (C-5), 157.4 (C-3).

### *2.3.10. 3-Methoxy-16a-(4’-phenyl-1’H-1’,2’,3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17β-ol (**22d**)*

Compound **14** (342 mg, 1 mmol) and phenylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **22d** (368 mg, 82%) as a white solid. Mp: 204–205 $^oC$; $R_f$= 0.38 (ss B). (Found C, 75.63; H, 7.72. $C_{28}H_{33}N_3O_2$ (443.58) requires C, 75.81; H, 7.50%). $^1H$ NMR (δ, ppm, DMSO-$d_6$): 0.73 (s, 3H, 18-$H_3$), 2.73 (m, 2H, 6-$H_2$), 3.67 (s, 3H, 3-$OCH_3$), 4.36 (t, 1H, *J* = 13.5 Hz, 16a-$H_2$), 4.54 (dd, 1H, *J* = 13.5 Hz, *J* = 4.0 Hz, 16a-$H_2$), 4.91 (d, 1H, *J* = 4.0 Hz, 17-H), 6.58 (s, 1H, 4-H), 6.67 (d, 1H, *J* = 8.5 Hz, 2-H), 7.15 (d, 1H, *J* = 8.5 Hz, 1-H), 7.32 (t, 1H,

*J* = 7.0 Hz, 4”-H), 7.44 (t, 2H, *J* = 7.0 Hz, 3”- and 5”-H), 7.86 (d, 2H, *J* = 7.0 Hz, 2”- and 6”-H), 8.61 (s, 1H, 5’-H). $^{13}$C NMR (δ, ppm, DMSO-$d_6$): 11.8 (C-18), 25.8, 26.7, 27.3, 29.1, 36.3, 38.1, 43.4, 43.5, 43.8, 47.5, 53.5 (C-13), 54.8 (3-$OCH_3$), 83.1 (C-17), 111.4 (C-2), 113.3 (C-4), 121.4 (C-5’), 125.0 (C-2” and -6”), 126.0 (C-1), 127.6 (C-4”), 128.8 (C-3” and -5”), 130.8 (C-1”), 132.0 (C-10), 137.3 (C-5), 146.1 (C-4’), 156.9 (C-3).

*2.3.11.3-Methoxy-16a-[4’(4’’-nitro-benzoyloxymethyl)-1’H-1’,2’,3’-triazol-1’-yl]methylestra-1,3,5(10)-trien-17β-ol (**22e**)*

Compound **14** (342 mg, 1 mmol) and propargyl 4-nitrobenzoate (2 mmol, 410 mg) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **22e** (445 mg, 81%) as a yellow solid. Mp: 86–88 $^{o}$C; $R_f$= 0.28 (ss B). (Found C, 66.08; H, 6.43. $C_{30}H_{34}N_4O_6$ (546.61) requires C, 65.92; H, 6.27%). $^1$H NMR (δ, ppm, DMSO-$d_6$): 0.69 (s, 3H, 18-$H_3$), 2.68 (m, 2H, 6-$H_2$), 3.57 (s, 3H, 3-$OCH_3$), 4.38 (dd, 1H, *J* = 13.5 Hz, *J* = 9.0 Hz, 16a-$H_2$), 4.52 (dd, 1H, *J* = 13.5 Hz, *J* = 4.5 Hz, 16a-$H_2$), 4.86 (d, 1H, *J* = 4.5 Hz, 17-H), 5.46 (s, 2H, 4’-$H_2$), 6.55 (d, 1H, *J* = 1.5 Hz, 4-H), 6.63 (dd, 1H, *J* = 8.5 Hz, 2-H), 7.10 (d, 1H, *J* = 8.5 Hz, 1-H), 8.16 (d, 2H, *J* = 8.5 Hz, 3”- and 5”-H), 8.28 (d, 2H, *J* = 8.5 Hz, 2”- and 6”-H), 8.31 (s, 1H, 5’-H). $^{13}$C NMR (δ, ppm, DMSO-$d_6$): 11.7 (C-18), 25.7, 26.6, 27.1, 29.0, 36.4, 38.0, 43.3, 43.4 (C-13), 43.7, 47.7, 53.1 (C-16a), 54.7 (3-$OCH_3$), 58.6 (4”-$CH_2$), 82.8 (C-17), 111.3 (C-2), 113.3 (C-4), 123.8 (C-2” and -6”), 125.2 (C-5’), 125.9 (C-1), 130.6 (C-3” and -5”), 131.8 (C-10), 134.7 (C-1’), 137.2 (C-5), 141.1 (C-4”), 150.2 (C-4’), 156.9 (C-3), 163.9 (C=O).

*2.3.12. 3-Methoxy-16a-(4’-hydroxymethyl-1’H-1’,2’3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17β-ol (**22f**)*

Compound **22e** (274 mg, 0.5 mmol) was dissolved in methanol (10 ml) containing $NaOCH_3$ (14 mg, 0.25 mmol), and the solution was allowed to stand for 24 h. It was then diluted with water, and the precipitate separating out was filtered off and recrystallized from a mixture of ethyl acetate/hexane to afford **22f** (175 mg, 88%) as a white crystalline product. Mp: 98–100 $^{o}$C; $R_f$= 0.28 (ss B). (Found C, 69.74; H, 7.72. $C_{23}H_{31}N_3O_3$ (397.51) requires C, 69.49; H, 7.86%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.81 (s, 3H, 18-$H_3$), 2.82 (m, 2H, 6-$H_2$), 3.50 (d, 1H, *J* = 7.0 Hz, 17-H),

3.76 (s, 3H, 3-$OCH_3$), 4.42 (d, 2H, $J$ = 7.0 Hz, 16a-$H_2$), 4.71 (s, 2H, 4'-$H_2$), 6.61 (s, 1H, 4-H), 6.69 (d, 1H, $J$ = 8.5 Hz, 2-H), 7.17 (d, 1H, $J$ = 8.5 Hz, 1-H), 7.68 (s, 1H, 5'-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 11.9 (C-18), 26.1, 27.2, 28.2, 29.6, 36.5, 38.4, 43.8, 44.0, 44.4 (C-13), 48.2, 54.6 (C-16a), 55.2 (3-$OCH_3$), 56.0 (4'-$CH_2$), 85.1 (C-17), 111.5 (C-2), 113.8 (C-4), 126.3 (C-1), 132.3 (C-10), 137.8 (C-5), 157.4 (C-3).

*2.3.13. 3-Methoxy-16a-(4'-cyclopropyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**23a**)*

Compound **15** (342 mg, 1 mmol) and cyclopropylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **23a** (261 mg, 64%) as a white solid. Mp: 67–69 $^{o}$C; $R_f$= 0.32 (ss B). (Found C, 73.85; H, 8.32. $C_{25}H_{33}N_3O_2$ (407.55) requires C, 73.68; H, 8.16%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.82 (m, 5H, 18-$H_3$ and cyclopropyl-$H_2$), 0.95 (m, 2H, cyclopropyl-$H_2$), 2.83 (m, 2H, 6-$H_2$), 3.53 (d, 1H, $J$ = 7.5 Hz, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.35 (t, 1H, $J$ = 7.5 Hz, 16a-$H_2$), 4.44 (dd, 1H, $J$ = 13.5 Hz, $J$ = 7.5 Hz, 16a-$H_2$), 6.62 (d, 1H, $J$ = 2.0 Hz, 4-H), 6.70 (dd, 1H, $J$ = 8.5 Hz, $J$ = 2.0 Hz, 2-H), 7.18 (d, 1H, $J$ = 8.5 Hz, 1-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 6.7 (C-1"), 7.7 (C-2" and -3"), 11.8 (C-18), 26.1, 27.2, 28.2, 29.7, 36.6, 38.4, 43.9, 44.3, 44,3 (C-16a), 48.3, 54.5 (C-13), 62.1 (3-$OCH_3$), 85.1 (C-17), 111.5 (C-2), 113.8 (C-4), 126.2 (C-1), 132.3 (C-10), 137.8 (C-5), 157.4 (C-3).

*2.3.14. 3-Methoxy-16β-(4'-cyclopentyl-1'H-1',2',3'-triazol-1-yl)methylestra-1,3,5(10)-trien-17a-ol (**23b**)*

Compound **15** (342 mg, 1 mmol) and cyclopentylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **23b** (380 mg, 87%) as yellow crystalline material. Mp: 67–68 $^{o}$C; $R_f$= 0.36 (ss B). (Found C, 74.28; H, 8.47. $C_{27}H_{37}N_3O_2$ (435.60) requires C, 74.45; H, 8.56%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.75 (s, 3H, 18-$H_3$), 2.85 (m, 2H, 6-$H_2$), 3.68 (s, 1H, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.44 (d, 2H, $J$ = 15.0 Hz, 16a-$H_2$), 6.62 (s, 1H, 4-H), 6.70 (d, 1H, $J$ = 8.5 Hz, 2-H), 7.20 (t, 1H, $J$ = 8.5 Hz, 1-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 17.9 (C-18), 25.1 (C-3" and -4"), 25.9, 26.1, 27.2, 28.0, 29.7, 30.4, 31.8, 36.6 (C-16a), 38.5, 43.3, 43.8, 45.1 (C-

13), 48.9, 55.2 (3-$OCH_3$), 62.1 (C-1”), 82.6 (C-17), 111.5 (C-2), 113.7 (C-4), 113.8 (C-5’), 126.2 (C-1), 132.1 (C-10), 137.8 (C-5), 137.8 (C-4’), 157.4 (C-3).

*2.3.15. 3-Methoxy-16β-(4’-cyclohexyl-1’H-1’,2’,3’-triazol-1’-yl)methyestra-1,3,5(10)-trien-17a-ol (**23c**)*

Compound **15** (342, 1 mmol) and cyclohexylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **23c** (306 mg, 68%) as a white solid. Mp: 90-92 $^oC$; $R_f$ = 0.37 (ss B). (Found C, 74.95; H, 8.83. $C_{28}H_{41}N_3O_2$ (449.63) requires C, 74.80; H, 8.74%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.75 (s, 3H, 18-$H_3$), 2.84 (m, 2H, 6-$H_2$), 3.67 (d, 1H, *J* = 1.0 Hz, 17-H), 3.77 (S, 3H, 3-$OCH_3$), 4.43 (m, 1H, 16a-$H_2$), 6.62 (d, 1H, *J* = 2.5 Hz, 4-H), 6.71 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.20 (t, 1H, *J* = 8.5 Hz, 1-H), 7.35 (s, 1H, 5’-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 17.9 (C-18), 25.9, 26.0, 26.1 (C-2” and -6”), 28.0, 29.7, 30.4, 31.8, 33.0, 35.2 (C-1”), 36.6, 38.5, 43.3, 45.1 (C-13), 48.9, 49.1, 54.3 (C-16a), 55.2 (3-$OCH_3$), 82.6 (C-1), 132.4 (C-10), 137.8 (C-5), 153.7 (C-4’), 157.7 (C-3).

*2.3.16. 3-Methoxy-16β-(4’-phenyl-1’H-1’,2’,3’-triazol-1’-yl)methy-estra-1,3,5(10)-trien-17a-ol (**23d**)*

Compound **15** (342 mg, 1 mmol) and phenylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (2.5:97.5 v/v) to yield pure **23d** (299 mg, 67%) as white crystals. Mp: 173–174 $^oC$; $R_f$= 0.34 (ss B). (Found C 75.98; H, 7.33. $C_{28}H_{33}N_3O_2$ (443.58) requires C, 75.81; H, 7.50%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.79 (s, 3H, 18-$H_3$), 2.85 (m, 2H, 6-$H_2$), 3.71 (d, 1H, *J* = 1.5 Hz, 17-H), 3.78 (s, 3H, 3-$OCH_3$), 4.46 (dd, 1H, *J* = 13.5 Hz, *J* = 8.0 Hz, 16a-$H_2$), 4.55 (dd, 1H, *J* = 13.5 Hz, *J* = 8.0 Hz, 16a-$H_2$), 6.63 (d, 1H, *J* = 2.0 Hz, 4-H), 6.72 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.21 (d, 1H, *J* = 8.5 Hz, 1-H), 7.27 (t, 1H *J* = 7.5 Hz, 4”-H), 7.42 (t, 2H, *J* = 7.5 Hz, 3”- and 5”-H), 7.83 (d, 2H, *J* = 7.5 Hz, 2”- and 6”-H), 7.87 (s, 1H, 5’-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 17.9 (C-18), 25.9, 27.9, 29.7, 30.4, 31.8, 38.5, 43.3, 45.1, (C-13), 48.8, 49.1, 54.5 (C-16a), 55.2 (3-$OCH_3$), 82.5 (C-17), 111.5 (C-2), 113.7 (C-4), 119.6 (C-5’), 125.7 (C-2” and -6”), 126.3 (C-1), 128.1 (C-4”), 128.8 (C-3” and -5”), 130.5 (C-1”), 132.4 (C-10), 137.8 (C-5), 147.8 (C-4’), 157.4 (C-3).

*2.3.17.3-Methoxy-16β-[4'(4''-nitro-benzoyloxymethyl)-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**23e**)*

Compound **15** (342, 1 mmol) and propargyl 4-nitro benzoate (2 mmol, 410 mg) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **23e** (370 mg, 67%) as a yellow crystalline material. Mp: 62–63 $^oC$; $R_f$ = 0.38 (ss B). (Found C, 66.14; H, 6.42. $C_{30}H_{34}N_4O_6$ (546.61) requires C, 65.92; H, 6.27%). $^1H$ NMR (δ, ppm, DMSO-$d_6$): 0.65 (s,3 H, 18-$H_3$), 2.74 (m,2H, 6-$H_2$), 3.68 (s, 3H, 3-$OCH_3$), 4.41 (dd, 1H, *J* = 13.0 Hz, *J* = 8.5 Hz, 16a-$H_2$), 4.56 (dd, 1H, *J* = 13.0 Hz, *J* = 8.5 Hz, 16a-$H_2$), 4.63 (d, 1H, *J* = 4.5 Hz, 17-H), 6.58 (s, 1H, 4-H), 6.66 (d, 1H, *J* = 8.5 Hz, 2-H), 7.16 (d, 1H, *J* = 8.5 Hz, 1-H), 8.19 (d, 2H, *J* = 8.5 Hz, 3''- and 5''-H), 8.34 (d, 2H, *J* = 8.5 Hz, 2''- and 6''-H). $^{13}C$ NMR (δ, ppm, DMSO-$d_6$): 17.5 (C-18), 25.6, 27.5, 29.6, 31.8, 38.2, 43.0, 44.5, 47.9 (C-13), 48.2, 49.1, 53.6 (C-16a), 54.8 (3-$OCH_3$), 58.7 (4'-$CH_2$), 80.8 (C-17), 111.3 (C-2), 113.3 (C-4), 123.8 (C-1), 126.1 (C-5'), 130.6 (C-2'' and -6''), 131.9 (C-3'' and -5''), 133.0 (C-10), 134.7 (C-1''), 137.3 (C-5), 141.4 (C-4''), 150.2 (C-4'), 156.9 (C-3), 163.9 (C=O).

*2.3.18. 3-Methoxy-16β-(4'-hydroxymethyl-1'H-1',2'3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**23f**)*

Compound **23e** (274 mg, 0.5 mmol) was dissolved in methanol (10 ml) containing $NaOCH_3$ (14 mg, 0.25 mmol), and the solution was allowed to stand for 24 h. It was then diluted with water, and the precipitate separating out was filtered off, dissolved in dichloromethane and washed with water. The organic phase was dried over $Na_2SO_4$, and evaporated *in vacuo* to afford **23f** (183 mg, 92%) as oil. $R_f$= 0.26 (ss B). (Found C, 69.28; H, 7.95. $C_{23}H_{31}N_3O_3$ (397.51) requires C, 69.49; H, 7.86%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.78 (s, 3H, 18-$H_3$), 2.85 (m, 2H, 6-$H_2$), 3.65 (s, 1H, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.46 (m, 2H, 16a-$H_2$), 4.78 (s, 2H, 4'-$H_2$), 6.62 (d, 1H, *J* = 2.0 Hz, 4-H), 6.72 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.19 (d, 1H, *J* = 8.5 Hz, 1-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 17.9 (C-18), 25.9, 27.9, 29.7, 30.3, 31.8, 38.5, 43.3, 45.2 (C-13), 48.8, 49.2, 54.6 (C-16a), 55.2 (3-$OCH_3$), 56.1 (4'-$CH_2$), 82.1 (C-17), 111.5 (C-2), 113.7 (C-4), 123.5 (C-5'), 126.3 (C-1), 132.4 (C-10), 137.8 (C-5), 157.4 (C-3).

*2.3.19. 3-Methoxy-16a-(4'-cyclopropyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**24a**)*

Compound **16** (342 mg, 1 mmol) and cyclopropylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (2.5:97.5 v/v) to yield pure **24a** (310 mg, 76%) as a white solid. Mp: 165–166 $^oC$; $R_f$= 0.40 (ss B). (Found C, 73.85; H, 8.34. $C_{25}H_{33}N_3O_2$ (407.55) requires C, 73.68; H, 8.16%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.74 (s, 3H, 18-$H_3$), 0.85 and 0.96 (2 x m, 4H, 2"- and 3"-$H_2$), 2.85 (m, 2H, 6-$H_2$), 3.63 (d, 1H, *J* = 5.0 Hz, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.28 (dd, 1H, *J* = 13.0 Hz, *J* = 5.0 Hz, 16a-$H_2$), 4.59 (t, 1H, *J* = 12.0 Hz, 16a-$H_2$), 6.63 (d, 1H, *J* = 2.0 Hz, 4-H), 6.71 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.22 (d, 1H, *J* = 8.5 Hz, 1-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 6.6 (C-1"), 7.7 and 7.8 (C-2" and -3"), 17.1 (C-18), 26.0, 28.0, 28.9, 29.8, 31.2, 38.9, 42.3, 46.3 (C-16a), 47.0, 50.5 (C-13), 55.2 (3-$OCH_3$), 78.8 (C-17), 111.4 (C-2), 113.7 (C-4), 120.6 (C-5'), 126.3 (C-1), 132.5 (C-10), 137.9 (C-5), 149.8 (C-4'), 157.4 (C-3).

*2.3.20. 3-Methoxy-16a-(4'-cyclopentyl-1'H-1',2',3'-triazol-1'-yl)methyl-estra-1,3,5(10)-trien-17a-ol (**24b**)*

Compound **16** (342 mg, 1 mmol) and cyclopentylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **24b** (383 mg, 88%) as yellow crystalline product. Mp: 171–173 $^oC$; $R_f$= 0.42 (ss B). (Found C, 74.67; H, 8.72. $C_{27}H_{37}N_3O_2$ (435.60) requires C, 74.45; H, 8.56%). $^1H$ NMR (δ, ppm, $CDCl_3$): 075 (s, 3H, 18-$H_3$), 1.25 (s, 8H, 2"-, 3"-, 4"- and 5"-$H_2$), 2.86 (m, 2H, 6-$H_2$), 3.18 (m, 1H, 1"-H), 3.64 (d, 1H, *J* = 5.0 Hz, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.29 (dd, 1H, *J* = 13.5 Hz, *J* = 5.5 Hz, 16a-$H_2$), 4.62 (dd, 1H, *J* = 13.5 Hz, J = 11.5 Hz, 16a-$H_2$), 6.63 (d, 1H, *J* = 2.0 Hz, 4-H), 6.71 (dd, 1H, *J* = 8.5 Hz, *J* = 2.0 Hz, 2-H), 7.22 (d, 1H, *J* = 8.5 Hz, 1-H), 7.36 (s, 1H, 5'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 17.2 (C-18), 25.1 (C-3" and -4"), 26.0, 28.0, 29.0, 29.7, 29.9, 31.2, 33.2, 36.7, 38.9, 42.4, 43.5, 46.3 (C-13), 47.0 (C-1"), 50.5 (C-16a), 55.2 (3-$OCH_3$), 78.8 (C-17), 111.4 (C-2), 113.8 (C-4), 120.6 (C-5'), 126.3 (C-1), 132.6 (C-10), 137.9 (C-5), 152.3 (C-4'), 157.4 (C-3).

*2.3.21. 3-Methoxy-16a-(4'-cyclohexyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**24c**)*

Compound **16** (342 mg, 1 mmol) and cyclohexylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **24c** (162 mg, 36%) as yellow crystals. Mp: 208–210 $^oC$; $R_f$= 0.42 (ss B). (Found C, 74.97; H, 8.56. $C_{28}H_{41}N_3O_2$ (449.63) requires C, 74.80; H, 8.74%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.75 (s, 3H, 18-$H_3$), 1.26 (s, 8H, 2”-, 3”-, 5”- and 6”-$H_2$), 2.88 (m, 2H, 6-$H_2$), 2.90 (m, 2H, 4”-$H_2$), 3.64 (d, 1H, *J* = 5.0 Hz, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.29 (dd, 1H, *J* = 13.5 Hz, *J* = 5.0 Hz, 16a-$H_2$), 4.62 (dd, 1H, *J* = 13.5 Hz, *J* = 11.0 Hz, 16a-$H_2$), 6.63 (d, 1H, *J* = 2.0 Hz, 4-H), 6.71 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.22 (d, 1H, *J* = 8.5 Hz, 1-H), 7.34 (s, 1H, 5’-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 17.2 (C-18), 26.0 and 26.1 (C-2”, -3”, -5” and -6”), 28.0, 29.0, 29.7, 29.8, 31.2, 33.0, 25.2, 38.9, 42.4, 43.5, 46.3 (C-13), 47.0 (C-1”), 50.5 (C-16a), 55.0 (3-$OCH_3$), 78.8 (C-17), 111.4 (C-2), 113.8 (C-4), 120.2 (C-5’), 126.3 (C-1), 132.6 (C-10), 137.9 (C-5), 153.3 (C-4’), 157.4 (C-3).

### *2.3.22. 3-Methoxy-16a-(4’-phenyl-1’H-1’,2’,3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17a-ol (**24d**)*

Compound **16** 342 mg, 1 mmol) and phenylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with $CH_2Cl_2$ yield pure **24d** (394 mg, 89%) as white solid. Mp: 189.5–191 $^oC$; $R_f$= 0.46 (ss B). (Found C, 75.65; H, 7.67. $C_{28}H_{33}N_3O_2$ (443.58) requires C, 75.81; H, 7.50%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.75 (s, 3H, 18-$H_3$), 2.86 (m, 2H, 6-$H_2$), 3.68 (d, 1H, *J* = 5.0 Hz, 17-H), 3.78 (s, 3H, 3-$OCH_3$), 4.41 (dd, 1H, *J* = 13.5 Hz, *J* = 6.0 Hz, 16a-$H_2$), 4.69 (dd, 1H, *J* = 14.5 Hz, *J* = 10.5 Hz, 16a-$H_2$), 6.64 (d, 1H, *J* = 2.0 Hz, 4-H), 6.72 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.22 (d, 1H, *J* = 8.5 Hz, 1-H), 7.34 (t, 1H, *J* = 7.5 Hz, 4”-H), 7.43 (t, 2H, *J* = 7.5 Hz, 3”- and 5”-H), 7.83 (d, 2H, *J* = 7.5 Hz, 2”- and 6”-H), 7.88 (s, 1H, 5’-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 17.1 (C-18), 26.0, 28.0, 29.8, 31.2, 38.9, 42.3, 43.5, 46.4 (C-13), 47.0, 50.7, 55.2 (3-$OCH_3$), 78.8 (C-17), 111.5 (C-2), 113.8 (C-4), 120.6 (C-5’), 125.6 (C-2” and -6”), 126.3 (C-1), 128.1 (C-4”), 128.8 (C-3” and -5”), 130.5 (C-1”), 132.5 (C-10), 137.9 (C-5), 147.3 (C-4’), 157.4 (C-3).

### *2.3.23. 3-Methoxy-16a-[4’-(4’’nitrobenzoyloxymethyl)-1’H-1’,2’,3’-triazol-1’-yl]methylestra-1,3,5(10)-trien-17a-ol (**24e**)*

Compound **16** (342, 1 mmol) and propargyl 4-nitrobenzoate (2 mmol, 210 mg) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with $CH_2Cl_2$/hexane (1:3, v/v) to yield pure (344 mg, 63%) as yellow crystals. Mp: 64 $^oC$; $R_f$= 0.45 (ss B). (Found, C, 66.14; H, 6.05. $C_{30}H_{34}N_4O_6$ (546.61) requires C, 65.92; H, 6.27%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.75 (s, 3H, 18-$H_3$), 2.84 (m, 2H, 6-$H_2$), 3.66 (d, 1H, *J* = 4.5 Hz, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.40 (dd, 1H, *J* = 13.5 Hz, *J* = 5.5 Hz, 16a-$H_2$), 4.66 (t, 1H, *J* = 13.5 Hz, 16a-$H_2$), 5.53 (s, 2H, 4'-$H_2$), 6.62 (t, 1H, *J* = 2.0 Hz, 4-H), 6.71 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.20 (d, 1H, *J* = 8.5 Hz, 1-H), 7.85 (s, 1H, 5'-H), 8.22 (d, 2H, *J* = 9.0 Hz, 3"- and 5"-H), 8.72 (d, 2H, *J* = 9.0 Hz, 2"- and 6"-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 17.1 (C-18), 22.7, 25.9, 28.0, 29.0, 29.8, 31.2, 38.9, 42.0, 43.5, 46.4 (C-13), 47.0 (4'-CH2), 78.8 (C-17), 111.5 (C-2), 113.8 (C-4), 114.0 (C-1'), 123.5 (C-2" and -6") 126.3 (C-5'), 130.9 (C-3" and -5"), 135.0 (C-10), 137.8 (C-5), 141.5 (C-4"), 150.6 (C-4'), 157.5 (C-3), 164.6 (C=O).

*2.3.24. 3-Methoxy-16a-(4'-hydroxymethyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**24f**)*

Compound **24e** (274 mg, 0.5 mmol) was dissolved in methanol (10 ml) containing $NaOCH_3$ (14 mg, 0.25 mmol), and the solution was allowed to stand for 24 h. It was then diluted with water, and the precipitate separating out was filtered off and recrystallized from a mixture of acetone/hexane to afford **24f** (187 mg, 94%) as a white crystalline product. Mp: 149–150 $^oC$; $R_f$ = 0.25 (ss B). (Found C, 69.55; H, 7.95. $C_{23}H_{31}N_3O_3$ (397.51) requires C, 69.49; H, 7.86%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.74 (s, 3H, 18-$H_3$), 2.85 (m, 2H, 6-$H_2$), 3.62 (d, 1H, *J* = 4.0 Hz, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.39 (m, 1H, 16a-$H_2$), 4.64 (m, 1H, 16a-$H_2$), 6.63 (s, 1H, 4-H), 6.71 (d, 1H, *J* = 8.5 Hz, 2-H), 7.21 (d, 1H, *J* = 8.5 Hz, 1-H), 7.77 (s, 1H, 5'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 11.9 (C-18), 26.0, 28.0, 28.9, 31.3, 31.9, 33.8 (C-13), 38.9, 41.9, 43.5, 46.4 (4'-$CH_2$), 46.9, 51.0 (C-16a), 55.2 (3-$OCH_3$), 78.6 (C-17), 111.5 (C-2), 113.8 (C-4), 123.4 (C-5'), 126.3 (C-1), 132.5 (C-10), 137.8 (C-5), 157.4 (C-3).

*2.3.25. 3-Benzyloxy-16β-(4'-cyclopropyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**25a**)*

Compound **17** (420 mg, 1 mmol) and cyclopropylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with

ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **25a** (394 mg, 84%) as a white solid. Mp: 278–280 $^oC$; $R_f$= 0.35 (ss B). (Found C, 77.16; H, 7.62. $C_{31}H_{37}N_3O_2$ (483.64) requires C, 76.98; H, 7.71%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.80 (s, 3H, 18-$H_3$), 0.86 and 0.97 (2 x m, 2 x 2H, 2”- and 3”-H), 2.83 (m, 2H, 6-$H_2$), 3.93 (d, *J* = 9.5 Hz, 1H, 17-H), 4.21 (m, 1H, 16a-$H_2$), 4.64 (m, 1H, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.71 (s, 1H, 4-H), 6.78 (d, 1H, *J* = 8.5 Hz, 2-H), 7.20 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 1H, *J* = 7.0 Hz, 4’-H), 7.38 (t, 2H, *J* = 7.0 Hz, 3’- and 5’-H), 7.43 (d, 2H, *J* = 7.0 Hz, 2’- and 6’-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 7.8 (C-2” and -3”), 12.3 (C-18), 26.2, 27.4, 29.7, 30.8, 37.5, 38.0, 41.4, 43.9, 44.3 (C-13), 48.7 (C-16), 67.8 (C-16a), 69.9 (Bn-$CH_2$), 80.7 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-2’ and -6’), 127.8 (C-4’), 128.5 (C-3’ and C-5’), 132.7 (C-10), 137.3 (C-1’), 137.8 (C-5), 156.8 (C-3).

### *2.3.26. 3-Benzyloxy-16β-(4’-cyclopentyl-1’H-1’,2’,3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17β-ol (**25b**)*

Compound **17** (420 mg, 1 mmol) and cyclopentylacetylene (2 mol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **25b** (350 mg, 68%) as a white solid. Mp: 288–290 $^oC$; $R_f$= 0.38 (ss B). Found C, 77.58; H, 7.92. $C_{33}H_{41}N_3O_2$ (511.70) requires C, 77.46; H, 8.08%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.79 (s, 3H, 18-$H_3$), 2.75 (s, 1H, 1”-H), 2.83 (m, 2H, 6-$H_2$), 3.94 (d, 1H, *J* = 9.5 Hz, 17-H), 4.24 (m, 1H, 16-$H_2$), 4.67 (m, 1H, 16-$H_2$), 5.03 (s., 2H, Bn-$H_2$), 6.71 (s, 1H, 4-H), 6.78 (d, 1H, *J* = 8.5 Hz, 2-H), 7.19 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 1H, *J* = 7.5 Hz, 4’-H), 7.38 (t, 2H, *J* = 7.5 Hz, 3’- and 5’-H), 7.42 (d, 2H, *J* = 7.5 Hz, 2’- and 6’-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 12.3 (C-18), 25.1 (C-3” and -4”), 26.2, 27.5, 29.7, 30.8, 34.3 (C-2” and -5”), 37.5, 38.0, 41.4, 43.9, 44.3 (C-13), 48.7 (C-16), 62.1 (16a-$CH_2$), 69.9 (Bn-$CH_2$), 80.7 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-2’ and -6’), 127.8 (C-4’), 128.5 (C-3’ and -5’), 132.7 (C-10), 137.3 (C-1’), 137.8 (C-5), 156.8 (C-3).

