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D-Ring Modified Estrone Derivatives as Novel Potent Inhibitors of Steroid Sulfatase

Delphine S. Fischer,[a] L. W. Lawrence Woo,[a] Mary F. Mahon,[b] Atul Purohit,[c] Michael J. Reed[c] and Barry V. L. Potter[a,*]

[a]*Medicinal Chemistry, Department of Pharmacy and Pharmacology and Sterix Ltd., University of Bath, Claverton Down, Bath BA2 7AY, UK*

[b]*Department of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, UK*

[c]*Endocrinology and Metabolic Medicine and Sterix Ltd., Imperial College, Faculty of Medicine, St. Mary's Hospital, London W2 1NY, UK*

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Abstract—A series of novel D-ring modified derivatives of estrone was synthesized and tested as inhibitors of steroid sulfatase (STS). The steroidal D-ring was cleaved via an iodoform reaction and thermal condensation of the resulting marrianolic acid derivative gave 16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide derivatives, where a piperidinedione moiety is in place of the D-ring. This synthetic approach was found to give a higher overall yield than the literature method of Beckmann rearrangement. A range of alkyl side chains have been introduced on the nitrogen atom of the imido-ring and the corresponding 3-*O*-sulfamates synthesized. The new D-ring modified estrone derivatives bearing a propyl (**39**) and a 1-pyridin-3-ylmethyl (**46**) moiety had IC_{50} values of 1 nM when tested in placental microsomes for the inhibition of STS. These compounds are therefore up to 18-fold more potent than EMATE, the very first highly potent irreversible steroidal STS inhibitor.

Introduction

Estrogens, and to a lesser extent, androgens support the growth and development of hormone-dependent tumors.[1,2] In women with hormone-dependent breast cancer (HDBC), the estrogen concentration in tumor tissues is much higher than that circulating in plasma.[3] There is now substantial evidence suggesting that in situ production of estrone (E1) and estradiol (E2) from inactive precursors is a possible explanation for this tissue/plasma gradient.[4] Inhibition of the enzymes involved in the synthesis of active estrogenic steroids therefore represents an attractive approach for the treatment of HDBC.

In post-menopausal women, in whom breast cancer most frequently arises, peripheral and intra-tumoral synthesis of estrogens were initially considered to occur almost exclusively via the aromatase pathway. The enzyme aromatase, which converts androstenedione into E1, has therefore been among the prime targets for depleting estrogen levels.[5] However, strong evidence has emerged over the past decade, both biochemically and clinically, that the sole inhibition of this enzyme could not afford an effective reduction of estrogenic stimulation to tumors,[6] the reason being that other pathways are involved in estrogen biosynthesis.

The sulfatase pathway, where the inactive precursor estrone-sulfate (E1S) is converted into E1 by the enzyme estrone-sulfatase is now considered to be the main source for the local production of estrogens in tumors, providing 10-fold more E1 than from the aromatase pathway.[7] Both, the higher availability in plasma and longer half-life of E1S compared with that of unconjugated estrogens have suggested that the former may act as a reservoir for the synthesis of active steroids in post-menopausal women.[8]

Recently, a C19 steroid has emerged as an important metabolite in the promotion of the growth and development of hormone-dependent breast tumors. Androstenediol, which originates from dehydroepiandrosterone

*Corresponding author. Tel.: +44-1225-386639; fax: +44-1225-386114; e-mail: prsbvlp@bath.ac.uk

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(DHEA) after its hydrolysis from DHEA-sulfate (DHEA-S), can bind to the estrogen receptor and stimulate the growth of tumor cells in vitro[9] and carcinogen-induced mammary tumors in vivo.[2b] There is strong evidence to suggest that DHEA-sulfatase, which converts DHEA-S into DHEA, and estrone-sulfatase are identical enzymes.[10] Therefore, as sulfated precursors can be converted into potent androgens and estrogens via one sulfatase enzyme, the development of STS inhibitors offers a viable approach for reducing estrogenic stimulation to tumors and combating HDBC.

We have reported several STS inhibitors over the past few years.[11] They all share the common structural feature of a phenyl sufamate ester that mimics the phenolic A-ring of the enzyme substrate, E1S and bear substituents that interact with those amino acids residues which normally recognize the steroid scaffold. On the development of estrone-based steroidal inhibitors, a wide variety of chemical groups has been introduced at C3, of which the 3-*O*-sulfamate was found to be the most potent.[12] The resulting compound, estrone-3-*O*-sulfamate (EMATE, **1**, Fig. 1) was the first highly potent STS inhibitor to be discovered, with an IC_{50} of 65 pM in intact MCF-7 breast cancer cells. It irreversibly inhibited the enzyme activity in a time- and concentration-dependent manner[13] and was active in vivo on oral administration.[14] However, it proved to be more estrogenic than ethinylestradiol on oral application to the rat.[15]

With the view of developing non-estrogenic steroidal inhibitors of estrone sulfatase, some new EMATE derivatives were synthesized. In particular, with the introduction of *N*-alkanoyl (**2**, Fig. 1) and *N*-alkylcarbamoyl (**3**, Fig. 1) side-chains at the 17β-position, Li and coworkers reported to have reduced the estrogenicity of EMATE and improved its inhibitory activity at the same time.[16] The alkylcarbamoyl/alkanoyl group at the 17β-position, presumably designed as a membrane insert, apparently enhances the potency of these compounds through hydrophobic interactions with amino acid residues of the enzyme active site around the D-ring of these steroidal inhibitors. Recently, 17α-derivatives of EMATE bearing different hydrophobic moieties (**4** and **5**, Fig. 1) were found to be potent irreversible inhibitors of STS.[17] This type of inhibition exemplifies the viability of targeting hydrophobic interactions in the region neighbouring the D-ring of EMATE-like inhibitors.

Our initial work in this area involved the opening of the D-ring of EMATE to give its 3-hydroxy-16,17-*seco*-estra-1,3,5(10)-triene-16,17-dioic acid (marrianolic acid or MA) derivative and its corresponding methyl ester. However, the three-ring marrianolic derivative proved to be only a poor inhibitor of STS (vide infra). To further explore the active site around the D-ring of EMATE, we designed and synthesized a series of novel steroidal inhibitors. These new molecules, which are 16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide derivatives of EMATE, have functionalities incorporated at the opposite ends of the steroid nucleus that contribute differently to the overall biological activity of the inhibitor. The design strategies are that, at the A-ring end, the 3-*O*-sulfamate group ensures recognition (mimics E1S) and EMATE-like irreversible inhibition while, at the D-ring end, a piperidinedione moiety mimics the D-ring of EMATE whilst serving as a versatile anchor for the introduction of a variety of side-chains that can exploit hydrophobic interactions in this region of the protein (Fig. 1). We report here a synthetic route to these structurally modified steroid derivatives, an SAR study of this new family of STS inhibitors and the X-ray crystal structure of one of the most potent inhibitors.