### *2.3.27. 3-Benzyloxy-16β-(4’-cyclohexyl-1’H-1’,2’,3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17β-ol (**25c**)*

Compound **17** (420 mg, 1 mmol) and cyclohexylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99, v/v) to yield pure **25c** (146 mg, 28%) as a white solid. Mp: 214–216

$^{o}$C; $R_f$= 0.38 (ss B). (Found C, 77.43; H, 8.36. $C_{34}H_{43}N_3O_2$ (525.72) requires C, 77.68; H, 8.24%). $^{1}$H NMR (δ, ppm, $CDCl_3$): 0.79 (s, 3H, 18-$H_3$), 2.79 (m, 4H, 3”- and 5”-H), 3.94 (d, *J* = 9.5 Hz, 1H, 17-H), 4.25 (m, 1H, 16a-$H_2$), 4.67 (m, 1H, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.71 (s, 1H, 4-H), 6.78 (d, 1H, J = 8.5 Hz, 2-H), 7.19 (d, 1H, *J* = 8.5 Hz, 1-H), 7.32 (d, 1H, *J* = 7.0 Hz, 4’-H), 7.38 (t, 2H, *J* = 7.0 Hz, 3’- and 5’-H), 7.42 (d, 2H, *J* = 7 Hz, 2’- and 6’-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 12.3 (C-18), 26.0 (C-4”), 26.1 (C-3” and -5”), 26.2, 27.5, 29.7, 30.8 (C-2” and -6”), 33.0 (C-1”), 37.5, 38.0, 41.4, 43.9, 44.3 (C-13), 48.7 (C-16), 62.1 (C-16a), 69.9 (Bn-$CH_2$), 80.7 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-2’ and -6’), 127.8 (C-4’), 128.5 (C-3’ and -5’), 132.7 (C-10), 137.3 (C-1’), 137.8 (C-5), 157.8 (C-3).

### *2.3.28. 3-Benzyloxy-16β-(4’-phenyl-1’H-1’,2’,3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17β-ol (**25d**)*

Compound **17** (420 mg, 1 mmol) and phenylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **25d** (391 mg, 75%) as a white solid. Mp: 202–204 $^{o}$C; $R_f$= 0.45 (ss B). (Found C, 78.73; H, 6.98. $C_{34}H_{37}N_3O_2$ (519.68) requires C, 78.58; H, 7.18%). $^{1}$H NMR (δ, ppm, $C_6D_6$): 0.68 (s, 3H, 18-$H_3$), 2.69 (m, 2H, 6-$H_2$), 3.43 (dd, *J* = 9.5 Hz, *J* = 4 Hz, 1H, 17-H), 3.77 (dd, 1H, J = 13.5 Hz, J = 7.0 Hz, 16a-$H_2$), 4.29 (dd, 1H, J = 13.5 Hz, J = 7.0 Hz, 16a-$H_2$), 4.83 (s, 2H, Bn-$H_2$), 6.79 (s, 1H, 4-H), 6.87 (d, 1H, *J* = 8.0 Hz, 2-H), 7.02 (s, 1H, 1-H), 7.08 (t, 1H, *J* = 7.5 Hz, 4’-H), 7,26 (t, 2H, *J* = 7.5 Hz, 3’- and 5’-H), 7.32 (d, 2H, *J* = 7.5 Hz, 2’- and 6’-H), 8.01 (d, 2H, *J* = 7.5 Hz, 2”- and 6”-H).

### *2.3.29. 3-Benzyloxy-16β-[4’-(4’’-nitro-benzoyloxymethyl)-1’H-1’,2’,3’-triazol-1’-yl]methyestra-1,3,5(10)-trien-17β-ol (**25e**)*

Compound **17** (420 mg, 1 mmol) and propargyl 4-nitrobenzoate (2 mmol, 210 mg) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **25e** (480 mg, 77%) as a yellow solid. Mp: 187–189 $^{o}$C; $R_f$= 0.45 (ss B). (Found C, 69.32; 5.98. $C_{36}H_{38}N_4O_6$ (622.71) requires C, 69.44; H, 6.15%). $^{1}$H NMR (δ, ppm, $CDCl_3$): 0.80 (s, 3H, 18-$H_3$), 2.82 (m, 2H, 6-$H_2$), 3.94 (d, *J* = 10.0 Hz, 1H, 17-H), 4.32 (dd, 1H, J = 13.0 Hz, J = 6.0 Hz, 16a-$H_2$), 4.72 (t, 1H, J = 6.0 Hz, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 5.52 (s, 2H, triazol-H), 6.71 (s, 1H, 4-H), 6.78 (d, 1H, *J* = 8.5 Hz, 2-H), 7.19 (d, 1H, *J* =

8.5 Hz, 1-H), 7.32 (t, 1H, *J* = 7.0 Hz, 4'-H), 7.38 (t, *J* = 7.5 Hz, 2H, 3'- and 5'-H), 7.42 (d, *J* = 7.5 Hz, 2H, 2'- and 6'-H), 8.22 (d, *J* = 8 Hz, 2H, 3"- and 5"-H), 8.27 (d, *J* = 8 Hz, 2H, 2"- and 6"-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 12.3 (C-18), 26.2, 27.4, 29.7, 30.8, 37.4, 38.0, 41.2, 43.8, 44.4 (C-13), 48.7 (C-16), 55.5 (C-16a), 58.7 (linker-$CH_2$), 69.9 (Bn-$CH_2$), 80.7 (C-17), 112.4 (C-2), 114.8 (C-4), 123.5 (C-2' and -6'), 126.3 (C-1), 127.4 (C-2" and -6"), 127.8 (C-4'), 128.5 (C-3" and -5"), 130.9 (C-3' and -5'), 132.5 (C-10), 135.1 (C-1"), 137.3 (C-1'), 137.8 (C-5), 150.7 (C-4"), 156.8 (C-3), 164.6 (C=O).

### *2.3.30. 3-Benzyloxy-16β-(4'-hydroxymethyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**25f**)*

Compound **25e** (210 mg, 0.5 mmol) was dissolved in methanol (10 ml) containing $NaOCH_3$ (14 mg, 0.25 mmol), and the solution was allowed to stand for 24 h. It was then diluted with water, and the precipitate separating out was filtered off and recrystallized from methanol to afford **25f** (232 mg, 98%) as a white crystalline product. Mp: 283–285 $^{o}$C; $R_f$= 0.25 (ss B). (Found C, 73.42; H, 7.35. $C_{29}H_{35}N_3O_3$ (473.61) requires C, 73.54; H, 7.45%). $^1$H NMR (δ, ppm, DMSO-$d_6$): 0.77 (s, 3H, 18-$H_3$), 3.77 (dd, 1H, J = 9.5 Hz, J = 3.5 Hz, 16a-$H_2$), 4.15 (t, 1H, J = 12.5 Hz, 16a-$H_2$), 5.12 (d, 1H, J = 5.5 Hz, 17-H), 6.68 (s, 1H, 4-H), 6.74 (d, 1H, *J* = 8.5 Hz, 2-H), 7.16 (d, *J* = 8.5 Hz, 1H, 1-H), 7.31 (d, 1H, *J* = 7.0 Hz, 4'-H), 7.37 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.41 (d, 2H, *J* = 7.0 Hz., 2'- and 6'-H), 7.98 (s, 1H, triazol-H). $^{13}$C NMR (δ, ppm, DMSO-$d_6$): 12.3 (C-18), 25.8, 26.9, 29.1, 30.0, 36.9, 37.8, 40.4, 43.4, 43.7 (C-13), 47.8 (C-16a), 55.0 (linker-$CH_2$), 68.9 (Bn-$CH_2$), 79.5 (C-17), 112.1 (C-2), 114.4 (C-4), 122.7 (triazol-CH), 126.0 (C-1), 127.4 (C-2' and -6'), 127.6 (C-4'), 128.3 (C-3' and -5'), 132.3 (C-10), 137.3 (C-5), 147.6 (triazol-C), 156.0 (C-3).

### *2.3.31. 3-Benzyloxy-16a-(4'-cyclopropyl-1'H-1',2,'3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**26a**)*

Compound **18** (420.0 mg, 1 mmol) and cyclopropylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **26a** (310 mg, 64%) as a white solid. Mp: 191–193 $^{o}$C; $R_f$= 0.35 (ss B). (Found C, 76.82; H, 7.94. $C_{31}H_{37}N_3O_2$ (483.64) requires C, 76.98; H, 7.71%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.83 (s, 3H, 18-$H_3$), 2.83 (m, 2H, 6-$H_2$), 3.54 (d, *J* = 7.5 Hz,

1H, 17-H), 4.35 (dd, 1H, *J* = 13.0 Hz, *J* = 7.5 Hz, 16a-$H_2$), 4.44 (dd, 1H, *J* = 13.0 Hz, *J* = 7.5 Hz, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.71 (s, 1H, 4-H), 6.77 (d, 1H, *J* = 8.5 Hz, 2-H), 7.19 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 2H, *J* = 7.5 Hz, 4'-H and triazol-H), 7.38 (t, 2H, *J* = 7.5 Hz, 3'- and 5'-H), 7.42 (d, 2H, *J* = 7.5 Hz, 2'- and 6'-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 6.6 (C-1"), 7.8 (C-2" and -3"), 11.8 (C-18), 26.1, 27.2, 28.2, 29.7, 36.6, 38.4, 43.9, 44.3, 44.3 (C-13), 48.3 (C-16), 54.5 (C-16a), 69.9 (Bn-$CH_2$), 85.2 (C-17), 112.3 (C-2), 114.8 (C-4), 120.0 (triazol-CH), 126.3 (C-1), 127.4 (C-2' and -6'), 127.8 (C-4'), 128.5 (C-3' and -5'), 132.6 (C-10), 137.3 (C-1'), 137.8 (C-5), 150.2 (triazol-C), 156.8 (C-3).

### *2.3.32. 3-Benzyloxy-16a-(4'-cyclopentyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**26b**)*

Compound **18** (420 mg, 1 mmol) and cyclopentylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **26b** (442 mg, 86%) as a white solid. Mp: 268–270 $^{o}$C; $R_f$= 0.36 (ss B). (Found C, 77.52; H, 7.93. $C_{33}H_{41}N_3O_2$ (511.70) requires C, 77.46; H, 8.08%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.83 (s, 3H, 18-$H_3$), 2.83 (m, 2H, 6-$H_2$), 3.19 (s, 1H, 1"-H), 3.46 (d, 1H, *J* = 7.0 Hz, 17-H), 4.42 (dd, 2H, *J* = 22.5 Hz, $J_,$ = 6.5 Hz, 16-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.71 (s, 1H, 4-H), 6.76 (d, 1H, *J* = 8.5 Hz, 2-H), 7.19 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 1H, *J* = 7.5 Hz, 4'-H), 7 .37 (t, 3H, *J* = 7.5 Hz, 3'-, 5'-H and triazol-H), 7.42 (d, 2H, *J* = 7.5 Hz, 2'- and 6'-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 11.9 (C-18), 25.1 (C-3" and -4"), 26.1, 27.2, 28.3, 29.7, 33.2 (C-2" and -5"), 36.6 (2C, C-1"), 36.7, 38.4, 43.9, 44.3 (C-13), 48.4 (C-16), 54.5 (C-16a), 69.9 (Bn-$CH_2$), 85.2 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-3' and -5'), 127.8 (C-4'), 128.5 (C-2' and -6'), 132.6 (C-10), 137.3 (C-1'), 137.8 (C-5), 156.7 (C-3).

### *2.3.33. 3-Benzyloxy-16a-(4'-cyclohexyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**26c**)*

Compound **18** (420 mg, 1 mmol) and cyclohexylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (2.5:77.5 v/v) to yield pure **26c** (386 mg, 76%) as a white solid. Mp: 261–263 $^{o}$C; $R_f$= 0.34 (ss B). (Found C, 77.93; H, 8.36. $C_{34}H_{43}N_3O_2$ (525.72) requires C, 77.68; H, 8.24%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.83 (s, 3H, 18-$H_3$), 2.83 (m, 2H, 6-$H_2$), 3.55 (d, *J* = 7.0

Hz, 1H, 17-H), 4.43 (m, 2H, 16-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.71 (s, 1H, 4-H), 6.77 (d, 1H, *J* = 8.5 Hz, 2-H), 7.19 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 2H, *J* = 7.0 Hz, 4'-H and triazol-H), 7.37 (t, 2H, *J* = 7.0 Hz. 3'- and 5'-H), 7.42 (d, 2H, *J* = 7 Hz, 2'- and 6'-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 11.9 (C-18), 25.9 (C-4"), 26.1 (C-3" and -5"), 27.2, 28.3, 29.7 (C-2" and -6"), 32.9, 33.0, 36.6, 38.4, 43.9, 44.2, 44.3 (C-13), 48.4 (C-16), 54.5 (C-16a), 69.9 (Bn-$CH_2$), 85.2 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-2' and -6'), 127.8 (C-4'), 128.5 (C-3' and -5'), 132.6 (C-10), 137.3 (C-1'), 137.8 (C-5), 156.7 (C-3).

*2.3.34. 3-Benzyloxy-16a-(4'-phenyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol* ***(26d)***

Compound **18** (420 mg, 1 mmol) and phenylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ 5:95 v/v) to yield pure **26d** (372 mg, 71%) as a white solid. Mp: 132–134 $^{o}$C; $R_f$= 0.38 (ss B). (Found C, 78.63; H, 6.97. $C_{34}H_{37}N_3O_2$ (519.68) requires C, 78.58; H, 7.18%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.84 (s, 3H, 18-$H_3$), 2.83 (m, 2H, 6-$H_2$), 3.58 (d, 1H, *J* = 7.5 Hz, 17-H), 4.46 (dd, 2H, *J* = 13.5 Hz, *J* = 8.0 Hz, 16a-$H_2$), 4.55 (dd, 1H, *J* = 13.5 Hz, *J* = 8.0 Hz, 16a-H2) 5.03 (s, 2H, Bn-$H_2$), 6.71 (s, 1H, 4-H), 6.78 (d, 1H, *J* = 8.5 Hz, 2-H), 7.19 (d, 1H, *J* = 8.5 Hz, 1-H), 7.30-7.86 (m, 11H, 2'-, 6'-, 3'-, 5'-, 4'-, 2"-, 6"-, 3"-, 5"-, 4"- and triazol-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 11.8 (C-18), 26.1, 27.2, 28.2, 29.6, 36.5, 38.4, 43.9, 44.3, 48.3 (C-16), 54.6 (C-16a), 62.1, 69.9 (Bn-$CH_2$), 85.2 (C-17), 112.3 (C-2), 114.8 (C-4), 123.8 (triazol-CH), 125.7 (C-2' and -6'), 126.3 (C-1'), 127.4 (C-2" and -6"), 127.8 (C-4'), 128.2 (C-4), 128.5 (C-3" and -5"), 128.8 (C-3' and -5'), 130.4 (C-10), 132.6 (C-1"), 137.3 (C-1'), 137.8 (C-5), 156.8 (C-3).

*2.3.35. 3-Benzyloxy-16a-[4'-(4''-nitro-benzoyloxymethyl)-1'H-1',2',3'-triazol-1'-yl]methylestra-1,3,5(10)-trien-17β-ol* ***(26e)***

Compound **18** (420 mg, 1 mmol) and propargyl 4-nitrobenzoate (2 mmol, 210 mg) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **26e** (484 mg, 77%) as a yellow solid. Mp: 94–96 $^{o}$C; $R_f$= 0.40 (ss B). (Found C, 69.73; H, 5.94. $C_{36}H_{38}N_4O_6$ (622.71) requires C, 69.44; H, 6.15%). $^1$H NMR (δ, ppm, DMSO-$d_6$): 0.70 (s, 3H, 18-$H_3$), 3.33 (m, 2H, 6-$H_2$), 4.38 (dd, 1H, *J* = 13.5 Hz, *J* = 9.0 Hz, 16a-$H_2$), 4.52 (dd, 1H, *J* = 13.5 Hz, *J* = 5.0 Hz, 16a-$H_2$), 4.86 (d, 1H, *J* = 5

Hz, 17-H), 5.02 (s, 2H, Bn-$H_2$), 5.47 (s, 2H, linker-$H_2$), 6.64 (d, 1H, J = 2.0 Hz, 4-H), 6.72 (dd, 1H, J = 8.5 Hz, *J* = 2.0 Hz, 2-H), 7.10 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 1H, *J* = 7.0 Hz, 4'-H), 7.37 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.42 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H), 8.16 (d, 2H, *J* = 9.0 Hz, 3"- and 5"-H), 8.28 (d, 2H, *J* = 9.0 Hz, 2"- and 6"-H), 8.32 (s, 1H, triazol-H). $^{13}$C NMR (δ, ppm, DMSO-$d_6$): 11.7 (C-18), 25.7, 26.6, 27.1, 29.0, 30.6, 36.4, 37.9, 43.4, 43.4 (C-13), 43.7 (C-16), 53.1 (C-16a), 58.6 (linker-$CH_2$), 68.9 (Bn-$CH_2$), 82.8 (C-17), 112.1 (C-2), 114.3 (C-4), 123.7 (C-2' and -6'), 125.1 (triazol-CH), 125.9 (C-1), 127.4 (C-2" and -6"), 127.5 (C-4'), 128.3 (C-3" and -5"), 130.6 (C-3' and -5'), 132.1 (C-10), 134.7 (C-1"), 137.2 (C-1'), 137.3 (C-5), 141.1 (triazol-C), 150.1 (C-4"), 155.9 (C-3), 163.9 (C=O).

### *2.3.36. 3-Benzyloxy-16a-(4'-hydroxymethyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**26f**)*

Compound **26e** (210 mg, 0.5 mmol) was dissolved in methanol (10 ml) containing $NaOCH_3$ (14 mg, 0.25 mmol), and the solution was allowed to stand for 24 h. It was then diluted with water, and the precipitate separating out was filtered off and recrystallized from a mixture of acetone/hexane to afford **26f** (190 mg, 89%) as a white crystalline product. Mp: 152–154 $^{o}$C; $R_f$= 0.20 (ss B). (Found C, 73.72; H, 7.63. $C_{29}H_{35}N_3O_3$ (473.61) requires C, 73.54; H, 7.45%). $^1$H NMR (δ, ppm, DMSO-$d_6$): 0.71 (s, 3H, 18-$H_3$), 2.73 (m, 2H, 6$H_2$), 3.29 (d, *J* = 8.0 Hz, 1H, 17-H), 4.28 (dd, 2H, *J* = 13.0 Hz, *J* = 10.0 Hz, 16a-$H_2$), 4.47 (dd, 1H, *J* = 13.0 Hz, *J* = 4.5 Hz, 16a-$H_2$), 4.51 (s, 2H, Bn-$H_2$), 4.87 (s, 1H, linker-$H_2$), 5.03 (s, 2H, triazol-$H_2$), 5.15 (s, 1H, linker-$H_2$), 6.68 (s, 1H, 4-H), 6.74 (d, 1H, *J* = 8.5 Hz, 2-H), 7.15 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 1H, *J* = 7.0 Hz, 4'-H), 7.37 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.41 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H), 7.97 (s, 1H, triazol-H). $^{13}$C NMR (δ, ppm, DMSO-$d_6$): 11.8 (C-18), 25.8, 26.7, 27.3, 29.1, 36.4, 38.1, 43.4, 43.5 (C-13), 43.9, 47.5 (C-16), 53.1 (C-16a), 54.9 (linker-$CH_2$), 68.9 (Bn-$CH_2$), 83.0 (C-17), 112.1 (C-2), 114.4 (C-4), 122.7 (triazol-CH), 126.0 (C-1), 127.4 (C-2' and -6'), 127.6 (C-4'), 128.3 (C-3' and -5'), 132.3 (C-10), 137.3 (C-1'), 137.4 (C-5), 147.6 (triazol-C), 156.0 (C-3).

### *2.3.37. 3-Benzyloxy-16β-(4'-cyclopropyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**27a**)*

Compound **19** (420.0 mg, 1 mmol) and cyclopropylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with

ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **27a** (454 mg, 93%) as white crystals. Mp: 199–201 $^oC$; $R_f$= 0.38 (ss B). (Found C, 77.15; H, 7.62. $C_{31}H_{37}N_3O_2$ (483.64) requires C, 76.98; H, 7.71%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.77 (s, 3H, 18-$H_3$), 0.87 and 0.98 (2 x s, 2 x 2H, 2”- and 3”-$H_2$), 2.05 (s, 1H, 1”-H), 2.84 (m, 2H, 6-$H_2$), 3.66 (s, 1H, 17-H), 4.42 (m, 2H, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.71 (s, 1H, 4-H), 6.78 (d, 1H, *J* = 8.5 Hz, 2-H), 7.21 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 1H, *J* = 7.0 Hz, 4’-H), 7.38 (t, 2H, *J* = 7.0 Hz, 3’- and 5’-H), 7.43 (d, 2H, *J* = 7.0 Hz, 2’- and 6’-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 6.7 (C-1”), 7.7 (C-2” and -3”), 17.9 (C-18), 25.9, 27.9, 29.7, 30.4, 31.8, 38.5, 43.3, 45.1 (C-13), 48.9, 49.1 (C-16), 62.1 (C-16a), 69.9 (Bn-$CH_2$), 82.6 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-2’ and -6’), 127.8 (C-4’), 128.5 (C-3’ and -5’), 132.7 (C-10), 137.3 (C-1’), 137.9 (C-5), 156.7 (C-3).

*2.3.38. 3-Benzyloxy-16β-(4’-cyclopentyl-1’H-1’,2’,3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17a-ol (**27b**)*

Compound **19** (420 mg, 1 mmol) and cyclopentylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **27b** (408 mg, 79%) as white crystalline. Mp: 220–222 $^oC$; $R_f$= 0.40 (ss B). (Found C, 77.32; H, 7.93. $C_{33}H_{41}N_3O_2$ (511.70) requires C, 77.46; H, 8.08%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.76 (s, 3H, 18-$H_3$), 2.84 (m, 2H, 6-$H_2$), 3.20 (s, 1H, 1”-H), 3.67 (s, 1H, 17-H), 4.43 (m, 2H, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.72 (s, 1H, 4-H), 6.78 (dd, 1H, *J* = 8.5 Hz, *J* = 2.0 Hz, 2-H), 7.21 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 1H, *J* = 7.0 Hz, 4’-H), 7.38 (t, 3H, *J* = 7.0 Hz, 3’- and 5’-H, triazol-H), 7.43 (d, 2H, *J* = 7.0 Hz, 2’- and 6’-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 18.0 (C-18), 25.1 (C-3” and -5”), 25.9, 28.0, 29.7, 30.4, 31.8 (C-2” and -6”), 33.2, 36.7, 38.5, 43.3, 45.1 (C-13), 48.9 (C-16), 49.1 (C-1”), 54.3 (C-16a), 69.9 (Bn-$CH_2$), 82.6 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-2’ and -6’), 127.8 (C-4’), 128.5 (C-3’ and -5’), 132.7 (C-10), 137.3 (C-1’), 137.9 (C-5), 156.7 (C-3).

*2.3.39. 3-Benzyloxy-16β-(4’-cyclohexyl-1’H-1’,2’,3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17a-ol (**27c**)*

Compound **19** (420 mg, 1 mmol) and cyclohexylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **27c** (360 mg, 68%) as white crystalline product.

Mp: 243–245 $^{o}$C; $R_f$= 0.38 (ss B). (Found C, 77.54; H, 8.38. $C_{34}H_{43}N_3O_2$ (525.72) requires C, 77.68; H, 8.24%). $^{1}$H NMR (δ, ppm, $CDCl_3$): 0.75 (s, 3H, 18-$H_3$), 2.84 (m, 2H, 6-$H_2$), 3.68 (s, 1H, 17-H), 4.44 (m, 2H, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.72 (s, 1H, 4-H), 6.78 (d, 1H, *J* = 8.5 Hz, 2-H), 7.21 (d, 1H, *J* = 8.5 Hz, 1-H), 7.32 (t, 1H, *J* = 7.0 Hz, 4'-H), 7.38 (t, 3H, *J* = 7.0 Hz, 3'- and 5'-H, triazol-H), 7.43 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 17.9 (C-18), 25.9 (C-4"), 26.0, 26.1 (C-3" and -5"), 27.9, 29.7, 30.4, 31.8 (C-2" and -6"), 32.1, 32.9 (C-1"), 38.5, 43.3, 45.1 (C-13), 48.9, 49.1 (C-16), 62.1 (C-16a), 69.9 (Bn-$CH_2$), 82.5 (C-17), 112.3 (C-2), 114.7 (C-4), 126.3 (C-1), 127.4 (C-2' and -6'), 127.8 (C-4'), 128.5 (C-3' and -5'), 132.7 (C-10), 137.2 (C-1'), 137.9 (C-5), 156.7 (C-3).

*2.3.40. 3-Benzyloxy-16β-(4'-phenyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**27d**)*

Compound **19** (420 mg, 1 mmol) and phenylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (10:90 v/v) to yield pure **27d** (487 mg, 93%) as white crystals. Mp: 202–204 $^{o}$C; $R_f$= 0.45 (ss B). (Found C, 78.68; H, 7.38. $C_{34}H_{37}N_3O_2$ (519.68) requires C, 78.58; H, 7.18%). $^{1}$H NMR (δ, ppm, $CDCl_3$): 0.79 (s, 3H, 18-$H_3$), 2.84 (m, 2H, 6-$H_2$), 3.72 (s, 1H, 17-H), 4.48 (dd, 1H, *J* = 13.5 Hz, *J* = 7.5 Hz, 16a-$H_2$), 4.56 (t, 1H, *J* = 13.5 Hz, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.72 (s, 1H, 4-H), 6.78 (d, 1H, *J* = 8.5 Hz, 2-H), 7.21 (d, 1H, *J* = 8.5 Hz, 1-H), 7.33 (t, 1H, *J* = 7.5 Hz, 4'-H), 7.38 (t, 2H, *J* = 7.5 Hz, 3'- and 5'-H), 7.42 (d, *J* = 3.5 Hz, 4H, 2'- and 6'-H, 3"- and 5"-H), 7.84 (d, 2H, *J* = 7.5 Hz, 2"- and 6"-H), 7.88 (s, 1H, triazol-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 17.9 (C-18), 25.9, 27.9, 29.7, 30.4, 31.8, 38.5, 43.3, 45.2 (C-13), 48.9, 49.1 (C-16), 54.6 (C-16a), 69.9 (Bn-$CH_2$), 82.6 (C-17), 112.3 (C-2), 114.8 (C-4), 119.6 (triazol-CH), 125.7 (C-2' and -6'), 126.3 (C-1'), 127.4 (C-2" and -6"), 127.8 (C-4'), 128.2 (C-4"), 128.5 (C-3" and -5"), 128.8 (C-3' and -5'), 130.5 (C-10), 132.64 (C-1"), 137.3 (C-1'), 137.9 (C-5), 147.7 (triazol-C); 156.8 (C-3).

*2.3.41. 3-Benzyloxy-16β-[4'-(4''-nitro-benzoyloxymethyl)-1'H-1',2',3'-triazol-1'-yl]methylestra-1,3,5(10)-trien-17a-ol (**27e**)*

Compound **19** (420.0 mg, 1 mmol) and propargyl 4-nitrobenzoate (2 mmol, 210 mg) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (10:90 v/v) to yield pure **27e** (550 mg, 88%) as yellow crystals. Mp: 177–179 $^{o}$C; $R_f$= 0.48 (ss B). (Found C, 69.55; H, 5.93. $C_{36}H_{38}N_4O_6$ (622.71) requires: C, 69.44; H, 6.15%). $^1$H NMR (δ, ppm, DMSO-$d_6$): 0.65 (s, 3H, 18-$H_3$), 2.73 (m, 2H, 6-$H_2$), 4.40 (dd, 1H, *J* = 13.0 Hz, *J* = 8.5 Hz, 16a-$H_2$), 4.56 (dd, 1H, *J* = 13.5 Hz, *J* = 7.5 Hz, 16a-$H_2$), 4.63 (d, 1H, *J* = 5.0 Hz, 17-H), 5.04 (s, 2H, Bn-$H_2$), 5.47 (s, 2H, triazol-$H_2$), 6.68 (s, 1H, 4-H), 6.74 (d, 1H, *J* = 8.5 Hz, 2-H), 7.16 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 1H, *J* = 7.0 Hz, 4'-H), 7.37 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.41 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H), 8.18 (d, 2H, *J* = 8.5 Hz, 3"- and 5"-H), 8.33 (d, 3H, *J* = 6 Hz, 2"- and 6"-H, triazol-H). $^{13}$C NMR (δ, ppm, DMSO-$d_6$): 17.5 (C-18), 25.6, 27.5, 29.2, 29.6, 31.8, 38.2, 42.9, 44.5 (C-13), 48.2, 49.1 (C-16), 53.6 (C-16a), 58.7 (linker-$CH_2$), 68.9 (Bn-$CH_2$), 80.8 (C-17), 112.1 (C-2), 114.4 (C-4), 123.8 (C-2' and C-6'), 125.0 (triazol-CH), 126.1 (C-1), 127.4 (C-2" and -6"), 127.6 (C-4'), 128.3 (C-3" and -5"), 130.6 (C-3' and -5'), 132.3 (C-10), 134.7 (C-1"), 137.3 (C-5 and C-1'), 141.1 (triazol-C), 150.2 (C-4"), 160.0 (C-3), 163.9 (C=O).

### *2.3.42. 3-Benzyloxy-16β-(4'-hydroxymethyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**27f**)*

Compound **27e** (210 mg, 0.5 mmol) was dissolved in methanol (10 ml) containing $NaOCH_3$ (14 mg, 0.25 mmol), and the solution was allowed to stand for 24 h. It was then diluted with water, and the precipitate separating out was filtered off and recrystallized from methanol to afford **27e** (273 mg, 99%) as a white crystalline product. Mp: 172–174 $^{o}$C; $R_f$= 0.25 (ss B). (Found C, 73.68; H, 7.66. $C_{29}H_{35}N_3O_3$ (473.61) requires C, 73.54; H, 7.45%). $^1$H NMR (δ, ppm, DMSO-$d_6$): 0.67 (s, 3H, 18-$H_3$), 2.74 (m, 2H, 6-$H_2$), 3.43 (s, 1H, 17-H), 4.34 (m, 1H, 16a-$H_2$), 4.50 (m, 3H, 16a-$H_2$ and Bn-H2), 4.61 (brs, 1H, OH), 5.04 (s, 2H, triazol-$H_2$), 5.16 (brs, 1H, OH), 6.69 (s, 1H, 4-H), 6.74 (d, 1H, *J* = 8.5 Hz, 2-H), 7.17 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (d, 1H, *J* = 7.0 Hz, 4'-H), 7.37 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.41 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H), 8.00 (s, 1H, triazol-H). $^{13}$C NMR (δ, ppm, DMSO-$d_6$): 17.5 (C-18), 25.6, 27.5, 29.2, 29.6, 31.9, 38.2, 43.0, 44.5 (C-13), 48.2, 49.1 (C-16), 53.5 (C-16a), 55.0 (linker-$CH_2$), 61.6, 68.9 (Bn-$CH_2$), 80.8 (C-17), 112.2 (C-2), 114.4 (C-4), 122.6 (triazol-CH), 126.6 (C-1), 127.4 (C-2' and -6'), 127.6 (C-4'), 128.3 (C-3' and -5'), 132.4 (C-10), 137.3 (C-5 and C-1'), 147.6 (triazol-C), 156.0 (C-3).

*2.3.43. 3-Benzyloxy-16a-(4'-cyclopropyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**28a**)*

Compound **20** (420.0 mg, 1 mmol) and cyclopropylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **28a** (305 mg, 63%) as white crystals. Mp: 143–144 $^oC$; $R_f$= 0.40 (ss B). (Found C, 77.15; H, 7.53. $C_{31}H_{37}N_3O_2$ (483.64) requires C, 76.98; H, 7.71%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.74 (s, 3H, 18-$H_3$), 0.87 and 0.97 (2 x s, 2 x 2H, 2"- and 3"-$H_2$), 2.85 (m, 2H, 6-$H_2$), 3.63 (d, 1H, *J* = 5.0 Hz, 17-H), 4.26 (dd, 1H, *J* = 13.5 Hz, *J* = 5.5 Hz, 16a-$H_2$), 4.60 (t, 1H, *J* = 13.5 Hz, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.72 (d, 1H, *J* = 2.0 Hz, 4-H), 6.78 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.22 (d, 1H, *J* = 8.5 Hz, 1-H), 7.32 (t, 1H, *J* = 7.5 Hz, 4'-H), 7.38 (t, 3H, *J* = 7.5 Hz, 3'- and 5'-H, triazol-H), 7.43 (d, 2H, *J* = 7.5 Hz, 2'- and 6'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 6.5 (C-1"), 7.9 (2C, C-2" and -3"), 17.1 (C-18), 26.0, 27.9, 28.9, 29.8, 31.2, 38.9, 42.3, 43.5, 46.3 (C-16a), 47.0 (C-16), 50.7 (C-13), 69.9 (Bn-$CH_2$), 78.7 (C-17), 112.2 (C-2), 114.8 (C-4), 120.8 (triazol-CH)), 126.3 (C-1), 127.4 (C-2' and -6'), 127.4 (C-4'), 128.5 (C-3' and -5'), 132.5 (C-10), 137.2 (C-1'), 137.9 (C-5), 149.6 (triazol-C), 156.7 (C-3).

*2.3.44. 3-Benzyloxy-16a-(4'-cyclopentyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**28b**)*

Compound **20** (420.0 mg, 1 mmol) and cyclopentylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (2.5:97.5 v/v) to yield pure **28b** (417 mg, 82%) as white crystals. Mp: 197–199 $^oC$; $R_f$= 0.42 (ss B). (Found: C, 77.62; H, 7.85. $C_{33}H_{41}N_3O_2$ (511.70) requires C, 77.46; H, 8.08%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.76 (s, 3H, 18-$H_3$), 2.85 (m, 2H, 6-$H_2$), 3.20 (s, 1H, 1"-H), 3.66 (d, 1H, *J* = 5.0 Hz, 17-H), 4.29 (dd, 1H, *J* = 13.5 Hz, *J* = 5.5 Hz, 16a-$H_2$), 4.62 (dd, 1H, *J* = 13.5 Hz, *J* = 9.5 Hz, 16a-$H_2$), 5.04 (s, 2H, Bn-$H_2$), 6.72 (s, 1H, 4-H), 6.78 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.21 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 1H, *J* = 7.0 Hz, 4'-H), 7.37 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.43 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 17.3 (C-18), 25.2 (2C), 26.1, 28.0, 29.1, 29.8 (2C), 31.3, 33.2, 36.8 (C-1"), 39.0, 42.4, 43.6, 46.4 (C-16a), 47.2 (C-16), 50.6 (C-13), 70.1 (Bn-$CH_2$), 79.0 (C-17), 112.4 (C-2), 115.0 (C-4), 126.3 (C-1), 127.4 (C-2' and -6'), 127.8 (C-4'), 128.5 (C-3' and -5'), 133.0 (C-10), 137.5 (C-1'), 137.9 (C-5), 156.9 (C-3).

*2.3.45. 3-Benzyloxy-16a-(4-cyclohexyl-1H-1,2,3-triazol-1-yl)methyl-estra-1,3,5(10)-trien-17a-ol (**28c**)*

Compound **20** (420.0 mg, 1 mmol) and cyclohexylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (2.5:97.5 v/v) to yield pure **28c** (200 mg, 76%) as a white solid. Mp: 223–225 $^oC$; $R_f$= 0.44 (ss B). (Found C, 77.82; H, 8.35. $C_{34}H_{43}N_3O_2$ (525.72) requires C, 77.68; H, 8.24%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.75 (s, 3H, 18-$H_3$), 2.84 (m, 3H, 6-H2, 1''-H), 3.64 (s, 1H, 17-H), 4.37 (m, 1H, 16a-$H_2$), 4.69 (m, 1H, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.72 (d, 1H, *J* = 1.5 Hz, 4-H), 6.78 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.22 (d, 1H, *J* = 8.5 Hz, 1-H), 7.32 (t, 1H, *J* = 7.0 Hz, 4'-H), 7.38 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.43 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H

*2.3.46. 3-Benzyloxy-16a-(4-phenyl-1H-1,2,3-triazol-1-yl)methyl-estra-1,3,5(10)-trien-17a-ol (**28d**)*

Compound **20** (420.0 mg, 1 mmol) and phenylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **28d** (337 mg, 64%) as a white solid. Mp: 205–206 $^oC$; $R_f$= 0.46 (ss B). (Found C, 78.42; H, 7.32. $C_{34}H_{37}N_3O_2$ (519.68) requires C, 78.58; H, 7.18%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.76 (s, 3H, 18-$H_3$), 2.87 (m, 2H, 6-$H_2$), 3.68 (d, 1H, *J* = 5.0 Hz, 17-H), 4.41 (dd, 1H, *J* = 13.5 Hz, *J* = 5.5 Hz, 16a-$H_2$), 4.69 (t, 1H, *J* = 13.5 Hz, 16a-$H_2$), 5.04 (s, 2H, Bn-$H_2$), 6.73 (s, 1H, 4-H), 6.79 (dd, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz, 2-H), 7.22 (d, 1H, *J* = 8.0 Hz, 1-H), 7.38 (m, 8H, 2'-, 3'-, 4'-, 5'- and 6'-H, 3''-, 4''- and 5''-H), 7.84 (d, 2H, *J* = 7.5 Hz, 2''- and 6''-H), 7.89 (s, 1H, triazol-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 17.1 (C-18), 26.0, 27.9, 29.8, 31.2, 38.9, 42.2, 43.5, 46.4 (C-13), 47.0 (C-16), 50.8 (C-16a), 69.9 (Bn-$CH_2$), 78.8 (C-17), 112.3 (C-2), 114.8 (C-4), 120.7 (triazol-CH), 125.7 (C-2' and -6'), 126.3 (C-1), 127.4 (C-2'' and -6''), 127.8 (C-4'), 128.3 (C-4''), 128.5 (C-3'' and -5''), 128.9 (C-3' and -5'), 130.2 (C-10), 132.8 (C-1'), 137.3 (C-1''), 137.9 (C-5), 147.1 (triazol-C), 156.7 (C-3).

*2.3.47. 3-Benzyloxy-16a-[4'-(4''-nitro-benzoyloxymethyl)-1'H-1',2',3'-triazol-1'-yl]methylestra-1,3,5(10)-trien-17a-ol (**28e**)*

Compound **20** (420 mg, 1 mmol) and propargyl 4-nitrobenzoate (2 mmol, 210 mg) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **28e** (610 mg, 98%) as a yellow solid. Mp: 75–77 $^oC$; $R_f$= 0.45 (ss B). (Found C, 69.57; H, 61.32. $C_{36}H_{38}N_4O_6$ (622.71) requires C, 69.44; H, 6.15%). $^1H$ NMR (δ, ppm, DMSO-$d_6$): 0.66 (s, 3H, 18-$H_3$), 2.71 (m, 2H, 6-$H_2$), 3.57 (s, 1H, 16-H), 4.29 (dd, 1H, *J* = 13.5 Hz, *J* = 8.5 Hz, 16a-$H_2$), 4.47 (dd, 1H, *J* = 13.5 Hz, *J* = 8.5 Hz, 16a-$H_2$), 4.85 (d, 1H, *J* = 5.0 Hz, 17-H), 5.44 (s, 2H, Bn-$H_2$), 6.65 (s, 1H, 4-H), 6.72 (d, 1H, *J* = 8.5 Hz, 2-H), 7.14 (d, 1H, *J* = 8.5 Hz, 1-H), 7.29 (t, 1H, *J* = 7.5 Hz, 4'-H), 7.35 (t, 2H, *J* = 7.5 Hz, 3'- and 5'-H), 7.40 (d, 2H, *J* = 7.5 Hz, 2'- and 6'-H), 8.17 (d, 2H, *J* = 8.5 Hz, 3"- and 5"-H), 8.28 (s, 1H, triazol H), 8.31 (d, 2H, *J* = 8.5 Hz, 2"- and 6"-H). $^{13}C$ NMR (δ, ppm, DMSO-$d_6$): 16.9 (C-18), 25.6, 27.5, 28.4, 29.2, 31.1, 38.5, 39.8, 39.9, 43.2, 45.9 (C-16a), 46.2 (C-16), 53.4 (C-13), 58.7 (linker $CH_2$), 68.9 (Bn-$CH_2$), 78.0 (C-17), 112.1 (C-2), 114.4 (C-4), 123.8 (C-2" and -6"), 125.0 (triazol CH), 126.1 (C-1), 127.4 (C-2' and -6'), 127.5 (C-4'), 128.3 (C-3' and -5'), 130.6 (C-3" and -5"), 132.3 (C-10), 134.7 (C-1'), 137.3 (C-5), 141.0 (C-1"), 150.2 (triazol C), 156.0 (C-3), 163.9 (C=O).

### *2.3.48. 3-Benzyloxy-16a-(4'-hydroxymethyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17α-ol (**28f**)*

Compound **28e** (220 mg, 0.5 mmol) was dissolved in methanol (10 ml) containing $NaOCH_3$ (14 mg, 0.25 mmol), and the solution was allowed to stand for 24 h. It was then diluted with water, and the precipitate separating out was filtered off and recrystallized from methanol to afford **28f** (126 mg, 53%) as a white crystalline product. Mp: 86–88 $^oC$; $R_f$= 0.25 (ss B). (Found C, 73.68; H, 7.63. $C_{29}H_{35}N_3O_3$ (473.61) requires C, 73.54; H, 7.45%). $^1H$ NMR (δ, ppm, DMSO-$d_6$): 0.68 (s, 3H, 18-$H_3$), 2.74 (m, 2H, 6-$H_2$), 3.58 (brs, 1H, OH), 4.26 (t, 1H, *J* = 8.5 Hz, 16a-$H_2$), 4.43 (dd, 1H, *J* = 13.0 Hz, *J* = 7.0 Hz, 16a-$H_2$), 4.51 (d, 2H, *J* = 5.0 Hz, linker $H_2$), 4.85 (d, 1H, *J* = 4.0 Hz, 17-H), 5.04 (s, 2H, Bn-$H_2$), 5.13 (brs, 1H, OH), 6.68 (s, 1H, 4-H), 6.74 (d, 1H, *J* = 8.5 Hz, 2-H), 7.17 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (d, 1H, *J* = 7.0 Hz, 4'-H), 7.37 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.42 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H), 7.97 (s, 1H, triazol H). $^{13}C$ NMR (δ, ppm, DMSO-$d_6$): 16.9 (C-18), 25.6, 27.5, 28.5, 29.2, 31.1, 38.5, 40.7, 43.2, 45.9, 46.2 (C-16), 47.9 (C-13), 50.6 (C-16a), 55.0 (linker $CH_2$), 68.9 (Bn-$CH_2$), 78.0 (C-17), 112.1 (C-2), 114.4 (C-4), 122.7 (triazol

CH), 126.1 (C-1), 127.4 (C-2’ and -6’), 127.6 (C-4’), 128.3 (C-3’ and -5’), 132.4 (C-10), 137.3 (C-1’), 137.4 (C-5), 147.6 (triazol C), 156.0 (C-3).

*2.4. Determination of the antiproliferative activities*

The growth-inhibitory effects of the compounds were tested *in vitro* by means of the MTT assay against a gynecological panel containing two breast cancer cell lines (MCF-7, MD-MB-231) and two cell lines isolated from cervical malignancies (HeLa, SiHa) [11]. All cell lines were obtained from the European Collection of Cell Cultures (Salisbury, UK). The cells were maintained in minimal essential medium supplemented with 10% fetal bovine serum (FBS), 1% non-essential amino acids and an antibiotic–antimycotic mixture (AAM). All chemicals, if otherwise not specified, were purchased from Sigma-Aldrich Ltd. (Budapest, Hungary). All cell lines were grown in a humidified atmosphere of 5% $CO_2$ at 37 $^{o}$C. For pharmacological investigations, 10 mM stock solutions of the tested compounds were prepared with dimethyl sulfoxide (DMSO). The highest applied DMSO concentration of the medium (0.3%) did not have any substantial effect on the determined cellular functions. Cells were seeded into 96-well plates (5000 cells/well), allowed to stand overnight under cell culturing conditions, and the medium containing the tested compounds at two final concentrations (10 or 30 μM) was then added. After a 72-hour incubation viability was determined by the addition of 20 μl 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) solution (5 mg/ml). The formazan crystals precipitated in 4 h were solubilized in DMSO and the absorbance was determined at 545 nm with an ELISA plate reader utilizing untreated cells as controls. The most effective compounds eliciting at least 60% growth inhibition at 10 μM were tested again with a set of dilutions (0.3−30 μM) in order to determine the $IC_{50}$ values by means of Graphpad Prism 4.0 (Graphpad Software; San Diego, CA, US). These promising compounds were additionally tested using nonmalignant murine fibroblasts (NIH-3T3) to obtain preliminary data concerning cancer selectivity of the tested molecules. Two independent experiments were performed with 5 parallel wells and cisplatin (Ebewe GmbH, Unterach, Austria), an agent administered clinically in the treatment of certain gynecological malignancies, was used as reference compound.

## 3. Results and discussion

*3.1. Synthetic studies*

To prepare novel steroid triazoles via 1,3-dipolar cycloaddition, we chose the 3-methoxy- and 3-benzyloxy-16-hydroxymethylestra-1,3,5(10)-trien-17-ol diastereomers (**5**–**8** and **9**–**12**). The synthesis strategy for the preparation of the starting diols (**21**–**28**) is illustrated in Scheme 1. The synthesis of steroidal 1,2,3-triazoles by CuAAC is outlined in Scheme 2.

Stereoselective tosylation of **5**–**8** and bromination of **9**–**12** gave **5b**–**8b** and **9c**–**12c**, respectively, which then underwent facile $S_N2$ substitution with $NaN_3$ in *N*,*N*-dimethylformamide to furnish the corresponding 16-azidomethyl compounds (**13**–**16** and **17**–**20**).

The 16-azido compounds were subjected to the azide–alkyne CuAAC reaction with different alkyl- and aryl-acetylenes. The azide–alkyne reactions of these compounds were carried out with CuI as catalyst in the presence of $Et_3N$ in $CH_2Cl_2$ under reflux conditions to obtain the required 3-methoxy- and 3-benzyloxyestra-1,3,5(10)-trien-16-(1',4'-substituted 1',2',3')-triazolyl derivatives (**21**–**24** and **25**–**28**).

*3.2. Determination of the antiproliferative properties of the 16-triazolylmethyl diastereomers*

We have published recently that introduction of a substituted triazole moiety onto different positions of the estrane skeleton might increase the antiproliferative properties of estrone derivatives [12]. It was also established that the presence of certain alkyl or aralkyl protecting groups at the phenolic OH function is advantageous. Concerning that 16-hydroxymethylene-17-hydroxy derivatives of estrone-3-methyl ether or 3-benzyl ether (**5a**–**12a**) displayed substantial cytostatic potential against different types of breast cancer cell lines, these compounds might be suitable for directed modifications with the aim of developing potentially more active antiproliferative steroidal derivatives [13]. In the light of the above-mentioned recent observations, here we aimed to combine the substituted triazole and the 16,17-disubstituted estrone 3-ether moieties. The present study included an evaluation of the direct antiproliferative capacities of the newly synthesized heterocyclic compounds (**21a**–**f**, **22a**–**f**, **23a**–**f**, **24a**–**f** and **25a**–**f**, **26a**–**f**, **27a**–**f**, **28a**–**f**). The antiproliferative activities were determined *in vitro* by means of MTT assays against human adherent cervical (SiHa, HeLa) and breast cancer (MCF-7 and MDA-MB-231) cell lines.

The antiproliferative activities of the newly synthesized heterocyclic compounds depended on the nature of the protecting group at the 3-hydroxy function and on the orientation of the substituents at C-16 and C-17. In general, the 3-methyl ethers (**21**–**24**) exhibited weak antiproliferative action; none of them exerted any substantial effect at 10 μM (Table 1). All diastereomers of the 3-benzyl ether series (**25**–**28**) proved to be more potent in comparison with their 3-methyl ether counterparts (Table 2). This is in agreement with our earlier results [14]. Based on the substantial difference of the two groups, i.e. that of 3-methyl ethers and 3-benzyl ethers, it can be concluded that only the latter derivatives are promising from pharmacological point of view.

Concerning the orientation of the substituents at position C-16 and C-17, the 16β,17β-derivatives (**25a**–**f**) displayed outstanding growth-inhibitory properties. Two derivatives bearing similar cycloalkyl groups at position C-4' displayed substantial selective antiproliferative action against the triple-negative breast cancer cell line MDA-MB-231 with $IC_{50}$ values in the low micromolar range. It should be underlined that **25b** and **25c** did not significantly influence the proliferation of other cell lines tested, including the non-cancerous fibroblast. Although both the 4'-cyclohexyl (**25c**) and the 4'-phenyl derivative (**25d**) have six-membered substituents, their cytostatic behavior is completely different. This might be attributed to the different steric structure of the two rings (chair or planar) at C-4'. Compound **25d** exerted potent antiproliferative action against all tested cell lines without any selectivity. The *cis-16α,17α*-3-benzyl ethers (**28a**–**f**) were less potent than their β,β-counterparts (**25a**–**f**), except for **28d**, which behaved similarly to its diastereomer **25d**. The *trans*-16β,17α-isomers (**27a**–**f**) exhibited activity exclusively on the breast cancer cell lines. Surprisingly, the tendency observed earlier (in the case of compounds **25a**–**f**) concerning the nature of C-4' substituent was not valid here. Only **26a** and **26e** inhibited cell growth markedly, but with no tumor selectivity. It's worth mentioning that *trans*-16α,17β isomer **26c** was the sole compound, which inhibited the proliferation of HPV 16+ squamous cell carcinoma SiHa, showing an $IC_{50}$ value comparable with that of cisplatin.

In view of the cell lines, it should be noted that triple-negative breast cancer cell line MDA-MB-231 proved to be the most sensitive and all calculated $IC_{50}$ values were lower than that of the reference agent cisplatin (19.1 μM).

Regarding the present and earlier results obtained for 16,17-disubstituted 3-benzyl ethers, it can be stated that introduction of a substituted triazolyl moiety onto the C-16 methylene group of the

*cis* isomers proved to be advantageous. In the case of compounds **25b** and **25c**, both the antiproliferative potential and the tumor selectivity were markedly improved.

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## References


[1] Tietze LF, Bell HP, Chandrasekhar S, Natural product hybrids as new leads drug discovery. Angew Chem Int Ed **2003**;42:3996–4028.

[2] Mehta G, Singh V, Hybrid system through natural product leads: An approach towards new molecular entities. Chem Soc Rev **2002**;31:324–334.

[3] Adamec J, Beckert R, Weiß D, Klimešová V, Waisser K, Möllmann U, Kaustová J, Buchta V. Hybride molecules of estrone: New Compound with potential antibacterial, antifungal and antiproliferative activities. Bioorg Med Chem **2007**;*15*:2898–2906.

[4] Kuduk, SD, Zheng FF, Sepp-Lorenzino L, Rosen N, Danishefsy SJ. Synthesis and Evaluation of geldanamycin-estradiol hybrids. Bioorg Med Chem **1999**;9:1233-1238.

[5] Gupta A, Saha P, Descôteaux C, Leblanc V, Asselin É, Bérubé G. Design, synthesis and biological evaluation of estradiol-chlorambucil hybrids as anticancer agents. Bioorg Med Chem Lett **2010;**20:1614-1618.

[6] Schneider Gy, Vass A, Vincze I, Sohár P. Neighbouring Group Partcipation in the 16-Hydroxymethyl-3-methoxyestre-1,3,5(10)-trien-17β-ol Series. Liebigs Ann Chem **1988**;267–273.

[7] Schneider Gy, Hackler L, Sohár P. Preparation of 16α-Hydroxymethyl-3-methoxyestra-1,3,5(10)-trien 17α-ol and Solvolysis Investigation. Liebigs Ann Chem **1988**;679-683.

[8] Tapolcsányi P, Wölfling J, Falkay G, Márki Á, Minorics R, Schneider Gy. Synthesis and receptor-binding examination of 16-hydroxymethyl-3,17-estradiol stereoisomers. Steroids **2002**;67:671-678.

[9] Meldal M, Tornøe CW. Cu-Catalyzed azide–alkyne cycloaddition. Chem Rev. **2008**;108:2952–3015.

[10] Szájli Á, Wölfling J, Mernyák E, Minorics R, Márki Á, Falkay G, Schneider Gy. Neighbouring group participation Part 16. Stereoselective synthesisi and receptor-binding examination of the four stereoisomers of 16-bromomethyl-3,17-estradiols. Steroids **2006**;*71*:141–153.

[11] Mosmann T. Rapid colorimetrc assay for cellural growth and survival: application to prolyferation and cytotoxicity assay. J immunol Methods 1983;65:55-63.

[12] Mernyák E, Kovács I, Minorics R, Sere P, Czégány Sinka I, Wölfling, Schneider G, Újfaludi Zs, Boros I, Ocsovszki I, Varjj ga M, Zupkó I. Synthesis of trans-16-triazolyl-13α-methyl-17-estradiol diastereomers and the effects of structural modifications on their in vitro antiproliferative activities. J Steroid Biochem Mol Biol **2015**;150:123–134.

[13] Sinka I, Kiss A, Mernyák E, Wölfling E, Schneider G. Ocsovszki I, Kuo CY, Wang HC, Zupkó I. Antiproliferative and antimetastatic properties of 3-benzyloxy-16-hydroxymethylene-estardiol analogs agains breast cancer cell lines. Eur J Pharm Sciences **2018**;123:362–370.

[14] Frank E, Molnar J, Zupko I, Kadar Z, Wölfling J. Synthesis of novel steroidal 17α-triazolyl derivatives via Cu(I)-catalyzed azide-alkyne cycloaddition, and an evaluation of their cytotoxic activity in vitro. Steroids **2011**;76:1141–1148.

## Legends for Schemes and Tables

**Scheme 1** Reagents and conditions: (i) NaOMe, HCOOEt, anhydrous toluene, 50 °C; (ii) $KBH_4$, MeOH; (iii) KOAc, $CH_3COOH$, NaOMe/MeOH.

**Scheme 2** Reagents and conditions: (i) appropriate alkyne, TEA, CuI, $CH_2Cl_2$, 40 °C, 24 h; (ii) NaOMe, MeOH, 24 h.

**Table 1** Antiproliferative activities of compounds **21a**–**f, 22a**–**f, 23a**–**f** and **24a**–**f**

**Table 2** Antiproliferative activities of compounds **25a**–**f, 26a**–**f, 27a**–**f** and **28a**–**f**

**Table 1**

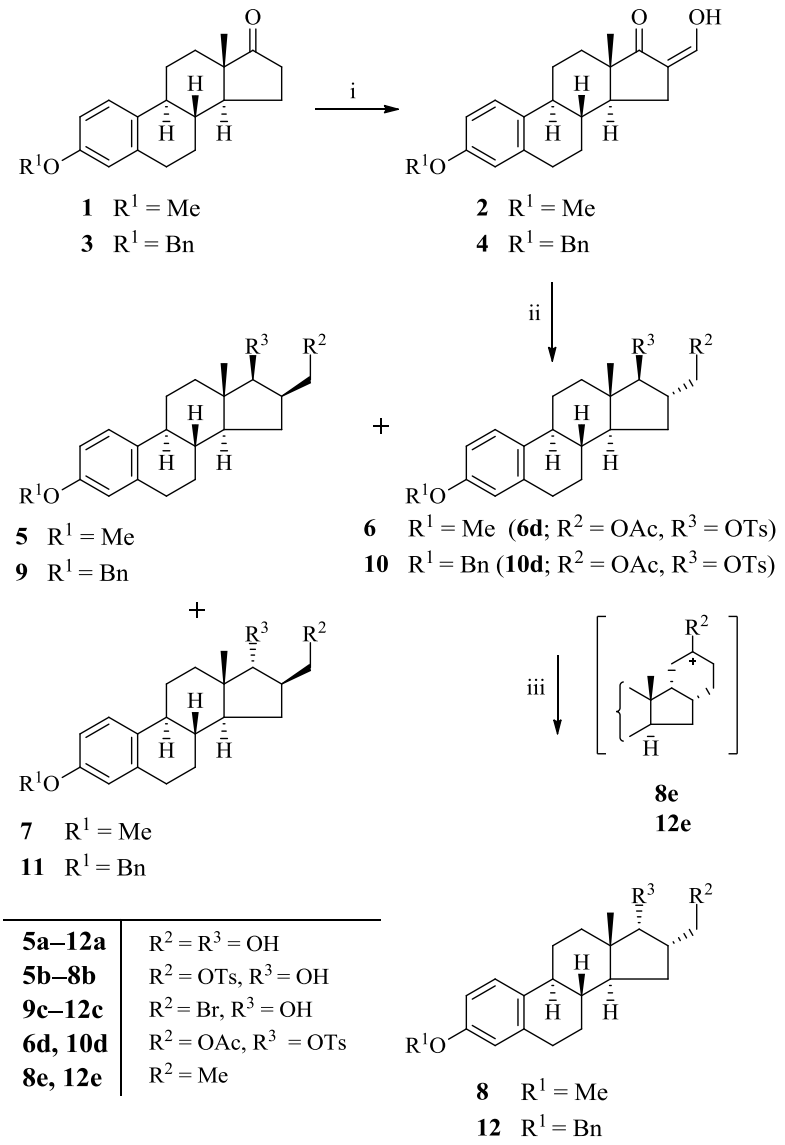
| | Conc. (μM) | Growth Inhibition, % ± SEM [calculated $IC_{50}$ (μM)] HeLa | SiHa | MCF-7 | MDA-MB-231 |
|---|---|---|---|---|---|
| **21** | | | | | |
| **a** | 10 | <20 | 21.28±1.88 | <20 | <20 |
| | 30 | <20 | 28.71±2.20 | 46.42±1.47 | <20 |
| **b** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 39.86±.38 | <20 | 57.42±1.77 | 29.88±1.57 |
| **c** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 40.22±1.02 | <20 | 70.84±1.55 | 37.96±1.55 |
| **d** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 44.16±0.48 | <20 | 54.93±1.78 | 38.28±1.84 |
| **e** | 10 | <20 | 23.91±1.61 | 34.23±3.10 | <20 |
| | 30 | 37.18±1.65 | 54.72±0.48 | 76.26±0.72 | 35.93±2.13 |
| **f** | 10 | <20 | 28.06±1.99 | 29.45±1.67 | <20 |
| | 30 | 41.03±0.77 | 57.69±1.12 | 70.23±1.35 | 34.81±2.88 |
| **22** | | | | | |
| **a** | 10 | <20 | 25.55±1.01 | <20 | <20 |
| | 30 | <20 | 34.78±2.47 | 57.43±1.91 | <20 |
| **b** | 10 | <20 | <20 | <20 | <20 |
| | 30 | <20 | 26.57±2.26 | 67.59±1.65 | <20 |
| **c** | 10 | <20 | <20 | <20 | <20 |
| | 30 | <20 | 29.90±2.59 | 69.68±0.77 | <20 |
| **d** | 10 | <20 | <20 | <20 | <20 |
| | 30 | <20 | 29.96±1.79 | 70.75±1.05 | 14.54±1.32 |
| **e** | 10 | <20 | <20 | <20 | <20 |
| | 30 | <20 | 38.69±2.09 | 63.12±2.14 | <20 |
| **f** | 10 | <20 | <20 | 22.02±1.61 | <20 |
| | 30 | <20 | 37.79±1.04 | 50.94±1.55 | <20 |
| **23** | | | | | |
| **a** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 31.14±1.28 | <20 | 28.72±0.93 | 25.08±3.15 |
| **b** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 58.25±2.03 | <20 | 48.01±1.31 | <20 |
| **c** | 10 | <20 | 30.97±2.69 | <20 | <20 |
| | 30 | <20 | 33.89±2.35 | <20 | <20 |
| **d** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 26.90±2.15 | <20 | 63.27±0.82 | <20 |
| **e** | 10 | <20 | <20 | <20 | <20 |
| | 30 | <20 | 37.53±3.00 | 33.94±0.75 | 28.19±0.96 |
| **f** | 10 | <20 | 29.13±1.59 | <20 | <20 |
| | 30 | 26.61±0.57 | 43.85±3.32 | 38.45±1.93 | 43.85±3.32 |
| **24** | | | | | |
| **a** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 89.01±0.47 | <20 | 78.65±0.78 | 46.21±1.54 |
| **b** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 34.18±0.81 | <20 | 31.07±2.36 | <20 |
| **c** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 49.11±0.55 | <20 | 43.22±1.52 | <20 |

| | | | | | |
|---|---|---|---|---|---|
| **d** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 42.13±1.66 | <20 | 55.41±0.76 | <20 |
| **e** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 83.66±0.34 | 42.06±2.50 | 70.11±1.06 | 50.27±2.00 |
| **f** | 10 | <20 | <20 | 22.34±2.06 | <20 |
| | 30 | 84.77±1.18 | 29.80±1.66 | 68.27±1.19 | 47.74±1.21 |
| cisplatin | 10 | 42.61±2.33 | 86.84±0.50 | 53.03±2.29 | 20.84±0.81 |
| | 30 | 99.93±0.26 | 90.18±1.78 | 86.90±1.24 | 74.47±1.20 |
| | | [12.43] | [7.84] | [5.78] | [19.13] |