Chemistry

The synthesis of 16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide derivatives of estrone can easily be performed via

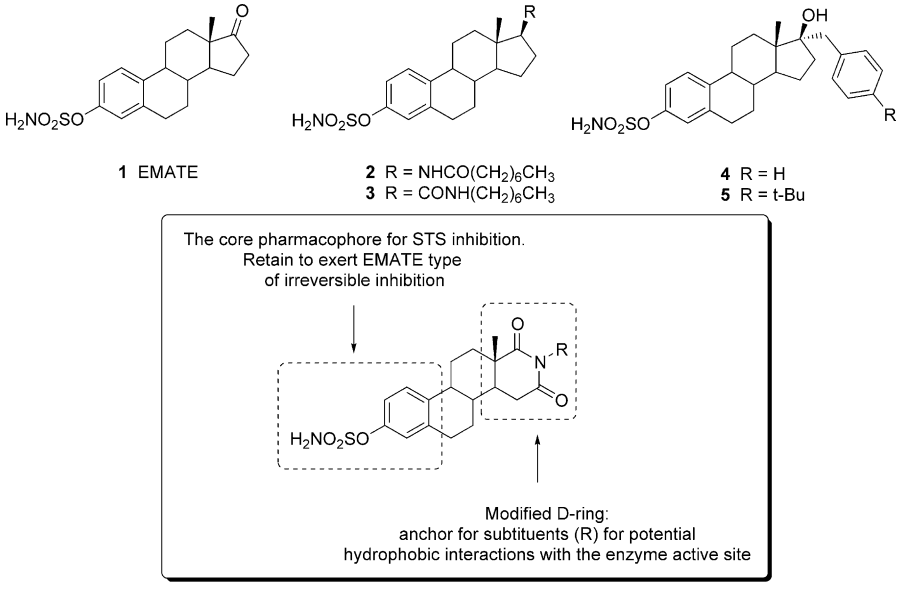
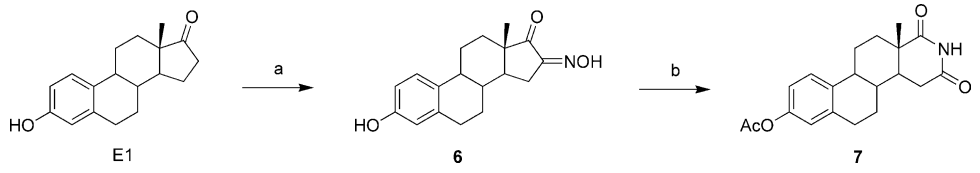


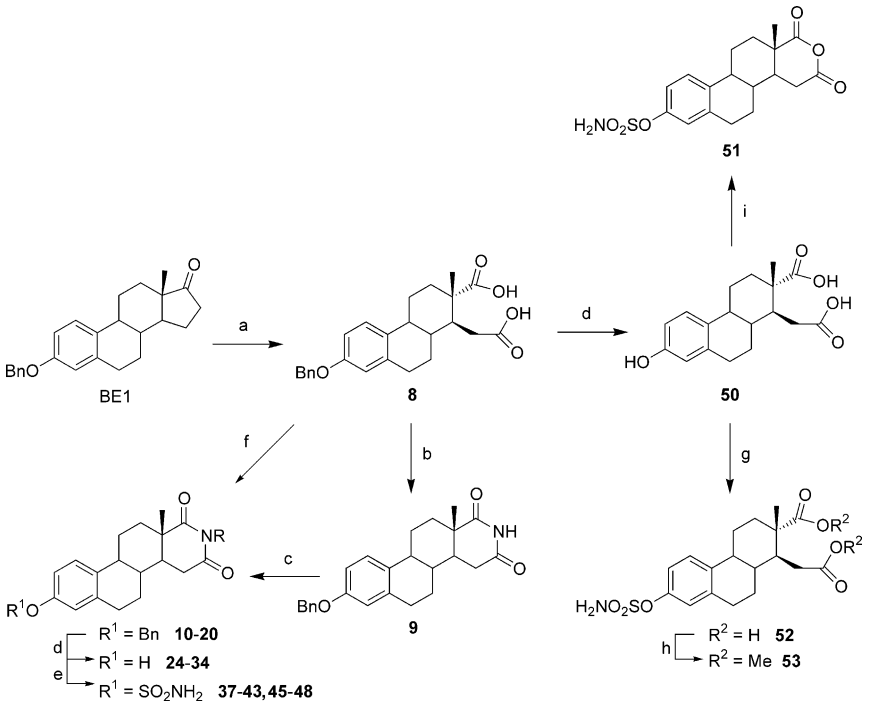
Figure 1. Structures of STS inhibitors **1**–**5** and strategies for the design of new targets **36**–**43** and **45**–**49**.

a Beckmann rearrangement of 16-oximino-estrone (**6**) (Scheme 1) as reported by Gupta and Jindal.[18] Introduction of the oxime group at the 16-position was achieved after deprotonation of E1 under the action of potassium *tert*-butoxide and reaction with an excess of isoamyl nitrite, affording **6** in a 63% yield. Beckmann rearrangement of the keto oxime **6** was then carried out in a refluxing mixture of acetic acid and acetic anhydride to afford **7** in a 57% yield. While the rearrangement of **6** has the advantage of yielding the intermediate **7** in two steps from E1, the overall yield of 36%, which is comparable to those reported in the literature, was rather poor. It was therefore decided to develop another strategy which would provide **7** or similar derivatives with higher yields.

Modifications of the D-ring of E1 through its cleavage via a haloform reaction[19] and closure by thermal condensation with an amine was proposed as an alternative method to access to the final compounds (Scheme 2). After halogenation at position 16 using an excess of base and iodine, the methylene ketone function of 3-benzyl-*O*-estrone (BE1) was cleaved into a dicarboxylic acid by refluxing in a concentrated solution of KOH. 3-Benzyl-*O*-marrianolic acid **8**, isolated with an optimised yield of 75%, was then subjected to a thermal cyclization in presence of urea. After briefly heating the reagents at 180 °C, this condensation led to the formation of a six-membered D-ring intermediate **9** in high yield (80–89%) with an overall yield of 55% from E1. Its *N*-alkylated derivatives were obtained after converting **9** into its conjugate base and reacting with various alkyl halides. In this way, a large number of side chains have been successfully introduced (Table 1) affording **10**–**20** in yields ranging from 75 to 97%. Despite the presence of an additional step, the alternative pathway to access to the intermediate **9** represents a significant improvement over the literature method for the preparation of imide derivatives of E1. Additionally, this pathway involves the synthesis of 3-benzyl-*O*-marrianolic acid, which is a more robust intermediate for the synthesis of a number of other derivatives of E1. It can also afford the *N*-alkylated analogues in one step when heated with an alkylamine (Scheme 2). We observed that this direct method gave better yields than the conventional *N*-alkylation for some derivatives (benzyl and 1-pyridin-3-ylmethyl) and allows the synthesis of those derivatives where the alkyl halides are commercially unavailable or deemed unreactive towards *N*-alkylation of **9**. The benzyl ether of the products **9**–**20** (see Table 1) was then cleaved by catalytic hydrogenation using Pd/C to afford their corresponding phenolic derivatives **21** and **24**–**34** in high yields. Compound **8** was also deben-