**Table 2**

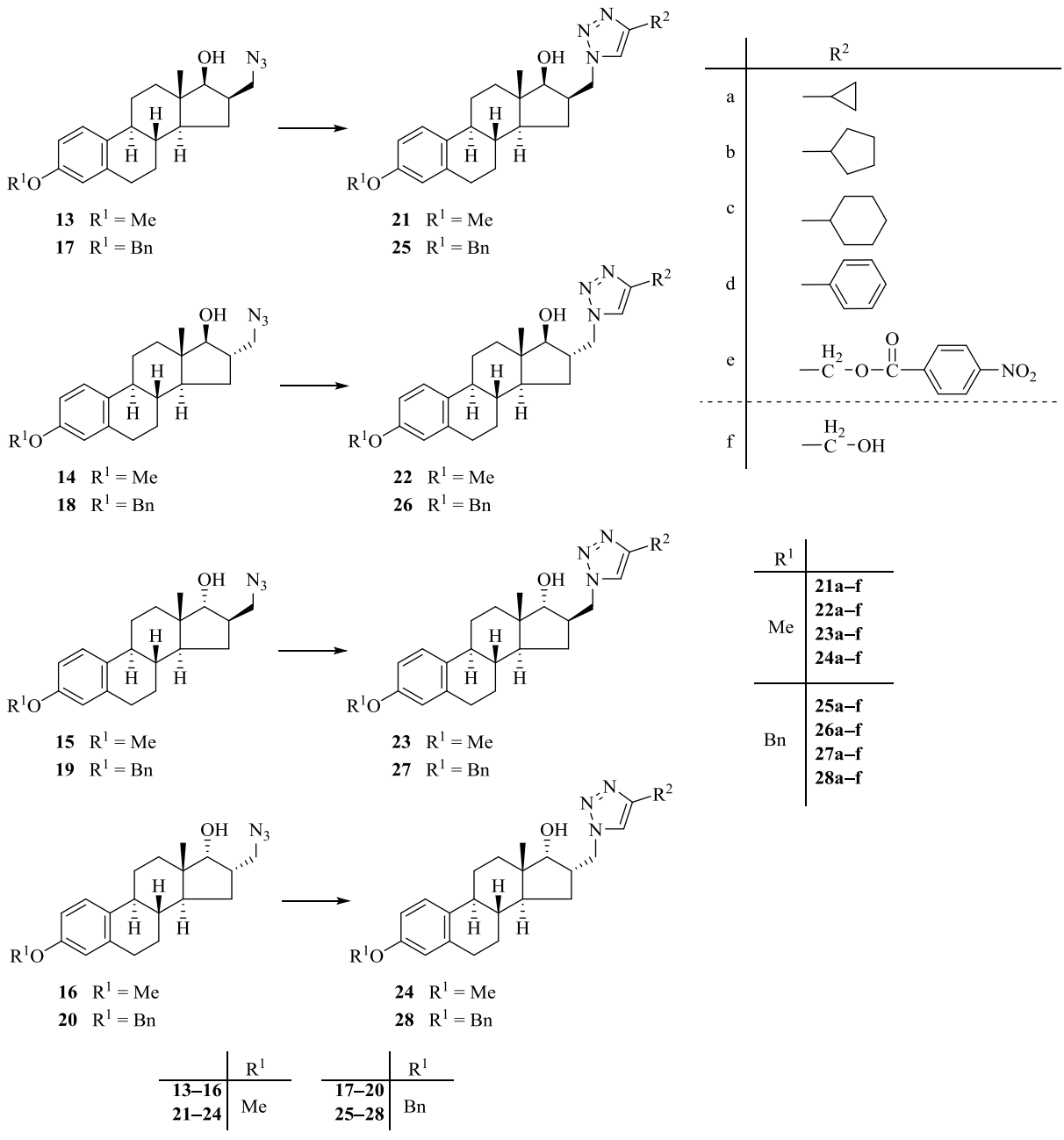
| | Conc. (μM) | Growth Inhibition, % ± SEM [calculated $IC_{50}$ (μM)] HeLa | SiHa | MCF-7 | MDA-MB-231 | NIH-3T3 |
|---|---|---|---|---|---|---|
| **25** | | | | | | |
| **a** | 10 | 44.94±1.04 | 21.17±2.05 | 41.71±0.64 | 47.32±1.15 | 44.91±1.36 |
| | 30 | 52.45±2.39 | 66.23±0.86 | 64.32±0.56 | 71.49±0.75 | 91.28±0.50 |
| **b** | 10 | 51.49±3.62 | 49.36±1.69 | 44.58±1.50 | 93.00±0.26 | 44.81±1.50 |
| | 30 | 62.58±2.21 | 73.94±2.04 | 50.52±3.26 | 93.71±0.09 [3.33] | 59.09±0.73 |
| **c** | 10 | 54.70±1.88 | 49.58±2.11 | 44.04±3.32 | 77.13±1.07 | |
| | 30 | 53.66±2.56 | 61.83±2.77 | 59.33±2.99 | 88.81±0.55 [5.91] | |
| **d** | 10 | 64.14±0.86 | 70.88±1.03 | 73.41±1.22 | 95.04±0.16 | 95.60±0.25 |
| | 30 | 90.12±0.99 [2.28] | 94.14±0.29 [4.05] | 80.16±3.40 [3.91] | 95.60±0.06 [3.65] | 98.22±0.04 [3.34] |
| **e** | 10 | <20 | <20 | 41.63±2.83 | 21.96±0.73 | |
| | 30 | 92.12±0.25 | 89.25±0.68 | 97.00±0.11 | 95.22±0.91 | |
| **f** | 10 | 45.08±0.72 | 41.26±1.25 | 55.41±1.26 | 55.57±1.50 | |
| | 30 | 39.39±0.49 | 52.60±1.31 | 62.52±0.67 | 88.92±0.99 | |
| **26** | | | | | | |
| **a** | 10 | 37.98±2.68 | <20 | 72.42±2.19 | 46.43±2.05 | 85.50±1.22 |
| | 30 | 96.56±0.11 | 96.71±0.17 | 98.72±0.09 [6.11] | 97.96±0.17 | 97.63±0.12 [5.97] |
| **b** | 10 | 38.55±1.32 | <20 | 31.80±1.35 | 17.13±2.36 | |
| | 30 | 43.97±2.23 | <20 | 84.44±0.71 | 37.72±2.28 | |
| **c** | 10 | 36.30±1.45 | <20 | 24.95±2.15 | <20 | |
| | 30 | 35.53±1.24 | <20 | 74.73±1.00 | <20 | |
| **d** | 10 | <20 | <20 | 47.25±1.78 | 45.55±2.63 | |
| | 30 | 22.15±1.29 | <20 | 57.30±0.77 | 59.79±1.22 | |
| **e** | 10 | <20 | <20 | 68.51±0.71 | 89.24±0.70 | 31.41±2.21 |
| | 30 | 96.98±0.33 | 96.91±0.14 | 99.12±0.07 [6.53] | 97.73±0.23 [5.69] | 99.01±0.05 [11.75] |
| **f** | 10 | 21.62±3.46 | <20 | 29.14±2.06 | 40.46±2.98 | 10.00±1.01 |
| | 30 | 30.79±2.92 | 27.28±1.90 | 43.28±1.53 | 76.93±1.60 | 23.40±0.60 |
| **27** | | | | | | |
| **a** | 10 | 24.26±2.63 | 34.00±1.43 | 58.38±3.20 | 56.24±0.98 | 25.56±2.21 |
| | 30 | 85.22±1.32 | 82.68±1.25 | 97.21±0.10 | 84.18±0.44 | 99.24±0.07 |
| **b** | 10 | 37.10±1.77 | 39.59±1.17 | 51.92±1.00 | 56.44±0.98 | |
| | 30 | 52.08±2.08 | 69.54±1.24 | 65.12±1.91 | 71.81±0.96 | |
| **c** | 10 | 38.89±2.60 | 64.05±1.24 | 49.68±1.66 | 72.37±1.27 | 13.99±1.79 |
| | 30 | 55.93±2.39 | 83.34±1.31 [9.29] | 61.26±1.72 | 85.81±1.04 [6.74] | 29.56±1.17 |
| **d** | 10 | 34.23±1.39 | 30.04±2.07 | 47.03±1.25 | 55.77±1.03 | |
| | 30 | 47.74±0.78 | 39.96±2.34 | 42.43±1.69 | 57.71±1.00 | |
| **e** | 10 | <20 | 21.53±1.81 | 35.74±1.33 | <20 | |
| | 30 | 99.06±0.09 | 96.91±0.06 | 98.50±0.93 | 99.01±0.52 | |
| **f** | 10 | <20 | 24.65±1.46 | 25.50±2.93 | 24.79±2.20 | |
| | 30 | 98.72±0.13 | 96.04±0.25 | 98.41±0.15 | 98.79±0.16 | |
| **28** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **a** | 10 | 35.48±1.91 | 46.07±1.13 | 52.88±0.82 | 25.61±2.84 | |
| | 30 | 63.44±1.79 | 69.86±0.55 | 73.39±0.74 | 52.16±2.52 | |
| **b** | 10 | 39.75±2.45 | <20 | 43.51±1.85 | 44.86±0.93 | |
| | 30 | 47.34±1.62 | <20 | 42.28±1.44 | 43.73±2.25 | |
| **c** | 10 | 56.71±0.57 | 39.93±3.14 | 48.56±0.48 | 30.30±1.64 | |
| | 30 | 58.21±0.73 | 31.15±2.86 | 49.93±1.33 | 31.60±3.08 | |
| **d** | 10 | 74.18±1.15 | 76.88±0.49 | 75.97±0.89 | 86.12±0.33 | 70.18±1.15 |
| | 30 | 91.17±0.33 | 87.39±0.86 | 88.99±0.25 | 90.72±1.00 | 91.12±1.64 |
| | | [2.30] | [4.14] | [3.87] | [3.89] | [3.71] |
| **e** | 10 | 27.42±2.16 | <20 | 52.86±1.30 | 29.58±1.69 | |
| | 30 | 92.94±0.17 | 91.91±0.23 | 96.38±0.07 | 94.09±0.43 | |
| **f** | 10 | 30.97±1.02 | 39.85±1.24 | 50.60±0.65 | 31.89±2.92 | |
| | 30 | 91.88±0.26 | 90.94±0.18 | 95.12±0.10 | 92.56±0.34 | |
| cisplatin | 10 | 42.61±2.33 | 86.84±0.50 | 53.03±2.29 | 20.84±0.81 | 94.20±0.39 |
| | 30 | 99.93±0.26 | 90.18±1.78 | 86.90±1.24 | 74.47±1.20 | 96.44±0.17 |
| | | [12.43] | [7.84] | [5.78] | [19.13] | [3.23] |




**Scheme 1. Reagents and conditions:** (i) NaOMe, HCOOEt, anhydrous toluene, 50 °C; (ii) $KBH_4$, MeOH; (iii) KOAc, $CH_3COOH$, NaOMe/MeOH

**Scheme 1.**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N3
R1O
H
R2
N
13 R1 = Me
17 R1 = Bn
21 R1 = Me
25 R1 = Bn
14 R1 = Me
18 R1 = Bn
22 R1 = Me
26 R1 = Bn
15 R1 = Me
19 R1 = Bn
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27 R1 = Bn
16 R1 = Me
20 R1 = Bn
24 R1 = Me
28 R1 = Bn
a
b
c
d
e
f
H2C-O-C
NO2
H2C-OH
R1
Me
Bn
21a–f
22a–f
23a–f
24a–f
25a–f
26a–f
27a–f
28a–f
13–16
21–24
17–20
25–28

**Scheme 2.**

# Stereocontrolled Synthesis of the Four Possible 3-Methoxy and 3-Benzyloxy-16-Triazolyl-methyl-estra-17-ol Hybrids and their Antiproliferative Activities

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ABSTRACT The four possible isomers of each of 3-methoxy- and 3-benzyloxyestra-1,3,5(10)-trien-17-ols (**5**–**8** and **9**–**12**) were converted through 16-*p*-tosyloxymethyl- or 16-bromomethyl derivatives into their 3-methoxy- and 3-benzyloxy-16-azidomethylestra(1,3,5(10)-triene derivatives (**13**–**16** and **17**–**20**). The regioselective Cu(I)-catalyzed 1,3-dipolar cycloaddition of these compounds with different terminal alkynes afforded novel 1,4-disubstituted diastereomers (**21a–f, 22a–f, 23a–f, 24a–f** and **25a–f, 26a–f, 27a–f, 28a–f**). The antiproliferative activities of the structurally related triazoles were determined *in vitro* with the microculture tetrazolium assay on four malignant human cell lines of gynecological origin (Hela, SiHa, MCF-7 and MDA-MB-231).

*Keywords:* 3-methoxy- and 3-benzyloxy-16-azidomethylestra-1,3,5(10)-triene-17-ols; 1,3-dipolar cycloaddition, 4′substituted-steroid triazoles; cytotoxic activity

## 1. Introduction

Among the hybrid natural products, hybrids of steroid frameworks have attracted great attention due to significant biological properties and numerous therapeutic effects of the basic compound. Steroids have become ideal synthons for the development of diverse conjugates due to their rigid framework and potential for varying levels of functionalization, broad biological activity profile and their ability to penetrate the cell membranes and bind to specific hormonal receptors [1-3].

The place, length and orientation of the linkers between the two parts of the hybrids stems unequivocally from the method of their synthesis. The literature provides a large number of methods to introduce the linker onto the sterane skeleton. The effect of the length and character of the linker are very often discussed [4]. However, only limited information is available with respect to the steric effect of the linkers on biological properties. As concerns the 16-substituted estrogenes, usually the 16α-substituted-17β-hydroxy compounds have been studied. The biological activity has generally not been studied for the whole isomer series [5].

In the 16-substituted 17-hydroxysteroids, the two chiral centres permit four stereochemical modifications. Since availability of the complete series of isomers would permit a number of interesting comparative examinations.

We have previously reported the preparation and configurational assignment of the four possible isomers of the 3-methoxy- and 3-benzyloxy-16-hydroxymethyl-estra-1,3,5(10)-trien-17-ol derivatives (**5a**–**8a** and **9a**–**12a**) [6–8]. Treatment of 3-methoxy- and 3-benzyloxyestra-16-hydroxymethylidene-estra-1,3,5(10)-trien-17-ones (**1** and **3**) with NaOMe and ethyl formate gave 3-methoxy- and 3-benzyloxy-16-hydroxymethylidene-estra-1,3,5(10)-trien-17 ones (**2** and **4**). The C-16 formyl compounds were reduced with $KBH_4$ in methanol yielding a mixture of three (**5a**–**7a** and **9a**–**11a**) of the four possible isomers of each of the 3-methoxy- and 3-benzyloxy-16-hydroxymethylestra-1,3,5(10)-trien-17-ol isomers in a ratio of 50:45:5 in 94% yield [6,8 ]. The fourth isomers (**8a** and **12a**) were prepared from 16α-acetoxymethyl-17β-toluenesulfonate mixed esters **6d** and **10d**, respectively, by neighbouring group participation during solvolysis in aqueous AcOH. The structures of the isomers were confirmed unambiguously by their IR, $^{1}H$ and $^{13}C$ NMR spectra (Scheme 1) [7,8].

**(Scheme 1)**

The four 3-methoxy- and 3-benzyloxy-estra-1,3,5(10)-trien-17-ol isomers (**5a**–**8a** and **9a**–**12a**) are suitable starting materials to prepare 16-triazolyl-methyl derivatives. Triazoles are attractive units because of their stability against metabolic degradation and their ability to form hydrogen bonds. The Cu(I)-catalysed azide–alkyne cycloaddition (CuAAC) is a facile method of wide applicability for the introduction of a triazole moiety into natural products [9]. In these compounds the triazole heterocycles and their substituted derivatives are connected through a methylene linker to the sterane skeleton. The 16-*p*-tolylsulfonyloxymethyl ester [5,6] and 16-bromomethyl derivatives [10] of the 16-hydroxymethyl starting materials were used for substitution reaction with $NaN_3$ in *N*,*N*-dimethylformamide to have the desired 3-methoxy- and 3-benzyloxy-16-azidomethylestra-1,3,5(10)-trien-17-ols (**13**–**16** and **17**–**20**). From these azido compounds several D-ring-substituted estrane derivatives containing a 1,2,3-triazole ring were synthesized by the reaction of **13**–**16** and **17**–**20** with various terminal alkynes through the use of the "click" chemistry approach to deliver compounds **21a–e**, **22a–e**, **23a–e, 24a–e, 25a–e, 26a–e, 27a–e** and **28a–e**.

## 2. Experimental

### *2.1. General*

Melting points (Mp) were determined on a Kofler block and are uncorrected. Specific rotations were measured in $CHCl_3$ (*c* 1) at 20 °C with a POLAMAT-A (Zeiss-Jena) polarimeter and are given in units of $10^{-1}$ deg $cm^2$ $g^{-1}$. Elementary analysis data were determined with a Perkin-Elmer CHN analyzer model 2400. The reactions were monitored by TLC on Kieselgel-G (Merck Si 254 F) layers (0.25 mm thick); solvent systems (ss): (A) diisopropyl ether, (B) acetone/toluene/hexane (30:35:35 v/v). The spots were detected by spraying with 5% phosphomolybdic acid in 50% aqueous phosphoric acid. The $R_f$ values were determined for the spots observed by illumination at 254 and 365 nm. Flash chromatography: silica gel 60, 40–63 μm. All solvents were distilled prior to use. NMR spectra were recorded on a Bruker DRX 500 and Bruker Ascend 500 instrument at 500 ($^1$H NMR) or 125 MHz ($^{13}$C NMR). Chemical shifts are reported in ppm (δ scale) and coupling constants (*J*) in Hertz. For the determination of multiplicities, the *J*-MOD pulse sequence was used.

*2.2. 3-Methoxy- and 3-benzyloxy-16-azidomethylestra-1,3,5(10)-trienes (**13**–**16** and **17**–**20**) General procedure*

Compounds **5b**–**8b** [5,6] (470 mg, 1 mmol) or **9c**–**12c** [8] (455 mg, 1 mmol) were dissolved in *N*,*N*-dimethylformamide (25 ml) and then $NaN_3$ (260 mg) was added. The mixture was stirred for 6 h at 80 °C, then poured into water (50 ml). The precipitate separating out was filtered off and subjected to chromatographic separation with $CH_2Cl_2$/hexane in different ratios.

*2.2.1. 3-Methoxy-16β-azidomethyl-estra-1,3,5(10)-trien-17β-ol (**13**)*

Compound **5b** (470 mg, 1 mmol) was used for the synthesis as described in Section 2.2. The crude product was chromatographed on silica gel with $CH_2Cl_2$/hexane (1:3 v/v) to yield pure **13** (318 mg, 93%). Mp 134–135 °C; $R_f$ = 0.65 (ss A); $[\alpha]_D^{20}$ = + 80 (*c* 1 in $CHCl_3$). (Found C, 70.23; H, 8.05. $C_{20}H_{27}N_3O_2$ (341.45) requires C, 70.35; H, 7.97%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.82 (s, 3H, 18-$H_3$), 2.87 (m, 2H, 6-$H_2$), 3.32 (dd, 1H, *J* = 12.5 Hz, *J* = 7.5 Hz, 16a-$H_2$), 3.61 (dd, 1H, *J* = 12.5 Hz, *J* = 7.5 Hz, 16a-$H_2$), 3.78 (s, 3H, 3-$OCH_3$), 3.87 (d, 1H, *J* = 10.0 Hz, 17-H), 6.64 (d, 1H, *J* = 2.5 Hz, 4-H), 6.72 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.20 (d, 1H, *J* = 8.5 Hz, 1-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 12.2 (C-18), 26.3, 27.5, 29.7, 30.4, 37.7, 38.2, 40.2, 44.0, 44.3 (C-13), 49.0, 53.4 (C-16a), 55.2 (3-$OCH_3$), 81.5 (C-17), 111.6 (C-2), 113.9 (C-4), 126.2 (C-1), 132.5 (C-10), 137.9 (C-5), 157.7 (C-3).

*2.2.2. 3-Methoxy-16α-azidomethylestra-1,3,5(10)-trien-17β-ol (**14**)*

Compound **6b** (470 mg, 1 mmol) was used for the synthesis as described in Section 2.2. The crude product was chromatographed on silica gel with $CH_2Cl_2$/hexane (1:3 v/v) to yield pure **14** (287 mg, 84%). Mp 85–86 °C; $R_f$ = 0.62 (ss A); $[\alpha]_D^{20}$ = + 48 (*c* 1 in $CHCl_3$). (Found C, 70.42; H, 7.65. $C_{20}H_{27}N_3O_2$ (341.45) requires C, 70.35; H, 7.97%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.84 (s, 3H, 18-$H_3$), 2.86 (m, 2H, 6-$H_2$), 3.43 (d, 1H, *J* = 7.5 Hz, 17-H), 3.48 (dd, 2H, *J* = 6.5 Hz, J = 3.5 Hz, 16a-$H_2$), 3.78 (s, 3H, 3-$OCH_3$), 6.63 (s, 1H, 4-H), 6.72 (dd, 1H, *J* = 6.5 Hz, *J* = 2.0 Hz, 2-H), 7.20 (d, 1H, *J* = 8.5 Hz, 1-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 11.8 (C-18), 26.1, 27.2, 28.0, 29.7, 36.6, 38.5, 43.6, 43.9, 44.2 (C-13), 48.5, 55.2 (3-$OCH_3$), 55.6 (C-16a), 85.1 (C-17), 111.5 (C-2), 113.8 (C-4), 126.3 (C-1), 132.4 (C-10), 137.8 (C-5), 157.5 (C-3).

*2.2.3. 3-Methoxy-16β-azidomethylestra-1,3,5(10)-trien-17α-ol (**15**)*

Compound **7b** (470 mg, 1 mmol) were used for the synthesis as described in Section 2.2. The crude porduct was chromatographed on silica gel with $CH_2Cl_2$/hexane (1:3 v/v) to yield pure **15** (275 mg, 80%). Mp 96–98; °C; $R_f$ = 0.60 (ss A); $[\alpha]_D^{20}$ = + 68 (*c* 1 in $CHCl_3$). (Found C, 70.26; H, 8.15. $C_{20}H_{27}N_3O_2$ (341.45) requires C, 70.35; H, 7.97%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.76 (s, 3H, 18-$H_3$), 2.86 (m, 2H, 6-$H_2$), 3.43 (dd, 2H, *J* = 7.5 Hz, J = 3.0 Hz, 16a-$H_2$), 3.61 (s, 1H, 17-H), 3.78 (s, 3H, 3-$OCH_3$), 6.64 (d, 1H, *J* = 2.5 Hz, 4-H), 6.72 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.22 (d, 1H, *J* = 8.5 Hz, 1-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 17.7 (C-18), 25.9, 27.9, 29.8, 30.3, 31.9, 38.6, 43.3, 45.0 (C-13), 48.9, 55.2 (3-$OCH_3$), 55.6 (C-16a), 83.0 (C-17), 111.5 (C-2), 113.8 (C-4), 126.3 (C-1), 132.4 (C-10), 137.9 (C-5), 157.5 (C-3).

*2.2.4. 3-Methoxy-16α-azidomethylestra-1,3,5(10)-trien-17α-ol (**16**)*

Compound **8b** (470 mg, 1 mmol) was used for the synthesis as described in Section 2.2. The crude product was chromatographed on silica gel with $CH_2Cl_2$/hexane (1:3 v/v) to yield pure **16** (283 mg, 86%). Mp 118–120 °C; $R_f$ = 0.65 (ss A); $[\alpha]_D^{20}$ = + 34 (*c* 1 in $CHCl_3$). (Found C, 70.55; H, 7.78. $C_{20}H_{27}N_3O_2$ (341.45) requires C, 70.35; H, 7.97%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.80 (s, 3H, 18-$H_3$), 2.87 (m, 2H, 6-$H_2$), 3.35 (dd, 1H, *J* = 12.0 Hz, *J* = 6.0 Hz, 16a-$H_2$), 3.53 (dd, 1H, *J* = 12.0 Hz, *J* = 9.5 Hz, 16a-$H_2$), 3.78 (s, 3H, 3-$OCH_3$), 3.84 (d, 1H, *J* = 6.0 Hz, 17-H), 6.63 (d, 1H, *J* = 2.5 Hz, 4-H), 6.72 (dd, 1H, *J* = 8.5 Hz, 2-H), 7.21 (d, 1H, *J* = 8.5 Hz, 1-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 17.3 (C-18), 26.1, 28.0, 29.2, 31.3, 39.1, 40.5, 43.6, 46.4 (C-13), 47.0, 52.4 (C-16a), 55.2 (3-$OCH_3$), 79.9 (C-17), 111.6 (C-2), 114.0 (C-4), 126.3 (C-1), 132.7 (C-10), 137.9 (C-5), 157.6 (C-3).

*2.2.5. 3-Benzyloxy-16β-azidomethylestra-1,3,5(10)-trien-17β-ol (**17**)*

Compound **9c** (455 mg, 1 mmol) was used for the synthesis as described in Section 2.2. The crude product was chromatographed on silica gel with $CH_2Cl_2$/hexane (1:1 v/v) to yield pure **17** (250 mg, 59%). Mp 115–117 °C; $R_f$ = 0.45 (ss A). (Found C, 74.55; H, 7.64. $C_{26}H_{31}N_3O_2$ (417.54) requires C, 74.79; H, 7.48%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.82 (s, 3H, 18-$H_3$), 2.86 (m, 2H, 6-$H_2$), 3.33 (dd, 1H, *J* = 12.0 Hz, *J* = 7.5 Hz, 16a-$H_2$), 3.60 (dd, 1H, *J* = 12.5 Hz, *J* = 7.5 Hz, 16a-$H_2$), 3.87 (d, 1H, *J* = 9.5 Hz, 17-H), 5.04 (s, 2H, Bn-$H_2$), 6.73 (s, 1H, 4-H), 6.79 (d, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz, 2-H), 7.21 (d, 1H, *J* = 8.0 Hz, 1-H), 7.32 (t, 1H, *J* = 7.5 Hz, 4'-H), 7.39 (t, 2H,

*J* = 7.5 Hz, 3'-H and 5'-H), 7.44 (d, 2H, *J* = 7.5 Hz, 2'-H and 6'-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 12.2 (C-18), 26.2, 27.5, 29.7, 30.3, 37.6, 38.1, 40.1, 43.9, 44.2 (C-13), 48.8 (C-16), 53.3 (C-16a), 69.9 (Bn-$CH_2$), 81.5 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.3 (C-2' and C-6'), 127.8 (C-4'), 128.5 (C-3' and C-5'), 132.7 (C-10), 137.3 (C-1'), 137.9 (C-5), 156.8 (C-3).

*2.2.6. 3-Benzyloxy-16α-azidomethylestra-1,3,5(10)-trien-17β-ol (**18**)*

Compound **10c** (455 mg, 1 mmol) was used for the synthesis as described in Section 2.2. The crude product was chromatographed on silica gel with $CH_2Cl_2$/hexane (3:1 v/v) to yield pure **18** (254 mg, 61%). Mp 75–77 °C; $R_f$ = 0.40 (ss A). (Found C, 74.87; H, 7.32. $C_{26}H_{31}N_3O_2$ (417.54) requires C, 74.79; H, 7.48%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.84 (s, 3H, 18-$H_3$), 2.85 (m, 2H, 6-$H_2$), 3.44 (t, 1H, *J* = 8.0 Hz, 17-H), 3.48 (m, 2H, 16a-$H_2$), 5.04 (s, 2H, Bn-$H_2$), 6.73 (s, 1H, 4-H), 6.79 (d, 1H, J = 8.5 Hz, 2-H), 7.21 (d, 1H, *J* = 8.5 Hz, 1-H), 7.32 (t, 1H, *J* = 7.0 Hz, 4'-H), 7.39 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.44 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 11.8 (C-18), 26.1, 27.2, 27.9, 29.7, 36.6, 38.5, 43.6, 43.9, 44.2 (C-13), 48.6 (C-16), 55.6 (C-16a), 69.9 (Bn-$CH_2$), 85.1 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-2' and -6'), 127.8 (C-4'), 128.5 (C-3' and -5'), 132.7 (C-10), 137.3 (C-1'), 137.9 (C-5), 156.8 (C-3).

*2.2.7. 3-Benzyloxy-16β-azidomethyl-estra-1,3,5(10)-trien-17α-ol (**19**)*

Copound **11c** (455 mg, 1 mmol) was used for the synthesis as described in Section 2.2. The crude product was chromatographed on silica gel with $CH_2Cl_2$/hexane (3:1 v/v) to yield pure **19** (23. mg, 40%). Mp. 134-136 °C. $R_f$ = 0.38 (ss A). (Found C, 74.92; H, 7.37. $C_{26}H_{31}N_3O_2$ (417.54) requires C, 74.79; H, 7.48%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.84 (s, 3H, 18-$H_3$), 2.85 (m, 2H, 6-$H_2$), 3.43 (d, 2H, *J* = 8.0 Hz, 17-H), 3.48 (t, 2H, J = 6.5 Hz, 16a-$H_2$), 5.04 (s, 2H, Bn-$H_2$), 6.73 (s, 1H, 4-H), 6.79 (d, 1H, *J* = 8.0 Hz, 2-H), 7.22 (d, 1H, *J* = 8.0 Hz 1-H), 7.33 (d, 1H, *J* = 7.0 Hz, 4'-H), 7.39 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.44 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 11.8 (C-18), 26.1, 27.2, 28.0, 29.7, 36.6, 38.4, 43.5, 43.9, 44.1 (C-13), 48.5 (C-16), 55.6 (C-16a), 69.9 (Bn-$CH_2$), 85.1 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-2' and -6'), 127.8 (C-4'), 128.5 (C-3' and -5'), 132.7 (C-10), 137.3 (C-1'), 137.9 (C-5), 156.7 (C-3).