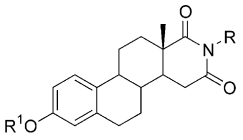


Scheme 1. Synthesis of **7** via a Beckmann rearrangement as described by Gupta and Jindal.[18] Reagents: (a) $KOC(CH_3)_3$, $(CH_3)_2CH(CH_2)_2ONO$; (b) Ac_2O/AcOH, reflux.



Scheme 2. Alternative method to Beckmann rearrangement for the synthesis of D-ring modified derivatives of E1. Reagents: (a) I_2, KOH, MeOH then KOH reflux; (b) urea, 180 °C; (c) NaH/DMF, RX; (d) Pd/C, H_2, MeOH/THF; (e) $ClSO_2NH_2$/DMA or NaH/DMF, $ClSO_2NH_2$; (f) RNH_2, 180 °C; (g) Et_3N/DMF, $ClSO_2NH_2$; (h) CH_2N_2/Et_2O; (i) imidazole/DMF, $ClSO_2NH_2$.

Table 1. A summary of all intermediates and final compounds prepared, with the IC_{50} values of EMATE and compounds **36–43**, **45–49** and **52** for the inhibition of STS in a human placental microsomes preparation

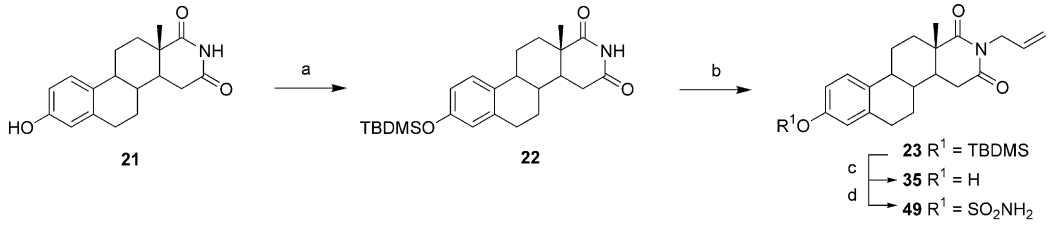


R	R_1 Bn	R_1 TBDMS	R_1 H	R_1 SO_2NH_2	IC_{50} (nM) of sulfamate SO_2NH_2
H	**9**	**22**	**21**	**36**	20
CH_3	**10**		**24**	**37**	12
CH_2CH_3	**11**		**25**	**38**	52
$(CH_2)_2CH_3$	**12**		**26**	**39**	1
$(CH_2)_3CH_3$	**13**		**27**	**40**	382
$(CH_2)_4CH_3$	**14**		**28**	**41**	150
$(CH_2)_5CH_3$	**15**		**29**	**42**	288
$(CH_2)_4Br$	**16**		**30**	**43**	12
CH_2–cyclopropyl	**17**		**31**	**45**	74
CH_2–pyridyl	**18**		**32**	**46**	1
CH_2–$C(CH_3)_3$-phenyl	**19**		**33**	**47**	23
CH_2–phenyl	**20**		**34**	**48**	3
$CH_2CH{=}CH_2$		**23**	**35**	**49**	75
3-*O*-Sulfamoyl-MA	(**52**)				20,000
EMATE	(**1**)				18

zylated in a similar manner to yield marrianolic acid **50** which was sulfamoylated in the presence of base/DMF to give the sulfamates **51** and **52** (Scheme 2). By reacting **52** with diazomethane, the dimethyl ester **53** was obtained.

For the introduction of unsaturated side chains onto the D-ring, a different protecting group had to be used since the debenzylation step, by hydrogenolysis, is likely to hydrogenate the unsaturated group concurrently. Hence, **9** was debenzylated to give the phenol **21** which was then protected as a *tert*-butyldimethylsilyl ether. Alkylation of the resulting compound **22** with allyl bromide easily yielded **23**, which was deprotected to **35** with tetrabutylammonium fluoride (Scheme 3). This particular approach, which was developed for the introduction of an *N*-allyl moiety, should also be applicable to the introduction of other unsaturated groups onto the nitrogen atom.

Sulfamoylation of the hydroxylated derivatives was then performed following a recent procedure described by Okada et al.[20] in which sulfamoylation of phenolic compounds is conducted in the aprotic solvent *N,N*-dimethylacetamide (DMA) in the absence of base. This method, which requires 2 equivalents of sulfamoyl chloride, gives a better yield of the sulfamate than the usual procedure in DMF, where a large excess of the reagent is required. The sulfamates **36–42**, **45** and **47–49** were obtained mostly in high yields after a short reaction time using 2.2 equivalents of sulfamoyl chloride in DMA. Sulfamoylation of **30** to afford **43**, however had been performed according to the method initially used in our group (NaH/DMF). Using the procedure of Okada et al., 3-sulfamoyloxy-*N*-(4′-chlorobutyl)-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (**44**) was also isolated with a higher yield than the anticipated bromo derivative **43** suggesting that under such conditions a halogen exchange from bromine to chlorine had occurred between the expected product and the excess of sulfamoyl chloride present in the reaction mixture. Attempts to separate both products by flash chromatography or



Scheme 3. Synthesis of the *N*-allyl derivative **49**. Reagents: (a) TBDMSCl/Imidazole, DMF; (b) NaH/DMF, CH_2CHCH_2Br; (c) TBAF/THF; (d) $ClSO_2NH_2$/DMA.

recrystallization failed. An HPLC run of the final crude product was found to contain 58.4% of **44** and 41.6% of **43**. Since the two products were well-separated by HPLC with respective t_R of 5.50 min and 6.50 min for **44** and **43** (elution with MeOH/H_2O 68:32), they were isolated and purified using preparative HPLC (see Experimental for analytical and preparative columns' properties). When the reaction was carried out using NaH/DMF and 6 equivalents of sulfamoyl chloride, **43** was isolated with a yield of 81% as the sole product of the reaction. Similarly, sulfamoylation of **32** was achieved with better yields of **46** when the original sulfamoylation conditions (NaH/DMF) were used. This is consistent with the difficulties that we have observed in the past in sulfamoylating compounds possessing pyridine motifs using Okada et al.'s procedure (unpublished results).

Results and Discussion

Inhibition of STS in vitro

The IC_{50} values of the compounds tested are presented in Table 1. EMATE is used as a standard reference although some new highly potent STS inhibitors have been recently reported in the literature.[21] Of the different compounds tested, the steroid derivatives bearing a propyl (**39**) and a 1-pyridin-3-ylmethyl (**46**) side chain were found to be the most potent, both sharing an IC_{50} of 1 nM in a placental microsomes preparation. The benzyl (**48**) derivative is also highly potent with an IC_{50} of 3 nM. These compounds were found to be better STS inhibitors than EMATE with, in particular, **39** and **46** being up to 18 times more active. In the *n*-alkyl series, compound **36**, which has no substitution at the *N*-atom, as well as **37** and **38**, bearing methyl and ethyl moieties, respectively exhibited similar potency to that of EMATE with respective IC_{50} values of 20, 12 and 52 nM. The fact that **36** is equipotent to EMATE has suggested that the replacement of the D-ring of EMATE with a six-membered piperidinedione ring has not been detrimental to its inhibitory activity. Ring opening of EMATE to the more hydrophilic marrianolic acid derivative **52** reduces the potency dramatically, which is in accordance with the finding that all STS inhibitors are hydrophobic. Our results have indicated that *N*-alkylations of the piperidinedione ring have resulted in an increase in potency. However, an unexpected sharp decrease in potency was observed for **40**–**42** (IC_{50} above 150 nM), where conformational flexibility of the alkyl groups might have prevented adequate fitting of the inhibitors into the enzyme active site. It is also possible that the hydrophobic pocket which these alkyl substituents are exploiting has, in fact, a limited capacity. From the different data obtained for these linear alkyl side chains, a preliminary structure–activity relationship graph has been drawn, where the IC_{50} of each compound is plotted as a function of the number of carbon atoms in the side chain (Fig. 2). It clearly underlines that the best compromise between the hydrophobicity and the length of the side chain was obtained with the propyl moiety. The moderate activity observed for compounds **45** and **49** (IC_{50} = 74 and 75 nM) underlines that moieties of similar size to the *n*-propyl group do not confer better activities.

The good inhibitory activities observed for the 1-pyridin-3-ylmethyl, *tert*-butyl-benzyl and benzyl derivatives **46**–**48** have suggested that the hydrophobic pocket around the D-ring in the active site tolerates steric bulk well. The finding that **46** is more potent than **48** may suggest the presence of hydrogen bond donating amino-acids within the hydrophobic pocket that interact with the 1-pyridin-3-ylmethyl moiety.

The inhibitory activity has improved for compound **43** although it might have a similar chain length to the

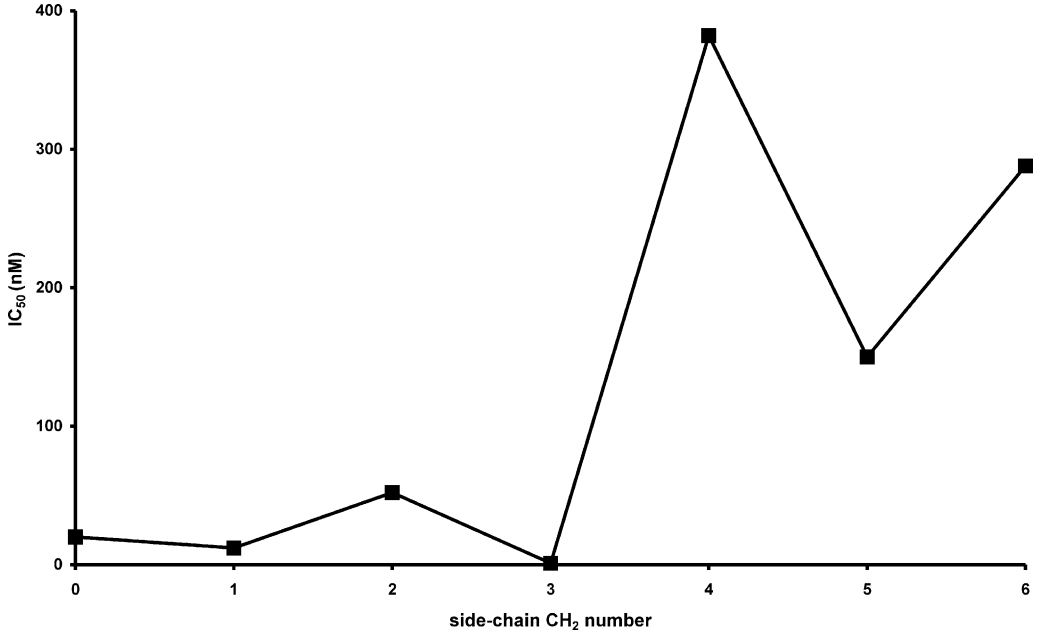


Figure 2. Structure–activity relationship for various side-chain lengths versus the inhibition of the conversion of estrone-sulfate into estrone catalysed by steroid sulfatase.

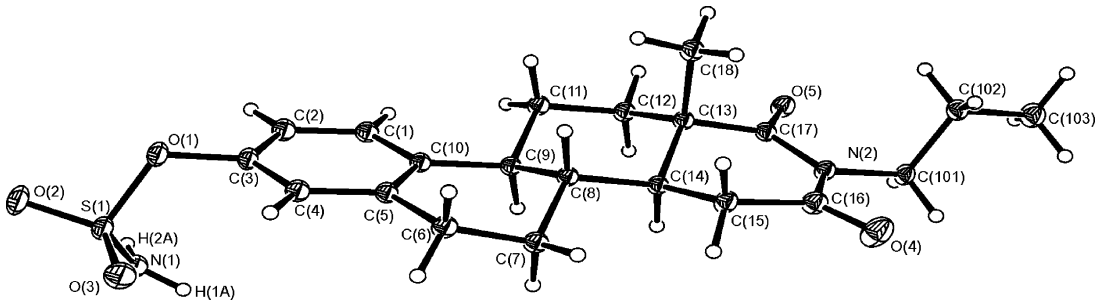


Figure 3. ORTEX[23] plot of the X-ray crystal structure of **39**. Ellipsoids are shown at the 30% probability level.

n-pentyl **41**. It is possible that the apparent increase in potency observed for **43** can be attributed to the high reactivity of its 4-bromobutyl substituent towards nucleophilic residues of amino acids in the active site of the enzyme. There is a literature precedent to show that steroids containing alkyl halide substituents are reactive compounds and enzyme inactivators.[22]

In order to elucidate the orientation of the atoms in the D-ring and in the side chain, as well as to gain structural information for molecular modelling studies, the crystal structure of the best inhibitor in the series, **39**, was determined. A crystal (approx. dimensions 0.20×0.17×0.08 mm), obtained from recrystallization in acetone/hexane, was used for data collection. The ORTEX[23] plot of the asymmetric unit of **39** is shown in Fig. 3 along with the labelling scheme used. The sulfamate group, all four rings, and the key features of the modified D-ring are clearly visible. As expected, the D-ring is in a half chair conformation since the imide function is planar.