*2.2.8. 3-Benzyloxy-16α-azidomethyl-estra-1,3,5(10)-trien-17α-ol (**20**)*

Compound **12c** (455 mg, 1 mmol) was used for the synthesis as described in Section 2.2. The crude was chromatographed on silica gel with $CH_2Cl_2$/hexane (1:1 v/v) to yield pure **20** (330 mg, 79%). Mp 90–92 °C. $R_f$ = 0.45 (ss A). (Found C, 74.68; H, 7.55. $C_{26}H_{31}N_3O_2$ (417.54) requires C, 74.79; H, 7.48%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.79 (s, 3H, 18-$H_3$), 2.71 (m, 2H, 6-$H_2$), 3.35 (dd, 1H, *J* = 12.0 Hz, *J* = 6.5 Hz, 16a-$H_2$), 3.52 (dd, 1H, *J* = 12.0 Hz, *J* = 6.5 Hz, 16a-$H_2$), 3.84 (d, 1H, *J* = 5.0 Hz, 17-H), 5.04 (s, 2H, Bn-$H_2$), 6.73 (s, 1H, 4-H), 6.79 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.22 (d, 1H, *J* = 8.5 Hz, 1-H), 7.33 (t, 1H, *J* = 7.5 Hz, 4'-H), 7.39 (t, 2H, *J* = 7.5 Hz, 3'- and 5'-H), 7.44 (d, 2H, *J* = 7.5 Hz, 2'- and 6'-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 17.2 (C-18), 26.0, 27.9, 29.0, 29.7, 31.2, 38.9, 40.4, 43.5, 46.3 (C-13), 46.8 (C-16), 52.2 (C-16a), 69.9 (Bn-$CH_2$), 79.7 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-2' and -6'), 127.8 (C-4'), 128.5 (C-3' and -5'), 132.8 (C-10), 137.3 (C-1'), 138.0 (C-5), 156.7 (C-3).

*2.3. General procedure for the synthesis of triazoles (**21a–e**, **22a–e**, **23a–e, 24a–e**, **25a–e**, **26a–e**, **27a–e**, and **28a–e**)*

3-Methoxy-16-azidomethylestra-1,3,5(10)-trien-17-ol isomers (**13**–**16**) (342 mg, 1 mmol) or 3-benzyloxy-16-azidomethylestra-1,3,5(10)-trien-17-ol isomers (**17**–**20**) 418 mg, 1 mmol) were dissolved in $CH_2Cl_2$ (20 ml), then CuI (19 mg, 0.10 mmol), $Et_3N$ (0.2 ml, 2 mmol) and the appropriate terminal alkynes (2 mmol) were added. The mixtures were stirred under reflux for 24 h, then diluted with water (30 ml) and extracted with $CH_2Cl_2$ (2 × 30 ml). The combined organic phases were dried over $Na_2SO_4$ and evaporated *in vacuo*. The crude products were purified by flash chromatography using $CH_2Cl_2$/ethyl acetate in different ratios.

*2.3.1. 3-Methoxy-16β-(4'-cyclopropyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**21a**)*

Compound **13** (342 mg, 1 mmol) and cyclopropylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with $CH_2Cl_2$/hexane (3:1 v/v) to yield pure **21a** (210 mg, 51%) as a white solid. Mp: 189–191 °C; $R_f$ = 0.44 (ss B). (Found C, 73.84; H, 7.98. $C_{25}H_{33}N_3O_2$ (407.55) requires C, 73.68; H, 8.16%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.80 (s, 3H, 18-$H_3$), 0.83 (s, 2H, cyclopropyl-$H_2$), 0.94 (s, 2H, cyclopropyl-$H_2$), 2.72 (d, 1H, *J* = 7.0 Hz, 1''-H), 2.84 (m, 2H, 6-$H_2$), 3.77 (s, 3H, 3-$OCH_3$), 3.93 (d, 1H, *J* = 9.5 Hz, 17-H), 4.21 (dd, 1H, *J* = 13.0 Hz, *J* = 6.0 Hz, 16a-$H_2$), 4.62 (t, 1H, *J* = 8.0 Hz,

16a-$H_2$), 6.62 (s, 1H, 4-H), 6.71 (d, 1H, *J* = 8.5 Hz, 2-H), 7.20 (d, 1H, *J* = 8.5 Hz, 1-H), 7.29 (s, 1H, 5'-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 6.7 (C-1"), 7.68 (C-2" and -3"),12.3 (C-18), 26.2, 27.4, 29.7, 30.8, 37.5, 38.0, 41.4, 43.8, 44.3 (C-16a), 48.7, 51.7 (C-13), 55.2 (3-$OCH_3$), 80.7 (C-17), 111.5 (C-2), 113.8 (C-4), 126.3 (C-1), 132.4 (C-10), 137.8 (C-5), 157.5 (C-3).

*2.3.2. 3-Methoxy-16β-(4'-cyclopentyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**21b**)*

Compound **13** (342 mg, 1 mmol) and cyclopentylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with $CH_2Cl_2$ to yield pure **21b** (370 mg, 85%) as a white solid. Mp: 191−192 °C; $R_f$= 0.46 (ss B). (Found C, 74.62; H, 8.42. $C_{27}H_{37}N_3O_2$ (435.60) requires C, 74.45; H, 8.56%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.79 (s, 3H, 18-$H_3$), 2.85 (m, 2H, 6-$H_2$), 3.19 (s, 1H, 1"-H), 3.77 (s, 3H, 3-$OCH_3$), 3.94 (d, 1H, *J* = 9.5 Hz, 17-H), 4.24 (d, 1H, *J* = 8.0 Hz, 16a-$H_2$), 4.65 (s, 1H, 16a-$H_2$), 6.62 (s, 1H, 4-H), 6.71 (d, 1H, *J* = 8.5 Hz, 2-H), 7.20 (d, 1H, *J* = 8.5 Hz, 1-H), 7.34 (s, 1H, 5'-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 12.3 (C-18), 25.1 (C-3" and -4"), 26.2, 27.4, 29.7 (C-2" and 5"), 30.8, 33.2, 36.7, 37.5, 38.0, 42.4 (C-16a), 43.8, 44.3 (C-13), 48.7, 51.8, 55.2 (3-$OCH_3$), 62.1 (C-16), 80.7 (C-17), 111.5 (C-2), 113.7 (C-4), 126.3 (C-1), 132.4 (C-10), 137.8 (C-5), 157.4 (C-3).

*2.3.3. 3-Methoxy-16β-(4'-cyclohexyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**21c**)*

Compound **13** (342 mg, 1 mmol) and cyclohexylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **21c** (370 mg, 82%) as a white solid. Mp: 189−190 °C; $R_f$= 0,40 (ss B). (Found C, 74.92; H, 8.55. $C_{28}H_{41}N_3O_2$ (449.63) requires C, 74.80; H, 8.74%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.79 (s, 3H, 18-$H_3$), 2.84 (m, 2H, 6-$H_2$), 3.77 (s, 3H, 3-$OCH_3$), 3.94 (d, 1H, *J* = 9.5 Hz, 17-H), 4.24 (m, 1H, 16a-$H_2$), 4.65 (m, 1H, 16a-$H_2$), 6.62 (s, 1H, 4-H), 6.71 (d, 1H, *J* = 8.5 Hz, 2-H), 7.20 (d, 1H, *J* = 8.5 Hz, 1-H), 7.32 (s, 1H, 5'-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 12.3 (C-18), 26.0, 26.1 (C-2" and -6"), 26.2, 27.4, 29.7, 30.8, 33.0, 37.5, 38.0, 41.4 (C-1"), 43.8, 44.3 (C-13), 48.3, 55.2 (3-$OCH_3$), 62.1, 80.7 (C-17), 111.5 (C-2), 113.7 (C-4), 126.3 (C-1), 132.4 (C-10), 137.8 (C-5), 157.4 (C-3).

*2.3.4. 3-Methoxy-16β-(4'-phenyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**21d**)*

Compound **13** (342 mg, 1 mmol) and phenylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **21d** (368 mg, 83%) as a white solid. Mp: 232–234 $^oC$; $R_f$= 0.35 (ss B). (Found C, 75.98; H, 7.36. $C_{28}H_{33}N_3O_2$ (443.58) requires C, 75.81; H, 7.50%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.79 (s, 3H, 18-$H_3$), 2.73 (m, 2H, 6-$H_2$), 3.68 (s, 3H, 3-$OCH_3$), 3.79 (d, 1H, *J* = 10.0 Hz, 17-H), 4.20 (t, 1H, *J* = 13.5 Hz, 16a-$H_2$), 4.63 (dd, 1H, *J* = 13.5 Hz, *J* = 4.5 Hz, 16a-$H_2$), 6.59 (s, 1H, 4-H), 6.67 (d, 1H, *J* = 8.5 Hz, 2-H), 7.16 (d, 1H, *J* = 8.5 Hz, 1-H), 7.32 (t, 1H, *J* = 7.5 Hz, 4"-H), 7.44 (t, 2H, *J* = 7.5 Hz, 3"- and 5"-H), 7.85 (d, 2H, *J* = 7.5 Hz, 2"- and 6"-H), 8.60 (s, 1H, 5'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 12.4 (C-18), 25.8, 26.9, 29.1, 30.0, 36.9, 37.8, 40.4, 43.3, 43.7 (C-13), 47.8, 52.3 (C-16a), 54.8 (3-$OCH_3$), 79.5 (C-17), 111.4 (C-2), 113.3 (C-4), 121.5 (C-5'), 124.5 (C-2" and -6"), 126.0 (C-1), 127.6 (C-4"), 127.8 (C-3" and -5"), 130.9 (C-1"), 132.0 (C-10), 137.3 (C-5), 146.0 (C-4'), 156.9 (C-3).

*2.3.5. 3-Methoxy-16β-(4'-nitro-benzoyloxymethyl-1'H-1',2,'3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**21e**)*

Compound **13** (342 mg, 1 mmol) and propargyl 4-nitrobenzoate (2 mmol, 410 mg) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **21e** (475 mg, 86%) as a yellow solid. Mp: 134–135.5 $^oC$; $R_f$= 30 (ss B). (Found C, 66.12; H, 6.08. $C_{30}H_{34}N_4O_6$ (546.61) requires C, 65.92; H, 6.27%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.73 (s, 3H, 18-$H_3$), 2.70 (m, 2H, 6-$H_2$), 3.66 (s, 3H, 3-$OCH_3$), 4.18 (dd, 1H, *J* = 13.5 Hz, *J* = 11.5 Hz, 16a-H2), 4.58 (dd, 1H, *J* = 13.5 Hz, *J* = 4.5 Hz, 16a-$H_2$), 5.02 (d, 1H, *J* = 4.5 Hz, 17-H), 5.44 (s, 2H, 4'-$H_2$), 6.55 (d, 1H, *J* = 1.5 Hz, 4-H), 6.63 (dd, 1H, *J* = 8.5 Hz, *J* = 2.0 Hz, 2-H), 7.12 (d, 1H, *J* = 8.5 Hz, 1-H), 8.16 (d, 2H, *J* = 8.5 Hz, 3"- and 5"-H), 8.31 (t, 3H, *J* = 8.5 Hz, 2"- and 6"-H, 5'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 12.3 (C-18), 25.8, 26.9, 29.1, 30.0, 36.9, 37.8, 40.4, 43.3, 43.7 (C-13), 47.8, 52.2 (C-16a), 54.7 (3-$OCH_3$), 58.7 (4'-$CH_2$), 79.5 (C-17), 111.3 (C-2), 113.3 (C-4), 123.8 (C-2" and -6"), 125.1 (C-5'), 126.0 (C-1), 130.6 (C-3" and -5"), 131.9 (C-10), 134.7 (C-1"), 137.2 (C-5), 141.0 (C-4"), 150.2 (C-4'), 156.9 (C-3), 163.9 (C=O).

*2.3.6. 3-Methoxy-16β-(4'-hydroxymethyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**21f**)*

Compound **13** (274 mg, 0.5 mmol) was dissolved in methanol (10 ml) containing $NaOCH_3$ (14 mg, 0.25 mmol), and the solution was allowed to stand for 24 h. It was then diluted with water, and the precipitate separating out was filtered off and recrystallized from a mixture of ethyl acetate/hexane to afford **21f** (171 mg, 86%) as a white crystalline material. Mp: 194–195 $^{o}$C; $R_f$= 0.25 (ss B). (Found C, 69.23; H, 8.04. $C_{23}H_{31}N_3O_3$ (397.51) requires C, 69.49; H, 7.86%). $^1$H NMR (δ, ppm, DMSO-$d_6$): 0.76 (s, 3H, 18-$H_3$), 2.71 (m, 2H, 6-$H_2$), 3.68 (s, 3H, 3-$OCH_3$), 3.76 (d, 1H, *J* = 5.5 Hz, 17-H), 4.14 (t, 1H, *J* = 12.5 Hz, 16a-$H_2$), 4.49 (m, 3H, 4'-$H_2$ and 16a-$H_2$), 5.03 (d, 1H, *J* = 3.5 Hz, 17-OH), 5.15 (brs, 1H, $CH_2$-OH), 6.59 (s, 1H, 4-H), 6.66 (d, 1H, *J* = 8.5 Hz, 2-H), 7.16 (d, 1H, *J* = 8.5 Hz, 1-H), 7.99 (s, 1H, 5'-H). $^{13}$C NMR (δ, ppm, DMSO-$d_6$): 12.4 (C-18), 25.9, 26.9, 29.2, 30.0, 36.9, 37.9, 40.5, 43.4, 43.8 (C-13), 47.8, 52.0 (C-16a), 54.8 (3-$OCH_3$), 55.0 (4'-$CH_2$), 79.5 (C-17), 111.4 (C-2), 113.4 (C-4), 122.8 (C-5'), 126.1 (C-1), 132.0 (C-10), 137.3 (C-5), 147.6 (C-4'), 157.0 (C-3).

*2.3.7. 3-Methoxy-16a-(4'-cyclopropyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**22a**)*

Compound **14** (342 mg, 1 mmol) and cyclopropylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **22a** (261 mg, 64%) as a white solid. Mp: 67–69 $^{o}$C; $R_f$= 0.35 (ss B). (Found C, 73.55; H, 7.98. $C_{25}H_{33}N_3O_2$ (407.55) requires C, 73.68; H, 8.16%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.82 (m, 5H, 18-$H_3$ and cyclopropyl-$H_2$), 0.95 (m, 2H, cyclopropyl-$H_2$), 2.83 (m, 2H, 6-$H_2$), 3.53 (d, 1H, *J* = 7.5 Hz, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.35 (t, 1H, *J* = 7.5 Hz, 16a-$H_2$), 4.44 (dd, 1H, *J* = 13.5 Hz, *J* = 7.5 Hz, 16a-$H_2$), 6.62 (d, 1H, *J* = 2.0 Hz, 4-H), 6.70 (dd, 1H, *J* = 8.5 Hz, *J* = 2.0 Hz, 2-H), 7.18 (d, 1H, *J* = 8.5 Hz, 1-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 6.7 (C-1"), 7.7 (C-2" and -3"), 11.8 (C-18), 26.1, 27.2, 28.2, 29.7, 36.6, 38.4, 43.9, 44.3, 44,3 (C-16a), 48.3, 54.5 (C-13), 62.1 (3-$OCH_3$), 85.1 (C-17), 111.5 (C-2), 113.8 (C-4), 126.2 (C-1), 132.3 (C-10), 137.8 (C-5), 157.4 (C-3).

*2.3.8. 3-Methoxy-16a-(4'-cyclopentyl-1'H-1',2',3'-triazol-1-yl)methylestra-1,3,5(10)-trien-17β-ol (**22b**)*

Compound **14** (342 mg, 1 mmol) and cyclopentylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **22b** (290 mg, 66%) as a white solid. Mp: 163–165 $^oC$; $R_f$= 0.32 (ss B). (Found C, 74.63; H, 8.41. $C_{27}H_{37}N_3O_2$ (435.60) requires C, 74.45; H, 8.56%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.83 (s, 3H, 18-$H_3$), 1.68 (s, 4H, 3”- and 4”-$H_2$), 2.83 (m, 2H, 6-$H_2$), 3.19 (m, 1H, 1”-H), 3.56 (d, 1H, *J* = 7.0 Hz, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.43 (m, 2H, 16a-$H_2$), 6.62 (s, 1H, 4-H), 6.70 (d, 1H, *J* = 8.5 Hz, 2-H), 7.19 (d, 1H, *J* = 8.5 Hz, 1-H), 7.35 (s, 1H, 5’-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 11.9 (C-18), 25.1 (C-3” and -4”), 26.1, 27.2, 28.3, 29.7 (C-2” and -5”), 33.2, 36.6, 38.4, 43.9, 44.2, 44.3 (C-13), 48.4, 55.2 (3-$OCH_3$), 62.1 (C-16a), 85.3 (C-17), 111.5 (C-2), 113.8 (C-4), 126.3 (C-1), 132.3 (C-10), 137.8 (C-5), 157.5 (C-3).

### *2.3.9. 3-Methoxy-16a-(4’-cyclohexyl-1’H-1’,2’,3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17β-ol (**22c**)*

Compound **14** (342 mg, 1 mmol) and cyclohexylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **22c** (345 mg, 76%) as a white solid. Mp: 80–82 $^oC$; $R_f$= 0.34 (ss B). (Found 74.96; H, 8.54. $C_{28}H_{41}N_3O_2$ (449.63) requires C, 74.80; H, 8.74%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.83 (s, 3H, 18-$H_3$), 2.83 (m, 2H, 6-$H_2$), 3.55 (s, 1H, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.46 (s, 2H, 16a-$H_2$), 6.62 (d, 1H, *J* = 2.0 Hz, 4-H), 6.70 (dd, 1H, *J* = 8.5 Hz, *J* = 2.0 Hz, 2-H), 7.19 (d, 1H, *J* = 8.5 Hz, 1-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 11.9 (C-18), 26.0 and 26.1 (C-2” and -6”, C-3” and -5”), 27.2, 28.3, 29.7, 36.6, 38.4, 43.9, 44.3 (C-13), 48.4, 55.2 (3-$OCH_3$), 62.1 (C-1”), 62.1 (C-16a), 85.2 (C-17), 111.5 (C-2), 113.8 (C-4), 126.2 (C-1), 132.3 (C-10), 137.8 (C-5), 157.4 (C-3).

### *2.3.10. 3-Methoxy-16a-(4’-phenyl-1’H-1’,2’,3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17β-ol (**22d**)*

Compound **14** (342 mg, 1 mmol) and phenylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **22d** (368 mg, 82%) as a white solid. Mp: 204–205 $^oC$; $R_f$= 0.38 (ss B). (Found C, 75.63; H, 7.72. $C_{28}H_{33}N_3O_2$ (443.58) requires C, 75.81; H, 7.50%). $^1H$ NMR (δ, ppm, DMSO-$d_6$): 0.73 (s, 3H, 18-$H_3$), 2.73 (m, 2H, 6-$H_2$), 3.67 (s, 3H, 3-$OCH_3$), 4.36 (t,

1H, *J* = 13.5 Hz, 16a-$H_2$), 4.54 (dd, 1H, *J* = 13.5 Hz, *J* = 4.0 Hz, 16a-$H_2$), 4.91 (d, 1H, *J* = 4.0 Hz, 17-H), 6.58 (s, 1H, 4-H), 6.67 (d, 1H, *J* = 8.5 Hz, 2-H), 7.15 (d, 1H, *J* = 8.5 Hz, 1-H), 7.32 (t, 1H, *J* = 7.0 Hz, 4”-H), 7.44 (t, 2H, *J* = 7.0 Hz, 3”- and 5”-H), 7.86 (d, 2H, *J* = 7.0 Hz, 2”- and 6”-H), 8.61 (s, 1H, 5’-H). $^{13}$C NMR (δ, ppm, DMSO-$d_6$): 11.8 (C-18), 25.8, 26.7, 27.3, 29.1, 36.3, 38.1, 43.4, 43.5, 43.8, 47.5, 53.5 (C-13), 54.8 (3-$OCH_3$), 83.1 (C-17), 111.4 (C-2), 113.3 (C-4), 121.4 (C-5’), 125.0 (C-2” and -6”), 126.0 (C-1), 127.6 (C-4”), 128.8 (C-3” and -5”), 130.8 (C-1”), 132.0 (C-10), 137.3 (C-5), 146.1 (C-4’), 156.9 (C-3).

*2.3.11.3-Methoxy-16a-[4’(4’’-nitro-benzoyloxymethyl)-1’H-1’,2’,3’-triazol-1’-yl]methylestra-1,3,5(10)-trien-17β-ol (**22e**)*

Compound **14** (342 mg, 1 mmol) and propargyl 4-nitrobenzoate (2 mmol, 410 mg) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **22e** (445 mg, 81%) as a yellow solid. Mp: 86–88 $^{o}$C; $R_f$= 0.28 (ss B). (Found C, 66.08; H, 6.43. $C_{30}H_{34}N_4O_6$ (546.61) requires C, 65.92; H, 6.27%). $^1$H NMR (δ, ppm, DMSO-$d_6$): 0.69 (s, 3H, 18-$H_3$), 2.68 (m, 2H, 6-$H_2$), 3.57 (s, 3H, 3-$OCH_3$), 4.38 (dd, 1H, *J* = 13.5 Hz, *J* = 9.0 Hz, 16a-$H_2$), 4.52 (dd, 1H, *J* = 13.5 Hz, *J* = 4.5 Hz, 16a-$H_2$), 4.86 (d, 1H, *J* = 4.5 Hz, 17-H), 5.46 (s, 2H, 4’-$H_2$), 6.55 (d, 1H, *J* = 1.5 Hz, 4-H), 6.63 (dd, 1H, *J* = 8.5 Hz, 2-H), 7.10 (d, 1H, *J* = 8.5 Hz, 1-H), 8.16 (d, 2H, *J* = 8.5 Hz, 3”- and 5”-H), 8.28 (d, 2H, *J* = 8.5 Hz, 2”- and 6”-H), 8.31 (s, 1H, 5’-H). $^{13}$C NMR (δ, ppm, DMSO-$d_6$): 11.7 (C-18), 25.7, 26.6, 27.1, 29.0, 36.4, 38.0, 43.3, 43.4 (C-13), 43.7, 47.7, 53.1 (C-16a), 54.7 (3-$OCH_3$), 58.6 (4”-$CH_2$), 82.8 (C-17), 111.3 (C-2), 113.3 (C-4), 123.8 (C-2” and -6”), 125.2 (C-5’), 125.9 (C-1), 130.6 (C-3” and -5”), 131.8 (C-10), 134.7 (C-1’), 137.2 (C-5), 141.1 (C-4”), 150.2 (C-4’), 156.9 (C-3), 163.9 (C=O).

*2.3.12. 3-Methoxy-16a-(4’-hydroxymethyl-1’H-1’,2’3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17β-ol (**22f**)*

Compound **22e** (274 mg, 0.5 mmol) was dissolved in methanol (10 ml) containing $NaOCH_3$ (14 mg, 0.25 mmol), and the solution was allowed to stand for 24 h. It was then diluted with water, and the precipitate separating out was filtered off and recrystallized from a mixture of ethyl acetate/hexane to afford **22f** (175 mg, 88%) as a white crystalline product. Mp: 98–100 $^{o}$C; $R_f$=

0.28 (ss B). (Found C, 69.74; H, 7.72. $C_{23}H_{31}N_3O_3$ (397.51) requires C, 69.49; H, 7.86%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.81 (s, 3H, 18-$H_3$), 2.82 (m, 2H, 6-$H_2$), 3.50 (d, 1H, *J* = 7.0 Hz, 17-H), 3.76 (s, 3H, 3-$OCH_3$), 4.42 (d, 2H, *J* = 7.0 Hz, 16a-$H_2$), 4.71 (s, 2H, 4'-$H_2$), 6.61 (s, 1H, 4-H), 6.69 (d, 1H, *J* = 8.5 Hz, 2-H), 7.17 (d, 1H, *J* = 8.5 Hz, 1-H), 7.68 (s, 1H, 5'-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 11.9 (C-18), 26.1, 27.2, 28.2, 29.6, 36.5, 38.4, 43.8, 44.0, 44.4 (C-13), 48.2, 54.6 (C-16a), 55.2 (3-$OCH_3$), 56.0 (4'-$CH_2$), 85.1 (C-17), 111.5 (C-2), 113.8 (C-4), 126.3 (C-1), 132.3 (C-10), 137.8 (C-5), 157.4 (C-3).

*2.3.13. 3-Methoxy-16a-(4'-cyclopropyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**23a**)*

Compound **15** (342 mg, 1 mmol) and cyclopropylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **23a** (261 mg, 64%) as a white solid. Mp: 67–69 °C; $R_f$= 0.32 (ss B). (Found C, 73.85; H, 8.32. $C_{25}H_{33}N_3O_2$ (407.55) requires C, 73.68; H, 8.16%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.82 (m, 5H, 18-$H_3$ and cyclopropyl-$H_2$), 0.95 (m, 2H, cyclopropyl-$H_2$), 2.83 (m, 2H, 6-$H_2$), 3.53 (d, 1H, *J* = 7.5 Hz, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.35 (t, 1H, *J* = 7.5 Hz, 16a-$H_2$), 4.44 (dd, 1H, *J* = 13.5 Hz, *J* = 7.5 Hz, 16a-$H_2$), 6.62 (d, 1H, *J* = 2.0 Hz, 4-H), 6.70 (dd, 1H, *J* = 8.5 Hz, *J* = 2.0 Hz, 2-H), 7.18 (d, 1H, *J* = 8.5 Hz, 1-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 6.7 (C-1"), 7.7 (C-2" and -3"), 11.8 (C-18), 26.1, 27.2, 28.2, 29.7, 36.6, 38.4, 43.9, 44.3, 44,3 (C-16a), 48.3, 54.5 (C-13), 62.1 (3-$OCH_3$), 85.1 (C-17), 111.5 (C-2), 113.8 (C-4), 126.2 (C-1), 132.3 (C-10), 137.8 (C-5), 157.4 (C-3).

*2.3.14. 3-Methoxy-16β-(4'-cyclopentyl-1'H-1',2',3'-triazol-1-yl)methylestra-1,3,5(10)-trien-17a-ol (**23b**)*

Compound **15** (342 mg, 1 mmol) and cyclopentylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **23b** (380 mg, 87%) as yellow crystalline material. Mp: 67–68 °C; $R_f$= 0.36 (ss B). (Found C, 74.28; H, 8.47. $C_{27}H_{37}N_3O_2$ (435.60) requires C, 74.45; H, 8.56%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.75 (s, 3H, 18-$H_3$), 2.85 (m, 2H, 6-$H_2$), 3.68 (s, 1H, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.44 (d, 2H, *J* = 15.0 Hz, 16a-$H_2$), 6.62 (s, 1H, 4-H), 6.70 (d, 1H, *J* = 8.5 Hz, 2-H), 7.20 (t, 1H, *J* = 8.5 Hz, 1-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 17.9 (C-18), 25.1

(C-3" and -4"), 25.9, 26.1, 27.2, 28.0, 29.7, 30.4, 31.8, 36.6 (C-16a), 38.5, 43.3, 43.8, 45.1 (C-13), 48.9, 55.2 (3-$OCH_3$), 62.1 (C-1"), 82.6 (C-17), 111.5 (C-2), 113.7 (C-4), 113.8 (C-5'), 126.2 (C-1), 132.1 (C-10), 137.8 (C-5), 137.8 (C-4'), 157.4 (C-3).

*2.3.15. 3-Methoxy-16β-(4'-cyclohexyl-1'H-1',2',3'-triazol-1'-yl)methyestra-1,3,5(10)-trien-17a-ol (**23c**)*

Compound **15** (342, 1 mmol) and cyclohexylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **23c** (306 mg, 68%) as a white solid. Mp: 90-92 $^oC$; $R_f$ = 0.37 (ss B). (Found C, 74.95; H, 8.83. $C_{28}H_{41}N_3O_2$ (449.63) requires C, 74.80; H, 8.74%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.75 (s, 3H, 18-$H_3$), 2.84 (m, 2H, 6-$H_2$), 3.67 (d, 1H, *J* = 1.0 Hz, 17-H), 3.77 (S, 3H, 3-$OCH_3$), 4.43 (m, 1H, 16a-$H_2$), 6.62 (d, 1H, *J* = 2.5 Hz, 4-H), 6.71 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.20 (t, 1H, *J* = 8.5 Hz, 1-H), 7.35 (s, 1H, 5'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 17.9 (C-18), 25.9, 26.0, 26.1 (C-2" and -6"), 28.0, 29.7, 30.4, 31.8, 33.0, 35.2 (C-1"), 36.6, 38.5, 43.3, 45.1 (C-13), 48.9, 49.1, 54.3 (C-16a), 55.2 (3-$OCH_3$), 82.6 (C-1), 132.4 (C-10), 137.8 (C-5), 153.7 (C-4'), 157.7 (C-3).

*2.3.16. 3-Methoxy-16β-(4'-phenyl-1'H-1',2',3'-triazol-1'-yl)methy-estra-1,3,5(10)-trien-17a-ol (**23d**)*

Compound **15** (342 mg, 1 mmol) and phenylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (2.5:97.5 v/v) to yield pure **23d** (299 mg, 67%) as white crystals. Mp: 173–174 $^oC$; $R_f$= 0.34 (ss B). (Found C 75.98; H, 7.33. $C_{28}H_{33}N_3O_2$ (443.58) requires C, 75.81; H, 7.50%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.79 (s, 3H, 18-$H_3$), 2.85 (m, 2H, 6-$H_2$), 3.71 (d, 1H, *J* = 1.5 Hz, 17-H), 3.78 (s, 3H, 3-$OCH_3$), 4.46 (dd, 1H, *J* = 13.5 Hz, *J* = 8.0 Hz, 16a-$H_2$), 4.55 (dd, 1H, *J* = 13.5 Hz, *J* = 8.0 Hz, 16a-$H_2$), 6.63 (d, 1H, *J* = 2.0 Hz, 4-H), 6.72 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.21 (d, 1H, *J* = 8.5 Hz, 1-H), 7.27 (t, 1H *J* = 7.5 Hz, 4"-H), 7.42 (t, 2H, *J* = 7.5 Hz, 3"- and 5"-H), 7.83 (d, 2H, *J* = 7.5 Hz, 2"- and 6"-H), 7.87 (s, 1H, 5'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 17.9 (C-18), 25.9, 27.9, 29.7, 30.4, 31.8, 38.5, 43.3, 45.1, (C-13), 48.8, 49.1, 54.5 (C-16a), 55.2 (3-$OCH_3$), 82.5 (C-17), 111.5 (C-2), 113.7 (C-4), 119.6 (C-5'), 125.7 (C-2" and -6"),

126.3 (C-1), 128.1 (C-4”), 128.8 (C-3” and -5”), 130.5 (C-1”), 132.4 (C-10), 137.8 (C-5), 147.8 (C-4’), 157.4 (C-3).

*2.3.17.3-Methoxy-16β-[4’(4”-nitro-benzoyloxymethyl)-1’H-1’,2’,3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17a-ol (**23e**)*

Compound **15** (342, 1 mmol) and propargyl 4-nitro benzoate (2 mmol, 410 mg) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **23e** (370 mg, 67%) as a yellow crystalline material. Mp: 62–63 $^oC$; $R_f$ = 0.38 (ss B). (Found C, 66.14; H, 6.42. $C_{30}H_{34}N_4O_6$ (546.61) requires C, 65.92; H, 6.27%). $^1H$ NMR (δ, ppm, DMSO-$d_6$): 0.65 (s,3 H, 18-$H_3$), 2.74 (m,2H, 6-$H_2$), 3.68 (s, 3H, 3-$OCH_3$), 4.41 (dd, 1H, *J* = 13.0 Hz, *J* = 8.5 Hz, 16a-$H_2$), 4.56 (dd, 1H, *J* = 13.0 Hz, *J* = 8.5 Hz, 16a-$H_2$), 4.63 (d, 1H, *J* = 4.5 Hz, 17-H), 6.58 (s, 1H, 4-H), 6.66 (d, 1H, *J* = 8.5 Hz, 2-H), 7.16 (d, 1H, *J* = 8.5 Hz, 1-H), 8.19 (d, 2H, *J* = 8.5 Hz, 3”- and 5”-H), 8.34 (d, 2H, *J* = 8.5 Hz, 2”- and 6”-H). $^{13}C$ NMR (δ, ppm, DMSO-$d_6$): 17.5 (C-18), 25.6, 27.5, 29.6, 31.8, 38.2, 43.0, 44.5, 47.9 (C-13), 48.2, 49.1, 53.6 (C-16a), 54.8 (3-$OCH_3$), 58.7 (4’-$CH_2$), 80.8 (C-17), 111.3 (C-2), 113.3 (C-4), 123.8 (C-1), 126.1 (C-5’), 130.6 (C-2” and -6”), 131.9 (C-3” and -5”), 133.0 (C-10), 134.7 (C-1”), 137.3 (C-5), 141.4 (C-4”), 150.2 (C-4’), 156.9 (C-3), 163.9 (C=O).

*2.3.18. 3-Methoxy-16β-(4’-hydroxymethyl-1’H-1’,2’3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17a-ol (**23f**)*

Compound **23e** (274 mg, 0.5 mmol) was dissolved in methanol (10 ml) containing $NaOCH_3$ (14 mg, 0.25 mmol), and the solution was allowed to stand for 24 h. It was then diluted with water, and the precipitate separating out was filtered off, dissolved in dichloromethane and washed with water. The organic phase was dried over $Na_2SO_4$, and evaporated *in vacuo* to afford **23f** (183 mg, 92%) as oil. $R_f$= 0.26 (ss B). (Found C, 69.28; H, 7.95. $C_{23}H_{31}N_3O_3$ (397.51) requires C, 69.49; H, 7.86%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.78 (s, 3H, 18-$H_3$), 2.85 (m, 2H, 6-$H_2$), 3.65 (s, 1H, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.46 (m, 2H, 16a-$H_2$), 4.78 (s, 2H, 4’-$H_2$), 6.62 (d, 1H, *J* = 2.0 Hz, 4-H), 6.72 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.19 (d, 1H, *J* = 8.5 Hz, 1-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 17.9 (C-18), 25.9, 27.9, 29.7, 30.3, 31.8, 38.5, 43.3, 45.2 (C-13), 48.8, 49.2, 54.6 (C-16a), 55.2 (3-$OCH_3$), 56.1 (4’-$CH_2$), 82.1 (C-17), 111.5 (C-2), 113.7 (C-4), 123.5 (C-5’), 126.3 (C-1), 132.4 (C-10), 137.8 (C-5), 157.4 (C-3).

*2.3.19. 3-Methoxy-16a-(4'-cyclopropyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**24a**)*

Compound **16** (342 mg, 1 mmol) and cyclopropylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (2.5:97.5 v/v) to yield pure **24a** (310 mg, 76%) as a white solid. Mp: 165–166 $^oC$; $R_f$= 0.40 (ss B). (Found C, 73.85; H, 8.34. $C_{25}H_{33}N_3O_2$ (407.55) requires C, 73.68; H, 8.16%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.74 (s, 3H, 18-$H_3$), 0.85 and 0.96 (2 x m, 4H, 2"- and 3"-$H_2$), 2.85 (m, 2H, 6-$H_2$), 3.63 (d, 1H, *J* = 5.0 Hz, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.28 (dd, 1H, *J* = 13.0 Hz, *J* = 5.0 Hz, 16a-$H_2$), 4.59 (t, 1H, *J* = 12.0 Hz, 16a-$H_2$), 6.63 (d, 1H, *J* = 2.0 Hz, 4-H), 6.71 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.22 (d, 1H, *J* = 8.5 Hz, 1-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 6.6 (C-1"), 7.7 and 7.8 (C-2" and -3"), 17.1 (C-18), 26.0, 28.0, 28.9, 29.8, 31.2, 38.9, 42.3, 46.3 (C-16a), 47.0, 50.5 (C-13), 55.2 (3-$OCH_3$), 78.8 (C-17), 111.4 (C-2), 113.7 (C-4), 120.6 (C-5'), 126.3 (C-1), 132.5 (C-10), 137.9 (C-5), 149.8 (C-4'), 157.4 (C-3).

*2.3.20. 3-Methoxy-16a-(4'-cyclopentyl-1'H-1',2',3'-triazol-1'-yl)methyl-estra-1,3,5(10)-trien-17a-ol (**24b**)*

Compound **16** (342 mg, 1 mmol) and cyclopentylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **24b** (383 mg, 88%) as yellow crystalline product. Mp: 171–173 $^oC$; $R_f$= 0.42 (ss B). (Found C, 74.67; H, 8.72. $C_{27}H_{37}N_3O_2$ (435.60) requires C, 74.45; H, 8.56%). $^1H$ NMR (δ, ppm, $CDCl_3$): 075 (s, 3H, 18-$H_3$), 1.25 (s, 8H, 2"-, 3"-, 4"- and 5"-$H_2$), 2.86 (m, 2H, 6-$H_2$), 3.18 (m, 1H, 1"-H), 3.64 (d, 1H, *J* = 5.0 Hz, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.29 (dd, 1H, *J* = 13.5 Hz, *J* = 5.5 Hz, 16a-$H_2$), 4.62 (dd, 1H, *J* = 13.5 Hz, J = 11.5 Hz, 16a-$H_2$), 6.63 (d, 1H, *J* = 2.0 Hz, 4-H), 6.71 (dd, 1H, *J* = 8.5 Hz, *J* = 2.0 Hz, 2-H), 7.22 (d, 1H, *J* = 8.5 Hz, 1-H), 7.36 (s, 1H, 5'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 17.2 (C-18), 25.1 (C-3" and -4"), 26.0, 28.0, 29.0, 29.7, 29.9, 31.2, 33.2, 36.7, 38.9, 42.4, 43.5, 46.3 (C-13), 47.0 (C-1"), 50.5 (C-16a), 55.2 (3-$OCH_3$), 78.8 (C-17), 111.4 (C-2), 113.8 (C-4), 120.6 (C-5'), 126.3 (C-1), 132.6 (C-10), 137.9 (C-5), 152.3 (C-4'), 157.4 (C-3).

*2.3.21. 3-Methoxy-16a-(4'-cyclohexyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**24c**)*

Compound **16** (342 mg, 1 mmol) and cyclohexylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **24c** (162 mg, 36%) as yellow crystals. Mp: 208–210 $^oC$; $R_f$= 0.42 (ss B). (Found C, 74.97; H, 8.56. $C_{28}H_{41}N_3O_2$ (449.63) requires C, 74.80; H, 8.74%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.75 (s, 3H, 18-$H_3$), 1.26 (s, 8H, 2"-, 3"-, 5"- and 6"-$H_2$), 2.88 (m, 2H, 6-$H_2$), 2.90 (m, 2H, 4"-$H_2$), 3.64 (d, 1H, *J* = 5.0 Hz, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.29 (dd, 1H, *J* = 13.5 Hz, *J* = 5.0 Hz, 16a-$H_2$), 4.62 (dd, 1H, *J* = 13.5 Hz, *J* = 11.0 Hz, 16a-$H_2$), 6.63 (d, 1H, *J* = 2.0 Hz, 4-H), 6.71 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.22 (d, 1H, *J* = 8.5 Hz, 1-H), 7.34 (s, 1H, 5'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 17.2 (C-18), 26.0 and 26.1 (C-2", -3", -5" and -6"), 28.0, 29.0, 29.7, 29.8, 31.2, 33.0, 25.2, 38.9, 42.4, 43.5, 46.3 (C-13), 47.0 (C-1"), 50.5 (C-16a), 55.0 (3-$OCH_3$), 78.8 (C-17), 111.4 (C-2), 113.8 (C-4), 120.2 (C-5'), 126.3 (C-1), 132.6 (C-10), 137.9 (C-5), 153.3 (C-4'), 157.4 (C-3).

*2.3.22. 3-Methoxy-16a-(4'-phenyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**24d**)*

Compound **16** 342 mg, 1 mmol) and phenylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with $CH_2Cl_2$ yield pure **24d** (394 mg, 89%) as white solid. Mp: 189.5–191 $^oC$; $R_f$= 0.46 (ss B). (Found C, 75.65; H, 7.67. $C_{28}H_{33}N_3O_2$ (443.58) requires C, 75.81; H, 7.50%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.75 (s, 3H, 18-$H_3$), 2.86 (m, 2H, 6-$H_2$), 3.68 (d, 1H, *J* = 5.0 Hz, 17-H), 3.78 (s, 3H, 3-$OCH_3$), 4.41 (dd, 1H, *J* = 13.5 Hz, *J* = 6.0 Hz, 16a-$H_2$), 4.69 (dd, 1H, *J* = 14.5 Hz, *J* = 10.5 Hz, 16a-$H_2$), 6.64 (d, 1H, *J* = 2.0 Hz, 4-H), 6.72 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.22 (d, 1H, *J* = 8.5 Hz, 1-H), 7.34 (t, 1H, *J* = 7.5 Hz, 4"-H), 7.43 (t, 2H, *J* = 7.5 Hz, 3"- and 5"-H), 7.83 (d, 2H, *J* = 7.5 Hz, 2"- and 6"-H), 7.88 (s, 1H, 5'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 17.1 (C-18), 26.0, 28.0, 29.8, 31.2, 38.9, 42.3, 43.5, 46.4 (C-13), 47.0, 50.7, 55.2 (3-$OCH_3$), 78.8 (C-17), 111.5 (C-2), 113.8 (C-4), 120.6 (C-5'), 125.6 (C-2" and -6"), 126.3 (C-1), 128.1 (C-4"), 128.8 (C-3" and -5"), 130.5 (C-1"), 132.5 (C-10), 137.9 (C-5), 147.3 (C-4'), 157.4 (C-3).

*2.3.23. 3-Methoxy-16a-[4'-(4''nitrobenzoyloxymethyl)-1'H-1',2',3'-triazol-1'-yl]methylestra-1,3,5(10)-trien-17a-ol (**24e**)*

Compound **16** (342, 1 mmol) and propargyl 4-nitrobenzoate (2 mmol, 210 mg) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with $CH_2Cl_2$/hexane (1:3, v/v) to yield pure (344 mg, 63%) as yellow crystals. Mp: 64 $^oC$; $R_f$= 0.45 (ss B). (Found, C, 66.14; H, 6.05. $C_{30}H_{34}N_4O_6$ (546.61) requires C, 65.92; H, 6.27%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.75 (s, 3H, 18-$H_3$), 2.84 (m, 2H, 6-$H_2$), 3.66 (d, 1H, *J* = 4.5 Hz, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.40 (dd, 1H, *J* = 13.5 Hz, *J* = 5.5 Hz, 16a-$H_2$), 4.66 (t, 1H, *J* = 13.5 Hz, 16a-$H_2$), 5.53 (s, 2H, 4'-$H_2$), 6.62 (t, 1H, *J* = 2.0 Hz, 4-H), 6.71 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.20 (d, 1H, *J* = 8.5 Hz, 1-H), 7.85 (s, 1H, 5'-H), 8.22 (d, 2H, *J* = 9.0 Hz, 3"- and 5"-H), 8.72 (d, 2H, *J* = 9.0 Hz, 2"- and 6"-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 17.1 (C-18), 22.7, 25.9, 28.0, 29.0, 29.8, 31.2, 38.9, 42.0, 43.5, 46.4 (C-13), 47.0 (4'-CH2), 78.8 (C-17), 111.5 (C-2), 113.8 (C-4), 114.0 (C-1'), 123.5 (C-2" and -6") 126.3 (C-5'), 130.9 (C-3" and -5"), 135.0 (C-10), 137.8 (C-5), 141.5 (C-4"), 150.6 (C-4'), 157.5 (C-3), 164.6 (C=O).

*2.3.24. 3-Methoxy-16a-(4'-hydroxymethyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**24f**)*

Compound **24e** (274 mg, 0.5 mmol) was dissolved in methanol (10 ml) containing $NaOCH_3$ (14 mg, 0.25 mmol), and the solution was allowed to stand for 24 h. It was then diluted with water, and the precipitate separating out was filtered off and recrystallized from a mixture of acetone/hexane to afford **24f** (187 mg, 94%) as a white crystalline product. Mp: 149–150 $^oC$; $R_f$ = 0.25 (ss B). (Found C, 69.55; H, 7.95. $C_{23}H_{31}N_3O_3$ (397.51) requires C, 69.49; H, 7.86%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.74 (s, 3H, 18-$H_3$), 2.85 (m, 2H, 6-$H_2$), 3.62 (d, 1H, *J* = 4.0 Hz, 17-H), 3.77 (s, 3H, 3-$OCH_3$), 4.39 (m, 1H, 16a-$H_2$), 4.64 (m, 1H, 16a-$H_2$), 6.63 (s, 1H, 4-H), 6.71 (d, 1H, *J* = 8.5 Hz, 2-H), 7.21 (d, 1H, *J* = 8.5 Hz, 1-H), 7.77 (s, 1H, 5'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 11.9 (C-18), 26.0, 28.0, 28.9, 31.3, 31.9, 33.8 (C-13), 38.9, 41.9, 43.5, 46.4 (4'-$CH_2$), 46.9, 51.0 (C-16a), 55.2 (3-$OCH_3$), 78.6 (C-17), 111.5 (C-2), 113.8 (C-4), 123.4 (C-5'), 126.3 (C-1), 132.5 (C-10), 137.8 (C-5), 157.4 (C-3).

*2.3.25. 3-Benzyloxy-16β-(4'-cyclopropyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**25a**)*

Compound **17** (420 mg, 1 mmol) and cyclopropylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **25a** (394 mg, 84%) as a white solid. Mp: 278–280 $^oC$; $R_f$= 0.35 (ss B). (Found C, 77.16; H, 7.62. $C_{31}H_{37}N_3O_2$ (483.64) requires C, 76.98; H, 7.71%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.80 (s, 3H, 18-$H_3$), 0.86 and 0.97 (2 x m, 2 x 2H, 2”- and 3”-H), 2.83 (m, 2H, 6-$H_2$), 3.93 (d, *J* = 9.5 Hz, 1H, 17-H), 4.21 (m, 1H, 16a-$H_2$), 4.64 (m, 1H, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.71 (s, 1H, 4-H), 6.78 (d, 1H, *J* = 8.5 Hz, 2-H), 7.20 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 1H, *J* = 7.0 Hz, 4’-H), 7.38 (t, 2H, *J* = 7.0 Hz, 3’- and 5’-H), 7.43 (d, 2H, *J* = 7.0 Hz, 2’- and 6’-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 7.8 (C-2” and -3”), 12.3 (C-18), 26.2, 27.4, 29.7, 30.8, 37.5, 38.0, 41.4, 43.9, 44.3 (C-13), 48.7 (C-16), 67.8 (C-16a), 69.9 (Bn-$CH_2$), 80.7 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-2’ and -6’), 127.8 (C-4’), 128.5 (C-3’ and C-5’), 132.7 (C-10), 137.3 (C-1’), 137.8 (C-5), 156.8 (C-3).

*2.3.26. 3-Benzyloxy-16β-(4’-cyclopentyl-1’H-1’,2’,3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17β-ol (**25b**)*

Compound **17** (420 mg, 1 mmol) and cyclopentylacetylene (2 mol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **25b** (350 mg, 68%) as a white solid. Mp: 288–290 $^oC$; $R_f$= 0.38 (ss B). Found C, 77.58; H, 7.92. $C_{33}H_{41}N_3O_2$ (511.70) requires C, 77.46; H, 8.08%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.79 (s, 3H, 18-$H_3$), 2.75 (s, 1H, 1”-H), 2.83 (m, 2H, 6-$H_2$), 3.94 (d, 1H, *J* = 9.5 Hz, 17-H), 4.24 (m, 1H, 16-$H_2$), 4.67 (m, 1H, 16-$H_2$), 5.03 (s., 2H, Bn-$H_2$), 6.71 (s, 1H, 4-H), 6.78 (d, 1H, *J* = 8.5 Hz, 2-H), 7.19 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 1H, *J* = 7.5 Hz, 4’-H), 7.38 (t, 2H, *J* = 7.5 Hz, 3’- and 5’-H), 7.42 (d, 2H, *J* = 7.5 Hz, 2’- and 6’-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 12.3 (C-18), 25.1 (C-3” and -4”), 26.2, 27.5, 29.7, 30.8, 34.3 (C-2” and -5”), 37.5, 38.0, 41.4, 43.9, 44.3 (C-13), 48.7 (C-16), 62.1 (16a-$CH_2$), 69.9 (Bn-$CH_2$), 80.7 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-2’ and -6’), 127.8 (C-4’), 128.5 (C-3’ and -5’), 132.7 (C-10), 137.3 (C-1’), 137.8 (C-5), 156.8 (C-3).

*2.3.27. 3-Benzyloxy-16β-(4’-cyclohexyl-1’H-1’,2’,3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17β-ol (**25c**)*

Compound **17** (420 mg, 1 mmol) and cyclohexylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99, v/v) to yield pure **25c** (146 mg, 28%) as a white solid. Mp: 214–216 $^oC$; $R_f$= 0.38 (ss B). (Found C, 77.43; H, 8.36. $C_{34}H_{43}N_3O_2$ (525.72) requires C, 77.68; H, 8.24%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.79 (s, 3H, 18-$H_3$), 2.79 (m, 4H, 3”- and 5”-H), 3.94 (d, *J* = 9.5 Hz, 1H, 17-H), 4.25 (m, 1H, 16a-$H_2$), 4.67 (m, 1H, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.71 (s, 1H, 4-H), 6.78 (d, 1H, J = 8.5 Hz, 2-H), 7.19 (d, 1H, *J* = 8.5 Hz, 1-H), 7.32 (d, 1H, *J* = 7.0 Hz, 4’-H), 7.38 (t, 2H, *J* = 7.0 Hz, 3’- and 5’-H), 7.42 (d, 2H, *J* = 7 Hz, 2’- and 6’-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 12.3 (C-18), 26.0 (C-4”), 26.1 (C-3” and -5”), 26.2, 27.5, 29.7, 30.8 (C-2” and -6”), 33.0 (C-1”), 37.5, 38.0, 41.4, 43.9, 44.3 (C-13), 48.7 (C-16), 62.1 (C-16a), 69.9 (Bn-$CH_2$), 80.7 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-2’ and -6’), 127.8 (C-4’), 128.5 (C-3’ and -5’), 132.7 (C-10), 137.3 (C-1’), 137.8 (C-5), 157.8 (C-3).

*2.3.28. 3-Benzyloxy-16β-(4’-phenyl-1’H-1’,2’,3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17β-ol (**25d**)*

Compound **17** (420 mg, 1 mmol) and phenylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **25d** (391 mg, 75%) as a white solid. Mp: 202–204 $^oC$; $R_f$= 0.45 (ss B). (Found C, 78.73; H, 6.98. $C_{34}H_{37}N_3O_2$ (519.68) requires C, 78.58; H, 7.18%). $^1H$ NMR (δ, ppm, $C_6D_6$): 0.68 (s, 3H, 18-$H_3$), 2.69 (m, 2H, 6-$H_2$), 3.43 (dd, *J* = 9.5 Hz, *J* = 4 Hz, 1H, 17-H), 3.77 (dd, 1H, J = 13.5 Hz, J = 7.0 Hz, 16a-$H_2$), 4.29 (dd, 1H, J = 13.5 Hz, J = 7.0 Hz, 16a-$H_2$), 4.83 (s, 2H, Bn-$H_2$), 6.79 (s, 1H, 4-H), 6.87 (d, 1H, *J* = 8.0 Hz, 2-H), 7.02 (s, 1H, 1-H), 7.08 (t, 1H, *J* = 7.5 Hz, 4’-H), 7,26 (t, 2H, *J* = 7.5 Hz, 3’- and 5’-H), 7.32 (d, 2H, *J* = 7.5 Hz, 2’- and 6’-H), 8.01 (d, 2H, *J* = 7.5 Hz, 2”- and 6”-H).

*2.3.29. 3-Benzyloxy-16β-[4’-(4’’-nitro-benzoyloxymethyl)-1’H-1’,2’,3’-triazol-1’-yl]methyestra-1,3,5(10)-trien-17β-ol (**25e**)*

Compound **17** (420 mg, 1 mmol) and propargyl 4-nitrobenzoate (2 mmol, 210 mg) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **25e** (480 mg, 77%) as a yellow solid. Mp: 187–189 $^oC$; $R_f$= 0.45 (ss B). (Found C, 69.32; 5.98. $C_{36}H_{38}N_4O_6$ (622.71) requires C, 69.44; H, 6.15%).

$^1$H NMR (δ, ppm, $CDCl_3$): 0.80 (s, 3H, 18-$H_3$), 2.82 (m, 2H, 6-$H_2$), 3.94 (d, *J* = 10.0 Hz, 1H, 17-H), 4.32 (dd, 1H, J = 13.0 Hz, J = 6.0 Hz, 16a-$H_2$), 4.72 (t, 1H, J = 6.0 Hz, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 5.52 (s, 2H, triazol-H), 6.71 (s, 1H, 4-H), 6.78 (d, 1H, *J* = 8.5 Hz, 2-H), 7.19 (d, 1H, *J* = 8.5 Hz, 1-H), 7.32 (t, 1H, *J* = 7.0 Hz, 4'-H), 7.38 (t, *J* = 7.5 Hz, 2H, 3'- and 5'-H), 7.42 (d, *J* = 7.5 Hz, 2H, 2'- and 6'-H), 8.22 (d, *J* = 8 Hz, 2H, 3"- and 5"-H), 8.27 (d, *J* = 8 Hz, 2H, 2"- and 6"-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 12.3 (C-18), 26.2, 27.4, 29.7, 30.8, 37.4, 38.0, 41.2, 43.8, 44.4 (C-13), 48.7 (C-16), 55.5 (C-16a), 58.7 (linker-$CH_2$), 69.9 (Bn-$CH_2$), 80.7 (C-17), 112.4 (C-2), 114.8 (C-4), 123.5 (C-2' and -6'), 126.3 (C-1), 127.4 (C-2" and -6"), 127.8 (C-4'), 128.5 (C-3" and -5"), 130.9 (C-3' and -5'), 132.5 (C-10), 135.1 (C-1"), 137.3 (C-1'), 137.8 (C-5), 150.7 (C-4"), 156.8 (C-3), 164.6 (C=O).

### *2.3.30. 3-Benzyloxy-16β-(4'-hydroxymethyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**25f**)*

Compound **25e** (210 mg, 0.5 mmol) was dissolved in methanol (10 ml) containing $NaOCH_3$ (14 mg, 0.25 mmol), and the solution was allowed to stand for 24 h. It was then diluted with water, and the precipitate separating out was filtered off and recrystallized from methanol to afford **25f** (232 mg, 98%) as a white crystalline product. Mp: 283–285 $^{o}$C; $R_f$= 0.25 (ss B). (Found C, 73.42; H, 7.35. $C_{29}H_{35}N_3O_3$ (473.61) requires C, 73.54; H, 7.45%). $^1$H NMR (δ, ppm, DMSO-$d_6$): 0.77 (s, 3H, 18-$H_3$), 3.77 (dd, 1H, J = 9.5 Hz, J = 3.5 Hz, 16a-$H_2$), 4.15 (t, 1H, J = 12.5 Hz, 16a-$H_2$), 5.12 (d, 1H, J = 5.5 Hz, 17-H), 6.68 (s, 1H, 4-H), 6.74 (d, 1H, *J* = 8.5 Hz, 2-H), 7.16 (d, *J* = 8.5 Hz, 1H, 1-H), 7.31 (d, 1H, *J* = 7.0 Hz, 4'-H), 7.37 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.41 (d, 2H, *J* = 7.0 Hz., 2'- and 6'-H), 7.98 (s, 1H, triazol-H). $^{13}$C NMR (δ, ppm, DMSO-$d_6$): 12.3 (C-18), 25.8, 26.9, 29.1, 30.0, 36.9, 37.8, 40.4, 43.4, 43.7 (C-13), 47.8 (C-16a), 55.0 (linker-$CH_2$), 68.9 (Bn-$CH_2$), 79.5 (C-17), 112.1 (C-2), 114.4 (C-4), 122.7 (triazol-CH), 126.0 (C-1), 127.4 (C-2' and -6'), 127.6 (C-4'), 128.3 (C-3' and -5'), 132.3 (C-10), 137.3 (C-5), 147.6 (triazol-C), 156.0 (C-3).

### *2.3.31. 3-Benzyloxy-16a-(4'-cyclopropyl-1'H-1',2,'3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**26a**)*

Compound **18** (420.0 mg, 1 mmol) and cyclopropylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with

ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **26a** (310 mg, 64%) as a white solid. Mp: 191–193 $^oC$; $R_f$= 0.35 (ss B). (Found C, 76.82; H, 7.94. $C_{31}H_{37}N_3O_2$ (483.64) requires C, 76.98; H, 7.71%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.83 (s, 3H, 18-$H_3$), 2.83 (m, 2H, 6-$H_2$), 3.54 (d, *J* = 7.5 Hz, 1H, 17-H), 4.35 (dd, 1H, *J* = 13.0 Hz, *J* = 7.5 Hz, 16a-$H_2$), 4.44 (dd, 1H, *J* = 13.0 Hz, *J* = 7.5 Hz, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.71 (s, 1H, 4-H), 6.77 (d, 1H, *J* = 8.5 Hz, 2-H), 7.19 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 2H, *J* = 7.5 Hz, 4'-H and triazol-H), 7.38 (t, 2H, *J* = 7.5 Hz, 3'- and 5'-H), 7.42 (d, 2H, *J* = 7.5 Hz, 2'- and 6'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 6.6 (C-1"), 7.8 (C-2" and -3"), 11.8 (C-18), 26.1, 27.2, 28.2, 29.7, 36.6, 38.4, 43.9, 44.3, 44.3 (C-13), 48.3 (C-16), 54.5 (C-16a), 69.9 (Bn-$CH_2$), 85.2 (C-17), 112.3 (C-2), 114.8 (C-4), 120.0 (triazol-CH), 126.3 (C-1), 127.4 (C-2' and -6'), 127.8 (C-4'), 128.5 (C-3' and -5'), 132.6 (C-10), 137.3 (C-1'), 137.8 (C-5), 150.2 (triazol-C), 156.8 (C-3).

*2.3.32. 3-Benzyloxy-16a-(4'-cyclopentyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**26b**)*

Compound **18** (420 mg, 1 mmol) and cyclopentylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **26b** (442 mg, 86%) as a white solid. Mp: 268–270 $^oC$; $R_f$= 0.36 (ss B). (Found C, 77.52; H, 7.93. $C_{33}H_{41}N_3O_2$ (511.70) requires C, 77.46; H, 8.08%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.83 (s, 3H, 18-$H_3$), 2.83 (m, 2H, 6-$H_2$), 3.19 (s, 1H, 1"-H), 3.46 (d, 1H, *J* = 7.0 Hz, 17-H), 4.42 (dd, 2H, *J* = 22.5 Hz, $J_,$ = 6.5 Hz, 16-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.71 (s, 1H, 4-H), 6.76 (d, 1H, *J* = 8.5 Hz, 2-H), 7.19 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 1H, *J* = 7.5 Hz, 4'-H), 7 .37 (t, 3H, *J* = 7.5 Hz, 3'-, 5'-H and triazol-H), 7.42 (d, 2H, *J* = 7.5 Hz, 2'- and 6'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 11.9 (C-18), 25.1 (C-3" and -4"), 26.1, 27.2, 28.3, 29.7, 33.2 (C-2" and -5"), 36.6 (2C, C-1"), 36.7, 38.4, 43.9, 44.3 (C-13), 48.4 (C-16), 54.5 (C-16a), 69.9 (Bn-$CH_2$), 85.2 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-3' and -5'), 127.8 (C-4'), 128.5 (C-2' and -6'), 132.6 (C-10), 137.3 (C-1'), 137.8 (C-5), 156.7 (C-3).

*2.3.33. 3-Benzyloxy-16a-(4'-cyclohexyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**26c**)*

Compound **18** (420 mg, 1 mmol) and cyclohexylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with

ethyl acetate/$CH_2Cl_2$ (2.5:77.5 v/v) to yield pure **26c** (386 mg, 76%) as a white solid. Mp: 261–263 $^oC$; $R_f$= 0.34 (ss B). (Found C, 77.93; H, 8.36. $C_{34}H_{43}N_3O_2$ (525.72) requires C, 77.68; H, 8.24%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.83 (s, 3H, 18-$H_3$), 2.83 (m, 2H, 6-$H_2$), 3.55 (d, *J* = 7.0 Hz, 1H, 17-H), 4.43 (m, 2H, 16-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.71 (s, 1H, 4-H), 6.77 (d, 1H, *J* = 8.5 Hz, 2-H), 7.19 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 2H, *J* = 7.0 Hz, 4'-H and triazol-H), 7.37 (t, 2H, *J* = 7.0 Hz. 3'- and 5'-H), 7.42 (d, 2H, *J* = 7 Hz, 2'- and 6'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 11.9 (C-18), 25.9 (C-4"), 26.1 (C-3" and -5"), 27.2, 28.3, 29.7 (C-2" and -6"), 32.9, 33.0, 36.6, 38.4, 43.9, 44.2, 44.3 (C-13), 48.4 (C-16), 54.5 (C-16a), 69.9 (Bn-$CH_2$), 85.2 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-2' and -6'), 127.8 (C-4'), 128.5 (C-3' and -5'), 132.6 (C-10), 137.3 (C-1'), 137.8 (C-5), 156.7 (C-3).