Conclusion

A series of novel D-ring modified steroid derivatives was synthesized and evaluated for STS inhibition. In vitro evaluation of the activity of the compounds showed that they exhibited a range of potencies, with two highly potent derivatives, **39** and **46**, being identified having IC_{50} values of 1 nM. These two new inhibitors are up to 18-fold more potent than EMATE, the benchmark steroidal STS inhibitor. Additionally, they were found to be devoid of estrogenicity, making them promising candidates for future developments. In vivo activity and estrogenicity studies are reported elsewhere.[24]

Experimental

General

All chemicals were either purchased from Aldrich Chemical Co. (Gillingham, UK) or Lancaster Synthesis (Morecambe, UK). All organic solvents of A.R. grade were supplied by Fisher Scientific (Loughborough, UK). Anhydrous *N,N*-dimethylformamide (DMF) and *N,N*-dimethylacetamide (DMA), used for *N*-alkylations and sulfamoylation reactions, were purchased from Aldrich and were stored under a positive pressure of N_2 after use. Sulfamoyl chloride was prepared by an adaptation of the method of Appel and Berger[25] and was stored in the refrigerator under positive pressure of N_2 as a solution in toluene as described by Woo et al.[26] An appropriate volume of this solution was freshly concentrated in vacuo immediately before use. BE1 was prepared by an adaptation of a known procedure,[27] by reacting estrone with NaH and benzyl bromide in DMF.

E1 was purchased from Sequoia Research Products (Oxford, UK) and E1S from Sigma Chemical Co. (Poole, UK). [6,7-^{3}H]E1S (specific activity, 50 Ci/mmol) and [4-^{14}C]E1 (specific activity, 52 mCi/mmol) were purchased from New England Nuclear. [6,7-^{3}H]E1 (specific activity, 97 Ci/mmol) was obtained from the Amersham International Radiochemical Centre.

Thin-layer chromatography (TLC) was performed on precoated plates (Merck TLC aluminium sheets silica gel 60 F_{254}, Art. No. 5554). Product(s) and starting material (SM) were detected by either viewing under UV light or treating with an ethanolic solution of phosphomolybdic acid followed by heating. Flash column chromatography was performed on silica gel (Matrex C60). IR spectra were determined as KBr discs using a Perkin-Elmer Spectrum RXI FT-IR and peak positions are expressed in cm^{-1}. ^{1}H NMR and *DEPT*-edited ^{13}C NMR spectra were recorded with a JMN-GX 400 NMR spectrometer at 400 and 100 MHz, respectively, and chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS) as an internal standard. The following abbreviations are used to describe resonances in ^{1}H NMR and ^{13}C NMR spectra: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet etc. Chemical shifts for AB systems were approximated by taking the middle of each doublet. HPLC analyses were performed on a Waters Millenium 32 instrument equipped with a Waters 996 PDA detector. The traces were recorded on a Waters Radialpack C18, 8×100 mm column eluted with a methanol/water gradient at 2 mL/min. Preparative HPLC was performed on a Waters Nova-Pak C18, 25×100 mm column eluted with a methanol/water gradient at 20 mL/min. Mass spectra were recorded at the Mass Spectrometry Service Center, University of Bath. FAB-MS were carried out using *m*-nitrobenzyl alcohol (NBA) as the matrix. Elemental analyses were performed by the Microanalysis Service, University of

Bath. Melting points were determined using a Reichert-Jung Thermo Galen Kofler block and are uncorrected. The X-ray crystallographic study of **39** was carried out on a kappa CCD diffractometer with area detector.

Biological assays

Assays were performed essentially as described previously.[13] The ability of the compounds synthesized to inhibit steroid sulfatase activity was examined using placental microsomal preparations. Placental microsomes (100,000 g fraction) were prepared from a sulfatase-positive human placenta from a normal-term pregnancy.[28] To determine the IC_{50}s for the inhibition of estrone sulfatase, activity was measured in the presence of the inhibitor (0.1 nM–10 μM) using [^{3}H]E1S (4×10^5 dpm) adjusted to 20 μM with unlabelled substrate. After incubation of the substrate±inhibitor with placental microsomes (125 μg of protein/mL) for 30 min, the product formed was isolated from the mixture by extraction with toluene (4 mL), using [4-^{14}C]E1 to monitor procedural losses.

General synthetic procedures

Method 1. Synthesis of alkylated derivatives 10–17 and 19. The preparation of 3-benzyloxy-*N*-methyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (**10**) is given here as a representative procedure. Sodium hydride (60% dispersion in mineral oil, 62 mg, 1.54 mmol) was added to a stirred solution of **9** (500 mg, 1.28 mmol) in anhydrous DMF (15 mL) at 0 °C under an atmosphere of N_2. After evolution of hydrogen had ceased, methyl iodide (160 μL, 2.57 mmol) was added. The reaction mixture was stirred at room temperature for 45 min and poured into water (50 mL). The resulting solution was extracted into ethyl acetate (2×50 mL) and the organic layer washed with brine (4×25 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was purified by flash chromatography using chloroform as eluent to give **10** as a white solid (432 mg, 83%). For analysis, a sample was recrystallized from EtOH to give colorless crystals: mp 118–121 °C. IR (KBr) ν_{max} 3160–3060, 2920–2870, 1720, 1670, 1600–1500 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.17 (3H, s, C-18-H_3), 1.26–3.00 (11H, m), 2.86–2.91 (2H, m, C-6-H_2), 3.15 (3H, s, N-CH_3), 5.04 (2H, s, OCH_2Ar), 6.72 (1H, d, $J=2.7$ Hz, C-4-H), 6.80 (1H, dd, $J=8.6$ Hz and $J=2.7$ Hz, C-2-H), 7.21 (1H, d, $J=8.6$ Hz, C-1-H) and 7.32–7.45 (5H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 16.6 (q), 25.6, 25.8 (all t), 27.0 (q), 29.7, 33.5, 33.8 (all t), 38.5, 40.4 (all d), 41.5 (s), 42.6 (d), 69.9 (t), 112.6, 114.5, 126.1, 126.3 (2×), 127.7, 128.4 (2×) (all d), 131.5, 137.0, 137.2, 156.8, 171.8 and 178.7 (all s). MS *m*/*z* (FAB+) 404.4 [79, $(M+H)^+$], 91.1 [100, $(CH_2Ar)^+$]. HRMS *m*/*z* (FAB+) calcd for $C_{26}H_{30}NO_3$: 404.2226. Found: 404.2217. Anal. calcd for $C_{26}H_{29}NO_3$: C, 77.39; H, 7.24; N, 3.47. Found: C, 77.30; H, 7.22; N, 3.48.