*2.3.34. 3-Benzyloxy-16a-(4'-phenyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol* ***(26d)***

Compound **18** (420 mg, 1 mmol) and phenylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ 5:95 v/v) to yield pure **26d** (372 mg, 71%) as a white solid. Mp: 132–134 $^oC$; $R_f$= 0.38 (ss B). (Found C, 78.63; H, 6.97. $C_{34}H_{37}N_3O_2$ (519.68) requires C, 78.58; H, 7.18%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.84 (s, 3H, 18-$H_3$), 2.83 (m, 2H, 6-$H_2$), 3.58 (d, 1H, *J* = 7.5 Hz, 17-H), 4.46 (dd, 2H, *J* = 13.5 Hz, *J* = 8.0 Hz, 16a-$H_2$), 4.55 (dd, 1H, *J* = 13.5 Hz, *J* = 8.0 Hz, 16a-H2) 5.03 (s, 2H, Bn-$H_2$), 6.71 (s, 1H, 4-H), 6.78 (d, 1H, *J* = 8.5 Hz, 2-H), 7.19 (d, 1H, *J* = 8.5 Hz, 1-H), 7.30-7.86 (m, 11H, 2'-, 6'-, 3'-, 5'-, 4'-, 2"-, 6"-, 3"-, 5"-, 4"- and triazol-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 11.8 (C-18), 26.1, 27.2, 28.2, 29.6, 36.5, 38.4, 43.9, 44.3, 48.3 (C-16), 54.6 (C-16a), 62.1, 69.9 (Bn-$CH_2$), 85.2 (C-17), 112.3 (C-2), 114.8 (C-4), 123.8 (triazol-CH), 125.7 (C-2' and -6'), 126.3 (C-1'), 127.4 (C-2" and -6"), 127.8 (C-4'), 128.2 (C-4), 128.5 (C-3" and -5"), 128.8 (C-3' and -5'), 130.4 (C-10), 132.6 (C-1"), 137.3 (C-1'), 137.8 (C-5), 156.8 (C-3).

*2.3.35. 3-Benzyloxy-16a-[4'-(4''-nitro-benzoyloxymethyl)-1'H-1',2',3'-triazol-1'-yl]methylestra-1,3,5(10)-trien-17β-ol (**26e**)*

Compound **18** (420 mg, 1 mmol) and propargyl 4-nitrobenzoate (2 mmol, 210 mg) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **26e** (484 mg, 77%) as a yellow solid. Mp:

94–96 °C; $R_f$= 0.40 (ss B). (Found C, 69.73; H, 5.94. $C_{36}H_{38}N_4O_6$ (622.71) requires C, 69.44; H, 6.15%). $^1$H NMR (δ, ppm, DMSO-$d_6$): 0.70 (s, 3H, 18-$H_3$), 3.33 (m, 2H, 6-$H_2$), 4.38 (dd, 1H, *J* = 13.5 Hz, *J* = 9.0 Hz, 16a-$H_2$), 4.52 (dd, 1H, *J* = 13.5 Hz, *J* = 5.0 Hz, 16a-$H_2$), 4.86 (d, 1H, *J* = 5 Hz, 17-H), 5.02 (s, 2H, Bn-$H_2$), 5.47 (s, 2H, linker-$H_2$), 6.64 (d, 1H, J = 2.0 Hz, 4-H), 6.72 (dd, 1H, J = 8.5 Hz, *J* = 2.0 Hz, 2-H), 7.10 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 1H, *J* = 7.0 Hz, 4'-H), 7.37 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.42 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H), 8.16 (d, 2H, *J* = 9.0 Hz, 3"- and 5"-H), 8.28 (d, 2H, *J* = 9.0 Hz, 2"- and 6"-H), 8.32 (s, 1H, triazol-H). $^{13}$C NMR (δ, ppm, DMSO-$d_6$): 11.7 (C-18), 25.7, 26.6, 27.1, 29.0, 30.6, 36.4, 37.9, 43.4, 43.4 (C-13), 43.7 (C-16), 53.1 (C-16a), 58.6 (linker-$CH_2$), 68.9 (Bn-$CH_2$), 82.8 (C-17), 112.1 (C-2), 114.3 (C-4), 123.7 (C-2' and -6'), 125.1 (triazol-CH), 125.9 (C-1), 127.4 (C-2" and -6"), 127.5 (C-4'), 128.3 (C-3" and -5"), 130.6 (C-3' and -5'), 132.1 (C-10), 134.7 (C-1"), 137.2 (C-1'), 137.3 (C-5), 141.1 (triazol-C), 150.1 (C-4"), 155.9 (C-3), 163.9 (C=O).

### *2.3.36. 3-Benzyloxy-16a-(4'-hydroxymethyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17β-ol (**26f**)*

Compound **26e** (210 mg, 0.5 mmol) was dissolved in methanol (10 ml) containing $NaOCH_3$ (14 mg, 0.25 mmol), and the solution was allowed to stand for 24 h. It was then diluted with water, and the precipitate separating out was filtered off and recrystallized from a mixture of acetone/hexane to afford **26f** (190 mg, 89%) as a white crystalline product. Mp: 152–154 °C; $R_f$= 0.20 (ss B). (Found C, 73.72; H, 7.63. $C_{29}H_{35}N_3O_3$ (473.61) requires C, 73.54; H, 7.45%). $^1$H NMR (δ, ppm, DMSO-$d_6$): 0.71 (s, 3H, 18-$H_3$), 2.73 (m, 2H, 6$H_2$), 3.29 (d, *J* = 8.0 Hz, 1H, 17-H), 4.28 (dd, 2H, *J* = 13.0 Hz, *J* = 10.0 Hz, 16a-$H_2$), 4.47 (dd, 1H, *J* = 13.0 Hz, *J* = 4.5 Hz, 16a-$H_2$), 4.51 (s, 2H, Bn-$H_2$), 4.87 (s, 1H, linker-$H_2$), 5.03 (s, 2H, triazol-$H_2$), 5.15 (s, 1H, linker-$H_2$), 6.68 (s, 1H, 4-H), 6.74 (d, 1H, *J* = 8.5 Hz, 2-H), 7.15 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 1H, *J* = 7.0 Hz, 4'-H), 7.37 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.41 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H), 7.97 (s, 1H, triazol-H). $^{13}$C NMR (δ, ppm, DMSO-$d_6$): 11.8 (C-18), 25.8, 26.7, 27.3, 29.1, 36.4, 38.1, 43.4, 43.5 (C-13), 43.9, 47.5 (C-16), 53.1 (C-16a), 54.9 (linker-$CH_2$), 68.9 (Bn-$CH_2$), 83.0 (C-17), 112.1 (C-2), 114.4 (C-4), 122.7 (triazol-CH), 126.0 (C-1), 127.4 (C-2' and -6'), 127.6 (C-4'), 128.3 (C-3' and -5'), 132.3 (C-10), 137.3 (C-1'), 137.4 (C-5), 147.6 (triazol-C), 156.0 (C-3).

*2.3.37. 3-Benzyloxy-16β-(4'-cyclopropyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**27a**)*

Compound **19** (420.0 mg, 1 mmol) and cyclopropylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **27a** (454 mg, 93%) as white crystals. Mp: 199–201 $^oC$; $R_f$= 0.38 (ss B). (Found C, 77.15; H, 7.62. $C_{31}H_{37}N_3O_2$ (483.64) requires C, 76.98; H, 7.71%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.77 (s, 3H, 18-$H_3$), 0.87 and 0.98 (2 x s, 2 x 2H, 2"- and 3"-$H_2$), 2.05 (s, 1H, 1"-H), 2.84 (m, 2H, 6-$H_2$), 3.66 (s, 1H, 17-H), 4.42 (m, 2H, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.71 (s, 1H, 4-H), 6.78 (d, 1H, *J* = 8.5 Hz, 2-H), 7.21 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 1H, *J* = 7.0 Hz, 4'-H), 7.38 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.43 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 6.7 (C-1"), 7.7 (C-2" and -3"), 17.9 (C-18), 25.9, 27.9, 29.7, 30.4, 31.8, 38.5, 43.3, 45.1 (C-13), 48.9, 49.1 (C-16), 62.1 (C-16a), 69.9 (Bn-$CH_2$), 82.6 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-2' and -6'), 127.8 (C-4'), 128.5 (C-3' and -5'), 132.7 (C-10), 137.3 (C-1'), 137.9 (C-5), 156.7 (C-3).

*2.3.38. 3-Benzyloxy-16β-(4'-cyclopentyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**27b**)*

Compound **19** (420 mg, 1 mmol) and cyclopentylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **27b** (408 mg, 79%) as white crystalline. Mp: 220–222 $^oC$; $R_f$= 0.40 (ss B). (Found C, 77.32; H, 7.93. $C_{33}H_{41}N_3O_2$ (511.70) requires C, 77.46; H, 8.08%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.76 (s, 3H, 18-$H_3$), 2.84 (m, 2H, 6-$H_2$), 3.20 (s, 1H, 1"-H), 3.67 (s, 1H, 17-H), 4.43 (m, 2H, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.72 (s, 1H, 4-H), 6.78 (dd, 1H, *J* = 8.5 Hz, *J* = 2.0 Hz, 2-H), 7.21 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 1H, *J* = 7.0 Hz, 4'-H), 7.38 (t, 3H, *J* = 7.0 Hz, 3'- and 5'-H, triazol-H), 7.43 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 18.0 (C-18), 25.1 (C-3" and -5"), 25.9, 28.0, 29.7, 30.4, 31.8 (C-2" and -6"), 33.2, 36.7, 38.5, 43.3, 45.1 (C-13), 48.9 (C-16), 49.1 (C-1"), 54.3 (C-16a), 69.9 (Bn-$CH_2$), 82.6 (C-17), 112.3 (C-2), 114.8 (C-4), 126.3 (C-1), 127.4 (C-2' and -6'), 127.8 (C-4'), 128.5 (C-3' and -5'), 132.7 (C-10), 137.3 (C-1'), 137.9 (C-5), 156.7 (C-3).

*2.3.39. 3-Benzyloxy-16β-(4'-cyclohexyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**27c**)*

Compound **19** (420 mg, 1 mmol) and cyclohexylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **27c** (360 mg, 68%) as white crystalline product. Mp: 243–245 $^oC$; $R_f$= 0.38 (ss B). (Found C, 77.54; H, 8.38. $C_{34}H_{43}N_3O_2$ (525.72) requires C, 77.68; H, 8.24%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.75 (s, 3H, 18-$H_3$), 2.84 (m, 2H, 6-$H_2$), 3.68 (s, 1H, 17-H), 4.44 (m, 2H, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.72 (s, 1H, 4-H), 6.78 (d, 1H, *J* = 8.5 Hz, 2-H), 7.21 (d, 1H, *J* = 8.5 Hz, 1-H), 7.32 (t, 1H, *J* = 7.0 Hz, 4'-H), 7.38 (t, 3H, *J* = 7.0 Hz, 3'- and 5'-H, triazol-H), 7.43 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 17.9 (C-18), 25.9 (C-4"), 26.0, 26.1 (C-3" and -5"), 27.9, 29.7, 30.4, 31.8 (C-2" and -6"), 32.1, 32.9 (C-1"), 38.5, 43.3, 45.1 (C-13), 48.9, 49.1 (C-16), 62.1 (C-16a), 69.9 (Bn-$CH_2$), 82.5 (C-17), 112.3 (C-2), 114.7 (C-4), 126.3 (C-1), 127.4 (C-2' and -6'), 127.8 (C-4'), 128.5 (C-3' and -5'), 132.7 (C-10), 137.2 (C-1'), 137.9 (C-5), 156.7 (C-3).

*2.3.40. 3-Benzyloxy-16β-(4'-phenyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**27d**)*

Compound **19** (420 mg, 1 mmol) and phenylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (10:90 v/v) to yield pure **27d** (487 mg, 93%) as white crystals. Mp: 202–204 $^oC$; $R_f$= 0.45 (ss B). (Found C, 78.68; H, 7.38. $C_{34}H_{37}N_3O_2$ (519.68) requires C, 78.58; H, 7.18%). $^1H$ NMR (δ, ppm, $CDCl_3$): 0.79 (s, 3H, 18-$H_3$), 2.84 (m, 2H, 6-$H_2$), 3.72 (s, 1H, 17-H), 4.48 (dd, 1H, *J* = 13.5 Hz, *J* = 7.5 Hz, 16a-$H_2$), 4.56 (t, 1H, *J* = 13.5 Hz, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.72 (s, 1H, 4-H), 6.78 (d, 1H, *J* = 8.5 Hz, 2-H), 7.21 (d, 1H, *J* = 8.5 Hz, 1-H), 7.33 (t, 1H, *J* = 7.5 Hz, 4'-H), 7.38 (t, 2H, *J* = 7.5 Hz, 3'- and 5'-H), 7.42 (d, *J* = 3.5 Hz, 4H, 2'- and 6'-H, 3"- and 5"-H), 7.84 (d, 2H, *J* = 7.5 Hz, 2"- and 6"-H), 7.88 (s, 1H, triazol-H). $^{13}C$ NMR (δ, ppm, $CDCl_3$): 17.9 (C-18), 25.9, 27.9, 29.7, 30.4, 31.8, 38.5, 43.3, 45.2 (C-13), 48.9, 49.1 (C-16), 54.6 (C-16a), 69.9 (Bn-$CH_2$), 82.6 (C-17), 112.3 (C-2), 114.8 (C-4), 119.6 (triazol-CH), 125.7 (C-2' and -6'), 126.3 (C-1'), 127.4 (C-2" and -6"), 127.8 (C-4'), 128.2 (C-4"), 128.5 (C-3" and -

5”), 128.8 (C-3’ and -5’), 130.5 (C-10), 132.64 (C-1”), 137.3 (C-1’), 137.9 (C-5), 147.7 (triazol-C); 156.8 (C-3).

*2.3.41. 3-Benzyloxy-16β-[4’-(4’’-nitro-benzoyloxymethyl)-1’H-1’,2’,3’-triazol-1’-yl]methylestra-1,3,5(10)-trien-17a-ol (**27e**)*

Compound **19** (420.0 mg, 1 mmol) and propargyl 4-nitrobenzoate (2 mmol, 210 mg) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (10:90 v/v) to yield pure **27e** (550 mg, 88%) as yellow crystals. Mp: 177–179 $^{o}$C; $R_f$= 0.48 (ss B). (Found C, 69.55; H, 5.93. $C_{36}H_{38}N_4O_6$ (622.71) requires: C, 69.44; H, 6.15%). $^1$H NMR (δ, ppm, DMSO-$d_6$): 0.65 (s, 3H, 18-$H_3$), 2.73 (m, 2H, 6-$H_2$), 4.40 (dd, 1H, *J* = 13.0 Hz, *J* = 8.5 Hz, 16a-$H_2$), 4.56 (dd, 1H, *J* = 13.5 Hz, *J* = 7.5 Hz, 16a-$H_2$), 4.63 (d, 1H, *J* = 5.0 Hz, 17-H), 5.04 (s, 2H, Bn-$H_2$), 5.47 (s, 2H, triazol-$H_2$), 6.68 (s, 1H, 4-H), 6.74 (d, 1H, *J* = 8.5 Hz, 2-H), 7.16 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 1H, *J* = 7.0 Hz, 4’-H), 7.37 (t, 2H, *J* = 7.0 Hz, 3’- and 5’-H), 7.41 (d, 2H, *J* = 7.0 Hz, 2’- and 6’-H), 8.18 (d, 2H, *J* = 8.5 Hz, 3”- and 5”-H), 8.33 (d, 3H, *J* = 6 Hz, 2”- and 6”-H, triazol-H). $^{13}$C NMR (δ, ppm, DMSO-$d_6$): 17.5 (C-18), 25.6, 27.5, 29.2, 29.6, 31.8, 38.2, 42.9, 44.5 (C-13), 48.2, 49.1 (C-16), 53.6 (C-16a), 58.7 (linker-$CH_2$), 68.9 (Bn-$CH_2$), 80.8 (C-17), 112.1 (C-2), 114.4 (C-4), 123.8 (C-2’ and C-6’), 125.0 (triazol-CH), 126.1 (C-1), 127.4 (C-2” and -6”), 127.6 (C-4’), 128.3 (C-3” and -5”), 130.6 (C-3’ and -5’), 132.3 (C-10), 134.7 (C-1”), 137.3 (C-5 and C-1’), 141.1 (triazol-C), 150.2 (C-4”), 160.0 (C-3), 163.9 (C=O).

*2.3.42. 3-Benzyloxy-16β-(4’-hydroxymethyl-1’H-1’,2’,3’-triazol-1’-yl)methylestra-1,3,5(10)-trien-17a-ol (**27f**)*

Compound **27e** (210 mg, 0.5 mmol) was dissolved in methanol (10 ml) containing $NaOCH_3$ (14 mg, 0.25 mmol), and the solution was allowed to stand for 24 h. It was then diluted with water, and the precipitate separating out was filtered off and recrystallized from methanol to afford **27e** (273 mg, 99%) as a white crystalline product. Mp: 172–174 $^{o}$C; $R_f$= 0.25 (ss B). (Found C, 73.68; H, 7.66. $C_{29}H_{35}N_3O_3$ (473.61) requires C, 73.54; H, 7.45%). $^1$H NMR (δ, ppm, DMSO-$d_6$): 0.67 (s, 3H, 18-$H_3$), 2.74 (m, 2H, 6-$H_2$), 3.43 (s, 1H, 17-H), 4.34 (m, 1H, 16a-$H_2$), 4.50 (m, 3H, 16a-$H_2$ and Bn-H2), 4.61 (brs, 1H, OH), 5.04 (s, 2H, triazol-$H_2$), 5.16 (brs, 1H, OH), 6.69 (s, 1H, 4-H), 6.74 (d, 1H, *J* = 8.5 Hz, 2-H), 7.17 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (d, 1H, *J* = 7.0 Hz, 4’-H),

7.37 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.41 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H), 8.00 (s, 1H, triazol-H). $^{13}$C NMR (δ, ppm, DMSO-$d_6$): 17.5 (C-18), 25.6, 27.5, 29.2, 29.6, 31.9, 38.2, 43.0, 44.5 (C-13), 48.2, 49.1 (C-16), 53.5 (C-16a), 55.0 (linker-$CH_2$), 61.6, 68.9 (Bn-$CH_2$), 80.8 (C-17), 112.2 (C-2), 114.4 (C-4), 122.6 (triazol-CH), 126.6 (C-1), 127.4 (C-2' and -6'), 127.6 (C-4'), 128.3 (C-3' and -5'), 132.4 (C-10), 137.3 (C-5 and C-1'), 147.6 (triazol-C), 156.0 (C-3).

*2.3.43. 3-Benzyloxy-16a-(4'-cyclopropyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**28a**)*

Compound **20** (420.0 mg, 1 mmol) and cyclopropylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (1:99 v/v) to yield pure **28a** (305 mg, 63%) as white crystals. Mp: 143–144 $^{o}$C; $R_f$= 0.40 (ss B). (Found C, 77.15; H, 7.53. $C_{31}H_{37}N_3O_2$ (483.64) requires C, 76.98; H, 7.71%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.74 (s, 3H, 18-$H_3$), 0.87 and 0.97 (2 x s, 2 x 2H, 2"- and 3"-$H_2$), 2.85 (m, 2H, 6-$H_2$), 3.63 (d, 1H, *J* = 5.0 Hz, 17-H), 4.26 (dd, 1H, *J* = 13.5 Hz, *J* = 5.5 Hz, 16a-$H_2$), 4.60 (t, 1H, *J* = 13.5 Hz, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.72 (d, 1H, *J* = 2.0 Hz, 4-H), 6.78 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.22 (d, 1H, *J* = 8.5 Hz, 1-H), 7.32 (t, 1H, *J* = 7.5 Hz, 4'-H), 7.38 (t, 3H, *J* = 7.5 Hz, 3'- and 5'-H, triazol-H), 7.43 (d, 2H, *J* = 7.5 Hz, 2'- and 6'-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 6.5 (C-1"), 7.9 (2C, C-2" and -3"), 17.1 (C-18), 26.0, 27.9, 28.9, 29.8, 31.2, 38.9, 42.3, 43.5, 46.3 (C-16a), 47.0 (C-16), 50.7 (C-13), 69.9 (Bn-$CH_2$), 78.7 (C-17), 112.2 (C-2), 114.8 (C-4), 120.8 (triazol-CH)), 126.3 (C-1), 127.4 (C-2' and -6'), 127.4 (C-4'), 128.5 (C-3' and -5'), 132.5 (C-10), 137.2 (C-1'), 137.9 (C-5), 149.6 (triazol-C), 156.7 (C-3).

*2.3.44. 3-Benzyloxy-16a-(4'-cyclopentyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17a-ol (**28b**)*

Compound **20** (420.0 mg, 1 mmol) and cyclopentylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (2.5:97.5 v/v) to yield pure **28b** (417 mg, 82%) as white crystals. Mp: 197–199 $^{o}$C; $R_f$= 0.42 (ss B). (Found: C, 77.62; H, 7.85. $C_{33}H_{41}N_3O_2$ (511.70) requires C, 77.46; H, 8.08%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.76 (s, 3H, 18-$H_3$), 2.85 (m, 2H, 6-$H_2$), 3.20 (s, 1H, 1"-H), 3.66 (d, 1H, *J* = 5.0 Hz, 17-H), 4.29 (dd, 1H, *J* = 13.5 Hz, *J* = 5.5 Hz, 16a-$H_2$), 4.62 (dd, 1H, *J* = 13.5 Hz, *J* = 9.5 Hz, 16a-$H_2$), 5.04 (s, 2H, Bn-$H_2$), 6.72 (s, 1H, 4-H), 6.78 (dd, 1H, *J* = 8.5 Hz,

*J* = 2.5 Hz, 2-H), 7.21 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (t, 1H, *J* = 7.0 Hz, 4'-H), 7.37 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.43 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 17.3 (C-18), 25.2 (2C), 26.1, 28.0, 29.1, 29.8 (2C), 31.3, 33.2, 36.8 (C-1"), 39.0, 42.4, 43.6, 46.4 (C-16a), 47.2 (C-16), 50.6 (C-13), 70.1 (Bn-$CH_2$), 79.0 (C-17), 112.4 (C-2), 115.0 (C-4), 126.3 (C-1), 127.4 (C-2' and -6'), 127.8 (C-4'), 128.5 (C-3' and -5'), 133.0 (C-10), 137.5 (C-1'), 137.9 (C-5), 156.9 (C-3).

*2.3.45. 3-Benzyloxy-16a-(4-cyclohexyl-1H-1,2,3-triazol-1-yl)methyl-estra-1,3,5(10)-trien-17a-ol* ***(28c)***

Compound **20** (420.0 mg, 1 mmol) and cyclohexylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (2.5:97.5 v/v) to yield pure **28c** (200 mg, 76%) as a white solid. Mp: 223–225 $^{o}$C; $R_f$= 0.44 (ss B). (Found C, 77.82; H, 8.35. $C_{34}H_{43}N_3O_2$ (525.72) requires C, 77.68; H, 8.24%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.75 (s, 3H, 18-$H_3$), 2.84 (m, 3H, 6-H2, 1"-H), 3.64 (s, 1H, 17-H), 4.37 (m, 1H, 16a-$H_2$), 4.69 (m, 1H, 16a-$H_2$), 5.03 (s, 2H, Bn-$H_2$), 6.72 (d, 1H, *J* = 1.5 Hz, 4-H), 6.78 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz, 2-H), 7.22 (d, 1H, *J* = 8.5 Hz, 1-H), 7.32 (t, 1H, *J* = 7.0 Hz, 4'-H), 7.38 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.43 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H

*2.3.46. 3-Benzyloxy-16a-(4-phenyl-1H-1,2,3-triazol-1-yl)methyl-estra-1,3,5(10)-trien-17a-ol* ***(28d)***

Compound **20** (420.0 mg, 1 mmol) and phenylacetylene (2 mmol, 0.22 ml) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **28d** (337 mg, 64%) as a white solid. Mp: 205–206 $^{o}$C; $R_f$= 0.46 (ss B). (Found C, 78.42; H, 7.32. $C_{34}H_{37}N_3O_2$ (519.68) requires C, 78.58; H, 7.18%). $^1$H NMR (δ, ppm, $CDCl_3$): 0.76 (s, 3H, 18-$H_3$), 2.87 (m, 2H, 6-$H_2$), 3.68 (d, 1H, *J* = 5.0 Hz, 17-H), 4.41 (dd, 1H, *J* = 13.5 Hz, *J* = 5.5 Hz, 16a-$H_2$), 4.69 (t, 1H, *J* = 13.5 Hz, 16a-$H_2$), 5.04 (s, 2H, Bn-$H_2$), 6.73 (s, 1H, 4-H), 6.79 (dd, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz, 2-H), 7.22 (d, 1H, *J* = 8.0 Hz, 1-H), 7.38 (m, 8H, 2'-, 3'-, 4'-, 5'- and 6'-H, 3"-, 4"- and 5"-H), 7.84 (d, 2H, *J* = 7.5 Hz, 2"- and 6"-H), 7.89 (s, 1H, triazol-H). $^{13}$C NMR (δ, ppm, $CDCl_3$): 17.1 (C-18), 26.0, 27.9, 29.8, 31.2, 38.9, 42.2, 43.5, 46.4 (C-13), 47.0 (C-16), 50.8 (C-16a), 69.9 (Bn-$CH_2$), 78.8 (C-17), 112.3 (C-2), 114.8 (C-4), 120.7 (triazol-CH), 125.7 (C-2' and -6'), 126.3 (C-1), 127.4 (C-2" and -6"), 127.8

(C-4'), 128.3 (C-4"), 128.5 (C-3" and -5"), 128.9 (C-3' and -5'), 130.2 (C-10), 132.8 (C-1'), 137.3 (C-1"), 137.9 (C-5), 147.1 (triazol-C), 156.7 (C-3).

*2.3.47. 3-Benzyloxy-16a-[4'-(4''-nitro-benzoyloxymethyl)-1'H-1',2',3'-triazol-1'-yl]methylestra-1,3,5(10)-trien-17a-ol (**28e**)*

Compound **20** (420 mg, 1 mmol) and propargyl 4-nitrobenzoate (2 mmol, 210 mg) were used for the synthesis as described in Section 2.3. The crude product was chromatographed on silica gel with ethyl acetate/$CH_2Cl_2$ (5:95 v/v) to yield pure **28e** (610 mg, 98%) as a yellow solid. Mp: 75–77 $^oC$; $R_f$= 0.45 (ss B). (Found C, 69.57; H, 61.32. $C_{36}H_{38}N_4O_6$ (622.71) requires C, 69.44; H, 6.15%). $^1H$ NMR (δ, ppm, DMSO-$d_6$): 0.66 (s, 3H, 18-$H_3$), 2.71 (m, 2H, 6-$H_2$), 3.57 (s, 1H, 16-H), 4.29 (dd, 1H, *J* = 13.5 Hz, *J* = 8.5 Hz, 16a-$H_2$), 4.47 (dd, 1H, *J* = 13.5 Hz, *J* = 8.5 Hz, 16a-$H_2$), 4.85 (d, 1H, *J* = 5.0 Hz, 17-H), 5.44 (s, 2H, Bn-$H_2$), 6.65 (s, 1H, 4-H), 6.72 (d, 1H, *J* = 8.5 Hz, 2-H), 7.14 (d, 1H, *J* = 8.5 Hz, 1-H), 7.29 (t, 1H, *J* = 7.5 Hz, 4'-H), 7.35 (t, 2H, *J* = 7.5 Hz, 3'- and 5'-H), 7.40 (d, 2H, *J* = 7.5 Hz, 2'- and 6'-H), 8.17 (d, 2H, *J* = 8.5 Hz, 3"- and 5"-H), 8.28 (s, 1H, triazol H), 8.31 (d, 2H, *J* = 8.5 Hz, 2"- and 6"-H). $^{13}C$ NMR (δ, ppm, DMSO-$d_6$): 16.9 (C-18), 25.6, 27.5, 28.4, 29.2, 31.1, 38.5, 39.8, 39.9, 43.2, 45.9 (C-16a), 46.2 (C-16), 53.4 (C-13), 58.7 (linker $CH_2$), 68.9 (Bn-$CH_2$), 78.0 (C-17), 112.1 (C-2), 114.4 (C-4), 123.8 (C-2" and -6"), 125.0 (triazol CH), 126.1 (C-1), 127.4 (C-2' and -6'), 127.5 (C-4'), 128.3 (C-3' and -5'), 130.6 (C-3" and -5"), 132.3 (C-10), 134.7 (C-1'), 137.3 (C-5), 141.0 (C-1"), 150.2 (triazol C), 156.0 (C-3), 163.9 (C=O).

*2.3.48. 3-Benzyloxy-16a-(4'-hydroxymethyl-1'H-1',2',3'-triazol-1'-yl)methylestra-1,3,5(10)-trien-17α-ol (**28f**)*

Compound **28e** (220 mg, 0.5 mmol) was dissolved in methanol (10 ml) containing $NaOCH_3$ (14 mg, 0.25 mmol), and the solution was allowed to stand for 24 h. It was then diluted with water, and the precipitate separating out was filtered off and recrystallized from methanol to afford **28f** (126 mg, 53%) as a white crystalline product. Mp: 86–88 $^oC$; $R_f$= 0.25 (ss B). (Found C, 73.68; H, 7.63. $C_{29}H_{35}N_3O_3$ (473.61) requires C, 73.54; H, 7.45%). $^1H$ NMR (δ, ppm, DMSO-$d_6$): 0.68 (s, 3H, 18-$H_3$), 2.74 (m, 2H, 6-$H_2$), 3.58 (brs, 1H, OH), 4.26 (t, 1H, *J* = 8.5 Hz, 16a-$H_2$), 4.43 (dd, 1H, *J* = 13.0 Hz, *J* = 7.0 Hz, 16a-$H_2$), 4.51 (d, 2H, *J* = 5.0 Hz, linker $H_2$), 4.85 (d, 1H, *J* = 4.0 Hz, 17-H), 5.04 (s, 2H, Bn-$H_2$), 5.13 (brs, 1H, OH), 6.68 (s, 1H, 4-H), 6.74 (d, 1H, *J* = 8.5 Hz, 2-H),

7.17 (d, 1H, *J* = 8.5 Hz, 1-H), 7.31 (d, 1H, *J* = 7.0 Hz, 4'-H), 7.37 (t, 2H, *J* = 7.0 Hz, 3'- and 5'-H), 7.42 (d, 2H, *J* = 7.0 Hz, 2'- and 6'-H), 7.97 (s, 1H, triazol H). $^{13}$C NMR (δ, ppm, DMSO-$d_6$): 16.9 (C-18), 25.6, 27.5, 28.5, 29.2, 31.1, 38.5, 40.7, 43.2, 45.9, 46.2 (C-16), 47.9 (C-13), 50.6 (C-16a), 55.0 (linker $CH_2$), 68.9 (Bn-$CH_2$), 78.0 (C-17), 112.1 (C-2), 114.4 (C-4), 122.7 (triazol CH), 126.1 (C-1), 127.4 (C-2' and -6'), 127.6 (C-4'), 128.3 (C-3' and -5'), 132.4 (C-10), 137.3 (C-1'), 137.4 (C-5), 147.6 (triazol C), 156.0 (C-3).

*2.4. Determination of the antiproliferative activities*

The growth-inhibitory effects of the compounds were tested *in vitro* by means of the MTT assay against a gynecological panel containing two breast cancer cell lines (MCF-7, MD-MB-231) and two cell lines isolated from cervical malignancies (HeLa, SiHa) [11]. All cell lines were obtained from the European Collection of Cell Cultures (Salisbury, UK). The cells were maintained in minimal essential medium supplemented with 10% fetal bovine serum (FBS), 1% non-essential amino acids and an antibiotic–antimycotic mixture (AAM). All chemicals, if otherwise not specified, were purchased from Sigma-Aldrich Ltd. (Budapest, Hungary). All cell lines were grown in a humidified atmosphere of 5% $CO_2$ at 37 $^{o}$C. For pharmacological investigations, 10 mM stock solutions of the tested compounds were prepared with dimethyl sulfoxide (DMSO). The highest applied DMSO concentration of the medium (0.3%) did not have any substantial effect on the determined cellular functions. Cells were seeded into 96-well plates (5000 cells/well), allowed to stand overnight under cell culturing conditions, and the medium containing the tested compounds at two final concentrations (10 or 30 μM) was then added. After a 72-hour incubation viability was determined by the addition of 20 μl 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) solution (5 mg/ml). The formazan crystals precipitated in 4 h were solubilized in DMSO and the absorbance was determined at 545 nm with an ELISA plate reader utilizing untreated cells as controls. The most effective compounds eliciting at least 60% growth inhibition at 10 μM were tested again with a set of dilutions (0.3−30 μM) in order to determine the $IC_{50}$ values by means of Graphpad Prism 4.0 (Graphpad Software; San Diego, CA, US). These promising compounds were additionally tested using nonmalignant murine fibroblasts (NIH-3T3) to obtain preliminary data concerning cancer selectivity of the tested molecules. Two independent experiments were performed with 5 parallel wells and

cisplatin (Ebewe GmbH, Unterach, Austria), an agent administered clinically in the treatment of certain gynecological malignancies, was used as reference compound.

## 3. Results and discussion

### *3.1. Synthetic studies*

To prepare novel steroid triazoles via 1,3-dipolar cycloaddition, we chose the 3-methoxy- and 3-benzyloxy-16-hydroxymethylestra-1,3,5(10)-trien-17-ol diastereomers (**5**–**8** and **9**–**12**). The synthesis strategy for the preparation of the starting diols (**21**–**28**) is illustrated in Scheme 1. The synthesis of steroidal 1,2,3-triazoles by CuAAC is outlined in Scheme 2.

Stereoselective tosylation of **5**–**8** and bromination of **9**–**12** gave **5b**–**8b** and **9c**–**12c**, respectively, which then underwent facile $S_N2$ substitution with $NaN_3$ in *N*,*N*-dimethylformamide to furnish the corresponding 16-azidomethyl compounds (**13**–**16** and **17**–**20**).

The 16-azido compounds were subjected to the azide–alkyne CuAAC reaction with different alkyl- and aryl-acetylenes. The azide–alkyne reactions of these compounds were carried out with CuI as catalyst in the presence of $Et_3N$ in $CH_2Cl_2$ under reflux conditions to obtain the required 3-methoxy- and 3-benzyloxyestra-1,3,5(10)-trien-16-(1',4'-substituted 1',2',3')-triazolyl derivatives (**21**–**24** and **25**–**28**).

### *3.2. Determination of the antiproliferative properties of the 16-triazolylmethyl diastereomers*

We have published recently that introduction of a substituted triazole moiety onto different positions of the estrane skeleton might increase the antiproliferative properties of estrone derivatives [12]. It was also established that the presence of certain alkyl or aralkyl protecting groups at the phenolic OH function is advantageous. Concerning that 16-hydroxymethylene-17-hydroxy derivatives of estrone-3-methyl ether or 3-benzyl ether (**5a**–**12a**) displayed substantial cytostatic potential against different types of breast cancer cell lines, these compounds might be suitable for directed modifications with the aim of developing potentially more active antiproliferative steroidal derivatives [13]. In the light of the above-mentioned recent observations, here we aimed to combine the substituted triazole and the 16,17-disubstituted estrone 3-ether moieties. The present study included an evaluation of the direct antiproliferative

capacities of the newly synthesized heterocyclic compounds (**21a**–**f**, **22a**–**f**, **23a**–**f**, **24a**–**f** and **25a**–**f**, **26a**–**f**, **27a**–**f**, **28a**–**f**). The antiproliferative activities were determined *in vitro* by means of MTT assays against human adherent cervical (SiHa, HeLa) and breast cancer (MCF-7 and MDA-MB-231) cell lines.

The antiproliferative activities of the newly synthesized heterocyclic compounds depended on the nature of the protecting group at the 3-hydroxy function and on the orientation of the substituents at C-16 and C-17. In general, the 3-methyl ethers (**21**–**24**) exhibited weak antiproliferative action; none of them exerted any substantial effect at 10 μM (Table 1). All diastereomers of the 3-benzyl ether series (**25**–**28**) proved to be more potent in comparison with their 3-methyl ether counterparts (Table 2). This is in agreement with our earlier results [14]. Based on the substantial difference of the two groups, i.e. that of 3-methyl ethers and 3-benzyl ethers, it can be concluded that only the latter derivatives are promising from pharmacological point of view.

Concerning the orientation of the substituents at position C-16 and C-17, the 16β,17β-derivatives (**25a**–**f**) displayed outstanding growth-inhibitory properties. Two derivatives bearing similar cycloalkyl groups at position C-4' displayed substantial selective antiproliferative action against the triple-negative breast cancer cell line MDA-MB-231 with $IC_{50}$ values in the low micromolar range. It should be underlined that **25b** and **25c** did not significantly influence the proliferation of other cell lines tested, including the non-cancerous fibroblast. Although both the 4'-cyclohexyl (**25c**) and the 4'-phenyl derivative (**25d**) have six-membered substituents, their cytostatic behavior is completely different. This might be attributed to the different steric structure of the two rings (chair or planar) at C-4'. Compound **25d** exerted potent antiproliferative action against all tested cell lines without any selectivity. The *cis-16α,17α*-3-benzyl ethers (**28a**–**f**) were less potent than their β,β-counterparts (**25a**–**f**), except for **28d**, which behaved similarly to its diastereomer **25d**. The *trans*-16β,17α-isomers (**27a**–**f**) exhibited activity exclusively on the breast cancer cell lines. Surprisingly, the tendency observed earlier (in the case of compounds **25a**–**f**) concerning the nature of C-4' substituent was not valid here. Only **26a** and **26e** inhibited cell growth markedly, but with no tumor selectivity. It's worth mentioning that *trans*-16α,17β isomer **26c** was the sole compound, which inhibited the proliferation of HPV 16+ squamous cell carcinoma SiHa, showing an $IC_{50}$ value comparable with that of cisplatin.

In view of the cell lines, it should be noted that triple-negative breast cancer cell line MDA-MB-231 proved to be the most sensitive and all calculated $IC_{50}$ values were lower than that of the reference agent cisplatin (19.1 μM).

Regarding the present and earlier results obtained for 16,17-disubstituted 3-benzyl ethers, it can be stated that introduction of a substituted triazolyl moiety onto the C-16 methylene group of the *cis* isomers proved to be advantageous. In the case of compounds **25b** and **25c**, both the antiproliferative potential and the tumor selectivity were markedly improved.

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## References


[1] Tietze LF, Bell HP, Chandrasekhar S, Natural product hybrids as new leads drug discovery. Angew Chem Int Ed **2003**;42:3996–4028.

[2] Mehta G, Singh V, Hybrid system through natural product leads: An approach towards new molecular entities. Chem Soc Rev **2002**;31:324–334.

[3] Adamec J, Beckert R, Weiß D, Klimešová V, Waisser K, Möllmann U, Kaustová J, Buchta V. Hybride molecules of estrone: New Compound with potential antibacterial, antifungal and antiproliferative activities. Bioorg Med Chem **2007**;*15*:2898–2906.

[4] Kuduk, SD, Zheng FF, Sepp-Lorenzino L, Rosen N, Danishefsy SJ. Synthesis and Evaluation of geldanamycin-estradiol hybrids. Bioorg Med Chem **1999**;9:1233-1238.

[5] Gupta A, Saha P, Descôteaux C, Leblanc V, Asselin É, Bérubé G. Design, synthesis and biological evaluation of estradiol-chlorambucil hybrids as anticancer agents. Bioorg Med Chem Lett **2010;**20:1614-1618.

[6] Schneider Gy, Vass A, Vincze I, Sohár P. Neighbouring Group Partcipation in the 16-Hydroxymethyl-3-methoxyestre-1,3,5(10)-trien-17β-ol Series. Liebigs Ann Chem **1988**;267–273.

[7] Schneider Gy, Hackler L, Sohár P. Preparation of 16α-Hydroxymethyl-3-methoxyestra-1,3,5(10)-trien 17α-ol and Solvolysis Investigation. Liebigs Ann Chem **1988**;679-683.

[8] Tapolcsányi P, Wölfling J, Falkay G, Márki Á, Minorics R, Schneider Gy. Synthesis and receptor-binding examination of 16-hydroxymethyl-3,17-estradiol stereoisomers. Steroids **2002**;67:671-678.

[9] Meldal M, Tornøe CW. Cu-Catalyzed azide–alkyne cycloaddition. Chem Rev. **2008**;108:2952–3015.

[10] Szájli Á, Wölfling J, Mernyák E, Minorics R, Márki Á, Falkay G, Schneider Gy. Neighbouring group participation Part 16. Stereoselective synthesisi and receptor-binding examination of the four stereoisomers of 16-bromomethyl-3,17-estradiols. Steroids **2006**;*71*:141–153.

[11] Mosmann T. Rapid colorimetrc assay for cellural growth and survival: application to prolyferation and cytotoxicity assay. J immunol Methods 1983;65:55-63.

[12] Mernyák E, Kovács I, Minorics R, Sere P, Czégány Sinka I, Wölfling, Schneider G, Újfaludi Zs, Boros I, Ocsovszki I, Varjj ga M, Zupkó I. Synthesis of trans-16-triazolyl-13α-methyl-17-estradiol diastereomers and the effects of structural modifications on their in vitro antiproliferative activities. J Steroid Biochem Mol Biol **2015**;150:123–134.

[13] Sinka I, Kiss A, Mernyák E, Wölfling E, Schneider G. Ocsovszki I, Kuo CY, Wang HC, Zupkó I. Antiproliferative and antimetastatic properties of 3-benzyloxy-16-hydroxymethylene-estardiol analogs agains breast cancer cell lines. Eur J Pharm Sciences **2018**;123:362–370.

[14] Frank E, Molnar J, Zupko I, Kadar Z, Wölfling J. Synthesis of novel steroidal 17α-triazolyl derivatives via Cu(I)-catalyzed azide-alkyne cycloaddition, and an evaluation of their cytotoxic activity in vitro. Steroids **2011**;76:1141–1148.

## Legends for Schemes and Tables

**Scheme 1** Reagents and conditions: (i) NaOMe, HCOOEt, anhydrous toluene, 50 °C; (ii) $KBH_4$, MeOH; (iii) KOAc, $CH_3COOH$, NaOMe/MeOH.

**Scheme 2** Reagents and conditions: (i) appropriate alkyne, TEA, CuI, $CH_2Cl_2$, 40 °C, 24 h; (ii) NaOMe, MeOH, 24 h.

**Table 1** Antiproliferative activities of compounds **21a**–**f, 22a**–**f, 23a**–**f** and **24a**–**f**

**Table 2** Antiproliferative activities of compounds **25a**–**f, 26a**–**f, 27a**–**f** and **28a**–**f**

**Table 1**

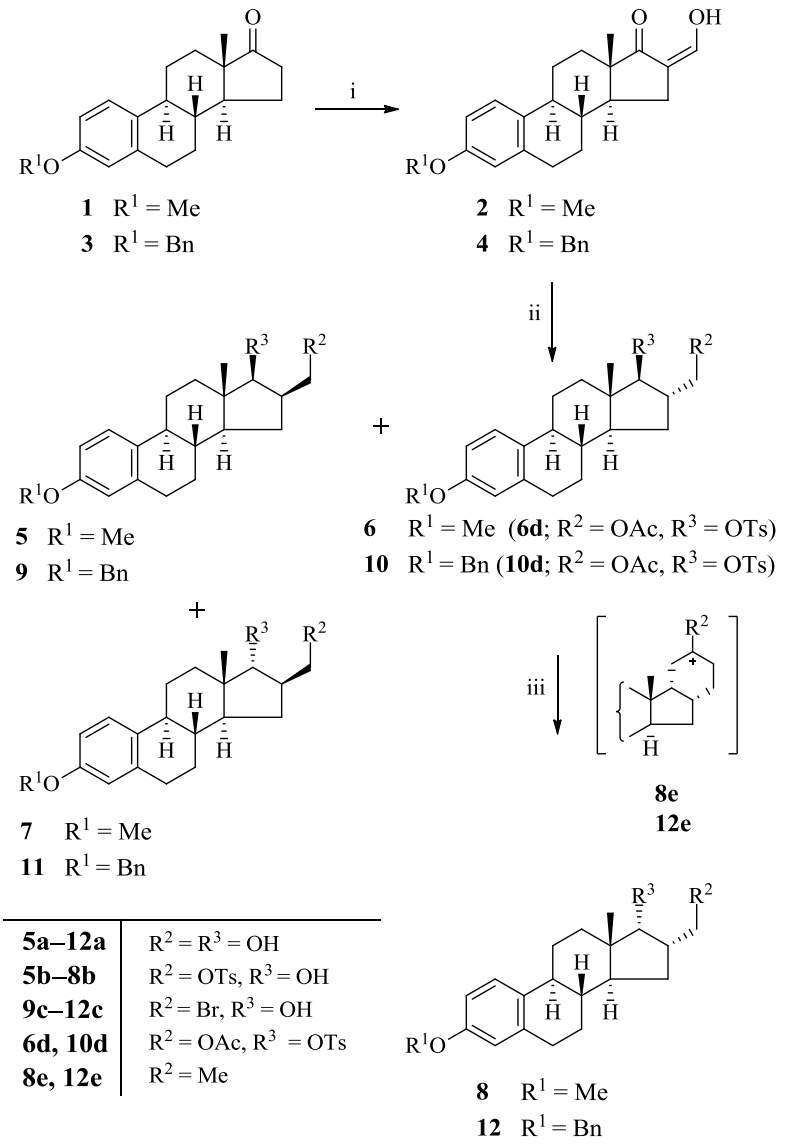
| | Conc. (μM) | Growth Inhibition, % ± SEM [calculated $IC_{50}$ (μM)] HeLa | SiHa | MCF-7 | MDA-MB-231 |
|---|---|---|---|---|---|
| **21** | | | | | |
| **a** | 10 | <20 | 21.28±1.88 | <20 | <20 |
| | 30 | <20 | 28.71±2.20 | 46.42±1.47 | <20 |
| **b** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 39.86±.38 | <20 | 57.42±1.77 | 29.88±1.57 |
| **c** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 40.22±1.02 | <20 | 70.84±1.55 | 37.96±1.55 |
| **d** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 44.16±0.48 | <20 | 54.93±1.78 | 38.28±1.84 |
| **e** | 10 | <20 | 23.91±1.61 | 34.23±3.10 | <20 |
| | 30 | 37.18±1.65 | 54.72±0.48 | 76.26±0.72 | 35.93±2.13 |
| **f** | 10 | <20 | 28.06±1.99 | 29.45±1.67 | <20 |
| | 30 | 41.03±0.77 | 57.69±1.12 | 70.23±1.35 | 34.81±2.88 |
| **22** | | | | | |
| **a** | 10 | <20 | 25.55±1.01 | <20 | <20 |
| | 30 | <20 | 34.78±2.47 | 57.43±1.91 | <20 |
| **b** | 10 | <20 | <20 | <20 | <20 |
| | 30 | <20 | 26.57±2.26 | 67.59±1.65 | <20 |
| **c** | 10 | <20 | <20 | <20 | <20 |
| | 30 | <20 | 29.90±2.59 | 69.68±0.77 | <20 |
| **d** | 10 | <20 | <20 | <20 | <20 |
| | 30 | <20 | 29.96±1.79 | 70.75±1.05 | 14.54±1.32 |
| **e** | 10 | <20 | <20 | <20 | <20 |
| | 30 | <20 | 38.69±2.09 | 63.12±2.14 | <20 |
| **f** | 10 | <20 | <20 | 22.02±1.61 | <20 |
| | 30 | <20 | 37.79±1.04 | 50.94±1.55 | <20 |
| **23** | | | | | |
| **a** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 31.14±1.28 | <20 | 28.72±0.93 | 25.08±3.15 |
| **b** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 58.25±2.03 | <20 | 48.01±1.31 | <20 |
| **c** | 10 | <20 | 30.97±2.69 | <20 | <20 |
| | 30 | <20 | 33.89±2.35 | <20 | <20 |
| **d** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 26.90±2.15 | <20 | 63.27±0.82 | <20 |
| **e** | 10 | <20 | <20 | <20 | <20 |
| | 30 | <20 | 37.53±3.00 | 33.94±0.75 | 28.19±0.96 |
| **f** | 10 | <20 | 29.13±1.59 | <20 | <20 |
| | 30 | 26.61±0.57 | 43.85±3.32 | 38.45±1.93 | 43.85±3.32 |
| **24** | | | | | |
| **a** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 89.01±0.47 | <20 | 78.65±0.78 | 46.21±1.54 |
| **b** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 34.18±0.81 | <20 | 31.07±2.36 | <20 |
| **c** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 49.11±0.55 | <20 | 43.22±1.52 | <20 |

| | | | | | |
|---|---|---|---|---|---|
| **d** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 42.13±1.66 | <20 | 55.41±0.76 | <20 |
| **e** | 10 | <20 | <20 | <20 | <20 |
| | 30 | 83.66±0.34 | 42.06±2.50 | 70.11±1.06 | 50.27±2.00 |
| **f** | 10 | <20 | <20 | 22.34±2.06 | <20 |
| | 30 | 84.77±1.18 | 29.80±1.66 | 68.27±1.19 | 47.74±1.21 |
| cisplatin | 10 | 42.61±2.33 | 86.84±0.50 | 53.03±2.29 | 20.84±0.81 |
| | 30 | 99.93±0.26 | 90.18±1.78 | 86.90±1.24 | 74.47±1.20 |
| | | [12.43] | [7.84] | [5.78] | [19.13] |

**Table 2**

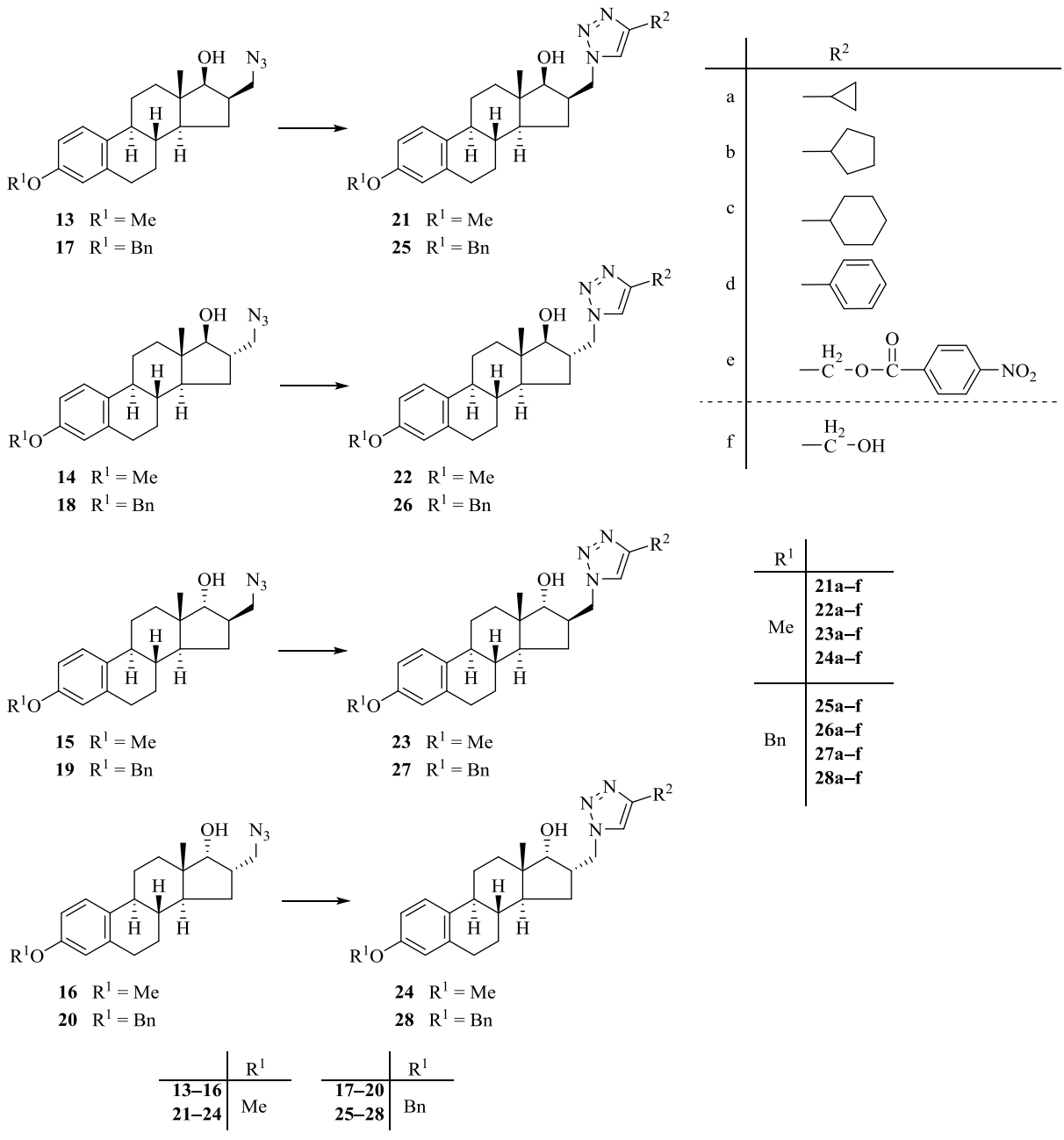
| | Conc. (μM) | Growth Inhibition, % ± SEM [calculated $IC_{50}$ (μM)] HeLa | SiHa | MCF-7 | MDA-MB-231 | NIH-3T3 |
|---|---|---|---|---|---|---|
| **25** | | | | | | |
| **a** | 10 | 44.94±1.04 | 21.17±2.05 | 41.71±0.64 | 47.32±1.15 | 44.91±1.36 |
| | 30 | 52.45±2.39 | 66.23±0.86 | 64.32±0.56 | 71.49±0.75 | 91.28±0.50 |
| **b** | 10 | 51.49±3.62 | 49.36±1.69 | 44.58±1.50 | 93.00±0.26 | 44.81±1.50 |
| | 30 | 62.58±2.21 | 73.94±2.04 | 50.52±3.26 | 93.71±0.09 [3.33] | 59.09±0.73 |
| **c** | 10 | 54.70±1.88 | 49.58±2.11 | 44.04±3.32 | 77.13±1.07 | |
| | 30 | 53.66±2.56 | 61.83±2.77 | 59.33±2.99 | 88.81±0.55 [5.91] | |
| **d** | 10 | 64.14±0.86 | 70.88±1.03 | 73.41±1.22 | 95.04±0.16 | 95.60±0.25 |
| | 30 | 90.12±0.99 [2.28] | 94.14±0.29 [4.05] | 80.16±3.40 [3.91] | 95.60±0.06 [3.65] | 98.22±0.04 [3.34] |
| **e** | 10 | <20 | <20 | 41.63±2.83 | 21.96±0.73 | |
| | 30 | 92.12±0.25 | 89.25±0.68 | 97.00±0.11 | 95.22±0.91 | |
| **f** | 10 | 45.08±0.72 | 41.26±1.25 | 55.41±1.26 | 55.57±1.50 | |
| | 30 | 39.39±0.49 | 52.60±1.31 | 62.52±0.67 | 88.92±0.99 | |
| **26** | | | | | | |
| **a** | 10 | 37.98±2.68 | <20 | 72.42±2.19 | 46.43±2.05 | 85.50±1.22 |
| | 30 | 96.56±0.11 | 96.71±0.17 | 98.72±0.09 [6.11] | 97.96±0.17 | 97.63±0.12 [5.97] |
| **b** | 10 | 38.55±1.32 | <20 | 31.80±1.35 | 17.13±2.36 | |
| | 30 | 43.97±2.23 | <20 | 84.44±0.71 | 37.72±2.28 | |
| **c** | 10 | 36.30±1.45 | <20 | 24.95±2.15 | <20 | |
| | 30 | 35.53±1.24 | <20 | 74.73±1.00 | <20 | |
| **d** | 10 | <20 | <20 | 47.25±1.78 | 45.55±2.63 | |
| | 30 | 22.15±1.29 | <20 | 57.30±0.77 | 59.79±1.22 | |
| **e** | 10 | <20 | <20 | 68.51±0.71 | 89.24±0.70 | 31.41±2.21 |
| | 30 | 96.98±0.33 | 96.91±0.14 | 99.12±0.07 [6.53] | 97.73±0.23 [5.69] | 99.01±0.05 [11.75] |
| **f** | 10 | 21.62±3.46 | <20 | 29.14±2.06 | 40.46±2.98 | 10.00±1.01 |
| | 30 | 30.79±2.92 | 27.28±1.90 | 43.28±1.53 | 76.93±1.60 | 23.40±0.60 |
| **27** | | | | | | |
| **a** | 10 | 24.26±2.63 | 34.00±1.43 | 58.38±3.20 | 56.24±0.98 | 25.56±2.21 |
| | 30 | 85.22±1.32 | 82.68±1.25 | 97.21±0.10 | 84.18±0.44 | 99.24±0.07 |
| **b** | 10 | 37.10±1.77 | 39.59±1.17 | 51.92±1.00 | 56.44±0.98 | |
| | 30 | 52.08±2.08 | 69.54±1.24 | 65.12±1.91 | 71.81±0.96 | |
| **c** | 10 | 38.89±2.60 | 64.05±1.24 | 49.68±1.66 | 72.37±1.27 | 13.99±1.79 |
| | 30 | 55.93±2.39 | 83.34±1.31 [9.29] | 61.26±1.72 | 85.81±1.04 [6.74] | 29.56±1.17 |
| **d** | 10 | 34.23±1.39 | 30.04±2.07 | 47.03±1.25 | 55.77±1.03 | |
| | 30 | 47.74±0.78 | 39.96±2.34 | 42.43±1.69 | 57.71±1.00 | |
| **e** | 10 | <20 | 21.53±1.81 | 35.74±1.33 | <20 | |
| | 30 | 99.06±0.09 | 96.91±0.06 | 98.50±0.93 | 99.01±0.52 | |
| **f** | 10 | <20 | 24.65±1.46 | 25.50±2.93 | 24.79±2.20 | |
| | 30 | 98.72±0.13 | 96.04±0.25 | 98.41±0.15 | 98.79±0.16 | |
| **28** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **a** | 10 | 35.48±1.91 | 46.07±1.13 | 52.88±0.82 | 25.61±2.84 | |
| | 30 | 63.44±1.79 | 69.86±0.55 | 73.39±0.74 | 52.16±2.52 | |
| **b** | 10 | 39.75±2.45 | <20 | 43.51±1.85 | 44.86±0.93 | |
| | 30 | 47.34±1.62 | <20 | 42.28±1.44 | 43.73±2.25 | |
| **c** | 10 | 56.71±0.57 | 39.93±3.14 | 48.56±0.48 | 30.30±1.64 | |
| | 30 | 58.21±0.73 | 31.15±2.86 | 49.93±1.33 | 31.60±3.08 | |
| **d** | 10 | 74.18±1.15 | 76.88±0.49 | 75.97±0.89 | 86.12±0.33 | 70.18±1.15 |
| | 30 | 91.17±0.33 | 87.39±0.86 | 88.99±0.25 | 90.72±1.00 | 91.12±1.64 |
| | | [2.30] | [4.14] | [3.87] | [3.89] | [3.71] |
| **e** | 10 | 27.42±2.16 | <20 | 52.86±1.30 | 29.58±1.69 | |
| | 30 | 92.94±0.17 | 91.91±0.23 | 96.38±0.07 | 94.09±0.43 | |
| **f** | 10 | 30.97±1.02 | 39.85±1.24 | 50.60±0.65 | 31.89±2.92 | |
| | 30 | 91.88±0.26 | 90.94±0.18 | 95.12±0.10 | 92.56±0.34 | |
| cisplatin | 10 | 42.61±2.33 | 86.84±0.50 | 53.03±2.29 | 20.84±0.81 | 94.20±0.39 |
| | 30 | 99.93±0.26 | 90.18±1.78 | 86.90±1.24 | 74.47±1.20 | 96.44±0.17 |
| | | [12.43] | [7.84] | [5.78] | [19.13] | [3.23] |




**Scheme 1. Reagents and conditions:** (i) NaOMe, HCOOEt, anhydrous toluene, 50 °C; (ii) $KBH_4$, MeOH; (iii) KOAc, $CH_3COOH$, NaOMe/MeOH

**Scheme 1.**


OH
N3
R1O
H
R2
N
13 R1 = Me
17 R1 = Bn
21 R1 = Me
25 R1 = Bn
14 R1 = Me
18 R1 = Bn
22 R1 = Me
26 R1 = Bn
15 R1 = Me
19 R1 = Bn
23 R1 = Me
27 R1 = Bn
16 R1 = Me
20 R1 = Bn
24 R1 = Me
28 R1 = Bn
a
b
c
d
e
f
H2C-O-C
NO2
H2C-OH
R1
Me
Bn
21a–f
22a–f
23a–f
24a–f
25a–f
26a–f
27a–f
28a–f
13–16
21–24
17–20
25–28

**Scheme 2.**

**Supplementary Material**

**Click here to download Supplementary Material: SCH_supporting_info_16-triazolylmethyl.pdf**