Method 2. Hydrogenolysis (synthesis of 21 and 24–34). The preparation of 3-hydroxy-*N*-methyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (**24**) is given here as a representative procedure. Pd/C 10% (50% w/w of substrate used, 200 mg) was added to a solution of **10** (400 mg, 992 μmol) in MeOH/THF 2:1 (30 mL) and the resulting suspension hydrogenated at room temperature for 2 h using a hydrogen-filled balloon. Filtration and evaporation of the filtrate in vacuo gave **24** as a white crystalline solid (253 mg, 81%). For analysis, a sample was recrystallized from ethyl acetate to give white crystals: mp 328–330 °C. IR (KBr) ν_{max} 3460, 2940–2860, 1715, 1655, 1610–1510 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 1.09 (3H, s, C-18-H_3), 1.19–2.97 (11H, m), 2.68–2.73 (2H, m, C-6-H_2), 2.98 (3H, s, N–CH_3), 6.44 (1H, d, $J=2.3$ Hz, C-4-H), 6.52 (1H, dd, $J=8.5$ Hz and $J=2.3$ Hz, C-2-H), 7.06 (1H, d, $J=8.5$ Hz, C-1-H) and 9.05 (1H, s, OH); ^{13}C NMR (DMSO-d_6) δ 16.3 (q), 25.2 (t), 26.4 (q), 29.11 (t), 32.8, 33.5 (2×) (all t), 37.8 (d), ~39 (s, under solvent peaks), 40.9, 41.9, 112.7, 114.5, 125.8 (all d), 129.4, 136.7, 154.8, 171.3 and 178.2 (all s). MS *m*/*z* (FAB+) 314.1 [78, $(M+H)^+$], 97.1 [100]. HRMS *m*/*z* (FAB+) calcd for $C_{19}H_{24}NO_3$: 314.1756. Found: 314.1749. Anal. calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.60; H, 7.16; N, 4.35.

Method 3. Sulfamoylation according to Okada et al.[20] The preparation of 3-sulfamoyloxy-*N*-methyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (**37**) is given here as a representative procedure. The phenol **24** (100 mg, 319 μmol) was added to a stirred solution of sulfamoyl chloride (2.2 equiv) in anhydrous DMA (1 mL) at 0 °C under an atmosphere of N_2. The reaction mixture was stirred under N_2 for 3 h in which time it was allowed to warm to room temperature. It was then poured into cold brine (15 mL), and the resulting solution was extracted into ethyl acetate (2×20 mL). The organic layers were combined, washed with brine (5×20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give **37** as a white solid. The crude product was recrystallized from chloroform to give white crystals (84 mg, 67%): mp 219–222 °C. IR (KBr) ν_{max} 3300, 3230, 3100, 2945–2865, 1710, 1655, 1605–1500, 1390, 1190 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.18 (3H, s, C-18-H_3), 1.32–3.02 (11H, m), 2.89–2.93 (2H, m, C-6-H_2), 3.16 (3H, s, N-CH_3), 4.85 (2H, s, NH_2), 7.06 (1H, d, $J=2.3$ Hz, C-4-H), 7.11 (1H, dd, $J=8.5$ Hz and $J=2.3$ Hz, C-2-H) and 7.33 (1H, d, $J=8.5$ Hz, C-1-H). MS *m*/*z* (FAB+) 393.0 [100, $(M+H)^+$], 109.0 [43], 81.0 [64, $(SO_2NH_2+H)^+$]; MS *m*/*z* (FAB−) 545.3 [38, $(M+NBA)^-$], 391.2 [100, $(M-H)^-$]. HRMS *m*/*z* (FAB+) calcd for $C_{19}H_{25}N_2O_5S$: 393.1484. Found: 393.1472. Anal. calcd for $C_{19}H_{24}N_2O_5S$: C, 58.15; H, 6.16; N, 7.14. Found: C, 58.30; H, 6.17; N, 7.19.

All sulfamates, with the exception of **43**, **46**, **51** and **52** were prepared by the general procedure described above. The crude products were purified by flash chromatography using a gradient of chloroform/acetone and/or recrystallized.

Method 4. Preparation of the sulfamates 43 and 46. Sodium hydride (60% dispersion in mineral oil, 1.2 equiv) was added to a stirred solution of the substrate in anhydrous DMF at 0 °C under an atmosphere of N_2. After stirring the resulting suspension for an additional 15 min at 0 °C, sulfamoyl chloride was added (6 equiv)

and the reaction mixture was stirred under N_2 in which time it was allowed to warm to room temperature. It was then poured into brine (20 mL), and the resulting solution was extracted into ethyl acetate (2×20 mL). The organic layers were combined, washed with water (2×20 mL) then brine (2×20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography using a gradient of chloroform/acetone and/or recrystallized.

16-Oximino-estrone (6). Estrone (200 mg, 740 mmol) was added to a stirred solution of potassium *tert*-butoxide, freshly prepared by dissolving potassium metal (80 mg, 2.05 mmol) in 2 mL *tert*-butanol, under an atmosphere of N_2. The reaction mixture was stirred for 1 h at room temperature before addition of isoamyl nitrite (180 μL, 1.34 mmol) in a dropwise manner. The deep red mixture obtained was stirred overnight, then poured into water (20 mL). The resulting solution was extracted with ether (2×20 mL) and the aqueous layer was acidified with glacial acetic acid (10 mL) to give a light yellow precipitate. After standing for 2 h, the solid was isolated by filtration to give **6** as a yellow powder (140 mg, 63%). For analysis, a sample was recrystallized from acetone to give white crystals: mp 223–225 °C [lit.[29] (aq MeOH) 214–215 °C]. IR (KBr) ν_{max} 3385, 2920–2860, 1735, 1605–1500 cm^{-1}. ^1H NMR (DMSO-d_6) δ 0.89 (3H, s, C-18-H_3), 1.30–2.85 (11H, m), 2.70–2.81 (2H, m, C-6-H_2), 6.46 (1H, d, $J=2.3$ Hz, C-4-H), 6.52 (1H, dd, $J=8.3$ Hz and $J=2.3$ Hz, C-2-H), 7.05 (1H, d, $J=8.3$ Hz, C-1-H), 9.05 (1H, s, OH) and 12.39 (1H, s, NOH); ^{13}C NMR (DMSO-d_6) δ 14.1 (q), 25.1, 25.5, 26.2, 29.0, 30.9 (all t), 37.2, 43.2, 44.6 (all d), 48.5 (s), 112.7, 114.8, 125.8 (all d), 129.6, 136.9, 154.8, 155.2 and 204.6 (all s). MS *m/z* (FAB+) 453.2 [30, $(M+H+NBA)^+$], 300.1 [100, $(M+H)^+$]; MS *m/z* (FAB−) 451.3 [38, $(M-H+NBA)^-$], 298.2 [100, $(M-H)^-$]. HRMS *m/z* (FAB+) calcd for $C_{18}H_{22}NO_3$: 300.1600. Found: 300.1596. Anal. calcd for $C_{18}H_{21}NO_3 \cdot (AcOH)_{1/6}$: C, 71.17; H, 7.06; N, 4.53. Found: C, 71.30; H, 7.08; N, 4.35.

3-Acetoxy-17-*seco*-estra-1,3,5(10)-triene-16,17-imide (7). A suspension of **6** (150 mg, 501 mmol) in a mixture of 4.5 mL of glacial acetic acid and 7.5 mL of acetic anhydride was heated to reflux under an atmosphere of N_2 for 48 h. The solvent was then removed under reduced pressure and water added (30 mL). After careful neutralisation with aqueous NaOH, the resulting solution was extracted with ethyl acetate (2×20 mL). The organic layer was separated, washed with water (2×15 mL), then brine (2×15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Fractionation of the crude product by flash chromatography with chloroform as eluent gave **7** as a light yellow solid (111 mg, 65%): mp 189–193 °C [lit.[18] (acetone) 196–198 °C]. IR (KBr) ν_{max} 3205, 2940–2860, 1760, 1725, 1690, 1610–1495 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.11 (3H, s, C-18-H_3), 1.20–2.72 (11H, m), 2.77–2.84 (2H, m, C-6-H_2), 2.23 (3H, s, OAc), 6.81 (1H, d, $J=2.6$ Hz, C-4-H), 6.87 (1H, dd, $J=8.3$ Hz and $J=2.6$ Hz, C-2-H), 7.32 (1H, d, $J=8.3$ Hz, C-1-H) and 10.64 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ 16.0, 20.7 (all q), 24.8, 24.9, 28.8, 32.2, 32.5 (all t), 37.3 (d), ~39 (s, under solvent peaks), 40.3, 41.9, 118.6, 120.9, 125.9 (all d), 136.5, 137.1, 147.9, 168.8, 171.9 and 178.7 (all s). MS *m/z* (FAB+) 342.1 [100, $(M+H)^+$], 299.1 [40, $(M+H-Ac)^+$]; MS *m/z* (FAB–) 493.2 [34, $(M-H+NBA)^-$], 340.1 [100, $(M-H)^-$]. HRMS *m/z* (FAB+) calcd for $C_{20}H_{24}NO_4$: 342.1705. Found: 342.1705.

3-Benzyloxy-16,17-*seco*-estra-1,3,5(10)-triene-16,17-dioic acid (8). A solution of iodine (7.6 g, 29.94 mmol) in 95 mL of MeOH and a solution of KOH (13.7 g) in 27 mL of water and 61 mL of MeOH were added dropwise and alternatively to a stirred solution of BE1 (3.8 g, 10.54 mmol) in MeOH (1 L) so that the colour of the mix remains orange/brown. The addition was carried out over 45 min and the resulting light yellow solution was stirred overnight at room temperature under an atmosphere of N_2. The mixture was then concentrated and poured into water (800 mL). After acidification with HCl 5 M, the organic fraction was extracted into ether (600 mL), washed with aqueous sodium thiosulfate (4×100 mL), water (4×100 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The resulting yellow foam (4.54 g) was then dissolved in a solution of KOH (7.6 g) in MeOH/H_2O 1:2 (228 mL) and heated to reflux for 4 h. The final brown mixture was poured into water (800 mL) and after acidification with 5 M HCl the organics were extracted into ethyl acetate (300 mL). After washing with brine (4×200 mL), the organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo to give a yellow residue (4.32 g). This was recrystallized from chloroform/hexane 5:3 to give **8** as a creamy powder (3.25 g, 75%): mp 212–215 °C [lit.[19] (aq MeOH) 226–227 °C]. IR (KBr) ν_{max} 3050–2650, 1700, 1600–1500 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.02 (3H, s, C-18-H_3), 1.20–2.78 (11H, m), 2.72–2.76 (2H, m, C-6-H_2), 5.05 (2H, s, OCH_2Ar), 6.68 (1H, d, $J=2.5$ Hz, C-4-H), 6.75 (1H, dd, $J=8.7$ Hz and $J=2.5$ Hz, C-2-H), 7.18 (1H, d, $J=8.7$ Hz, C-1-H), 7.30–7.42 (5H, m, C_6H_5) and 12.14 (2H, s, CO_2H); ^{13}C NMR (DMSO-d_6) δ 15.4 (q), 25.8, 26.5, 29.7, 35.8, 36.1 (all t), 40.7, 41.8, 42.5 (all d), 46.2 (s), 68.9 (t), 112.3, 114.0, 126.3, 127.3 (2×), 127.5, 128.2 (2×) (all d), 131.6, 137.2 (2×), 156.0, 173.9 and 178.6 (all s). MS *m/z* (FAB+) 408.2 [41, M^+], 91.1 [100, $(CH_2Ar)^+$]. HRMS *m/z* (FAB+) calcd for $C_{25}H_{28}O_5$: 408.1937. Found: 408.1940.

3-Benzyloxy-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (9). 3-Benzyloxy-16,17-*seco*-estra-1,3,5(10)-triene-16,17-dioic acid (**8**) (3.25 g, 7.96 mmol) and urea (3.25 g, 54.11 mmol) were heated at 180 °C under an atmosphere of N_2 for 45 min. The resulting brown residue was crushed and acetone added (200 mL) to give a brown suspension. This mixture was concentrated to ca. 100 mL, silica gel was added and the solvent removed. The resulting powder was transferred onto a flash chromatography column. Elution with chloroform/acetone (96:4) gave **9** as a white solid (2.75 g, 89%). For analysis, a sample was recrystallized from EtOH to give colorless needles: mp 225–226 °C. IR (KBr) ν_{max} 3260, 2900–2870, 1720, 1700, 1600–1500 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.09 (3H, s, C-18-H_3), 1.20–2.72 (11H, m), 2.76–2.80 (2H, m, C-6-H_2), 5.05 (2H, s, OCH_2Ar), 6.72

(1H, d, $J=2.5$ Hz, C-4-H), 6.76 (1H, dd, $J=8.7$ Hz and $J=2.5$ Hz, C-2-H), 7.19 (1H, d, $J=8.7$ Hz, C-1-H), 7.31–7.44 (5H, m, C_6H_5) and 10.63 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ 16.2 (q), 25.1, 25.2, 29.2, 32.4, 32.7 (all t), 37.8, 40.3 (all d), 40.5 (s), 41.9 (d), 68.9 (t), 112.2, 114.1, 126.0, 127.3 (2×), 127.4, 128.2 (2×) (all d), 131.5, 137.0, 137.1, 156.0, 172.1 and 178.9 (all s). MS *m/z* (FAB+) 390.2 [58, $(M+H)^+$], 91.1 [100, $(CH_2Ar)^+$]. HRMS *m/z* (FAB+) calcd for $C_{25}H_{28}NO_3$: 390.2069. Found: 390.2059. Anal. calcd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 76.90; H, 6.99; N, 3.73.

3-Benzyloxy-*N*-ethyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (11). White solid (502 mg, 94%): mp 93–95 °C. IR (KBr) ν_{max} 2975–2865, 1715, 1665, 1605–1500 cm^{-1}. ^{1}H NMR ($CDCl_3$) 1.11 (3H, t, $J=7.2$ Hz, C-2′-H_3), 1.16 (3H, s, C-18-H_3), 1.31–2.98 (11H, m), 2.85–2.90 (2H, m, C-6-H_2), 3.81 (2H, m, N–CH_2), 5.04 (2H, s, OCH_2Ar), 6.72 (1H, d, $J=2.7$ Hz, C-4-H), 6.81 (1H, dd, $J=8.6$ Hz and $J=2.7$ Hz, C-2-H), 7.22 (1H, d, $J=8.6$ Hz, C-1-H) and 7.30–7.44 (5H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 13.1, 16.4 (all q), 25.5, 25.7, 29.6, 33.5, 33.6, 35.0 (all t), 38.5, 40.2 (all d), 41.3 (s), 42.4 (d), 69.8 (t), 112.4, 114.4, 126.0, 127.1 (2×), 127.6, 128.3 (2×) (all d), 131.4, 136.9, 137.0, 156.7, 171.1 and 178.0 (all s). MS *m/z* (FAB+) 418.3 [90, $(M+H)^+$], 91.0 [100, $(CH_2Ar)^+$]. HRMS *m/z* (FAB+) calcd for $C_{27}H_{31}NO_3$: 417.2304. Found: 417.2306.

3-Benzyloxy-*N*-propyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (12). White solid (524 mg, 94%). For analysis, a sample was recrystallized from EtOH to give white crystals: mp 95–98 °C. IR (KBr) ν_{max} 3035, 2960–2870, 1720, 1660, 1610–1500 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, t, $J=7.6$ Hz, C-3′-H_3), 1.16 (3H, s, C-18-H_3), 1.32–2.98 (13H, m), 2.83–2.88 (2H, m, C-6-H_2), 3.64–3.80 (2H, m, N–CH_2), 5.03 (2H, s, OCH_2Ar), 6.72 (1H, d, $J=2.7$ Hz, C-4-H), 6.80 (1H, dd, $J=8.6$ Hz and $J=2.7$ Hz, C-2-H), 7.21 (1H, d, $J=8.6$ Hz, C-1-H) and 7.30–7.44 (5H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 11.4, 16.6 (all q), 21.3, 25.6, 25.8, 29.8, 33.7, 33.8 (all t), 38.7, 40.4 (all d), 41.5 (s), 41.6 (t), 42.5 (d), 70.0 (t), 112.6, 114.5, 126.1, 127.3 (2×), 127.8, 128.4 (2×) (all d), 131.5, 137.0, 137.2, 156.8, 171.5 and 178.4 (all s). MS *m/z* (FAB+) 432.4 [88, $(M+H)^+$], 91.1 [100, $(CH_2Ar)^+$]. HRMS *m/z* (FAB+) calcd for $C_{28}H_{34}NO_3$: 432.2539. Found: 432.2522. Anal. calcd for $C_{28}H_{33}NO_3$: C, 77.93; H, 7.71; N, 3.25. Found: C, 77.60; H, 7.68; N, 3.26.

3-Benzyloxy-*N*-butyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (13). White solid (513 mg, 90%). For analysis, a sample was recrystallized from EtOH to give white needles: mp 100–103 °C. IR (KBr) ν_{max} 2960–2870, 1720, 1665, 1615–1500 cm^{-1}. ^{1}H NMR ($CDCl_3$) 0.92 (3H, t, $J=7.2$ Hz, C-4′-H_3), 1.16 (3H, s, C-18-H_3), 1.28–2.99 (15H, m), 2.84–2.89 (2H, m, C-6-H_2), 3.75 (2H, m, N–CH_2), 5.04 (2H, s, OCH_2Ar), 6.72 (1H, d, $J=2.5$ Hz, C-4-H), 6.81 (1H, dd, $J=8.6$ Hz and $J=2.5$ Hz, C-2-H), 7.22 (1H, d, $J=8.6$ Hz, C-1-H) and 7.29–7.45 (5H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 13.8, 16.5 (all q), 20.1, 25.5, 25.7, 29.6, 30.0, 33.5, 33.7 (all t), 38.5 (d), 39.7 (t), 40.2 (d), 41.3 (s), 42.4 (d), 69.8 (t), 112.4, 114.4, 126.0, 127.1 (2×), 127.6, 128.3 (2×) (all d), 131.4, 136.9, 137.0, 156.7, 171.3 and 178.2 (all s). MS *m/z* (FAB+) 446.3 [97, $(M+H)^+$], 91.0 [100, $(CH_2Ar)^+$]. HRMS *m/z* (FAB+) calcd for $C_{29}H_{36}NO_3$: 446.2695. Found: 446.2691. Anal. calcd for $C_{29}H_{35}NO_3$: C, 78.17; H, 7.92; N, 3.14. Found: C, 77.80; H, 7.89; N, 3.13.

3-Benzyloxy-*N*-pentyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (14). White solid (550 mg, 93%). For analysis, a sample was recrystallized from EtOH to give colorless needles: mp 104–107 °C. IR (KBr) ν_{max} 3100–3000, 2960–2870, 1720, 1660, 1610–1500 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, t, $J=7.2$ Hz, C-5′-H_3), 1.16 (3H, s, C-18-H_3), 1.20–2.98 (17H, m), 2.83–2.89 (2H, m, C-6-H_2), 3.66–3.82 (2H, m, N–CH_2), 5.03 (2H, s, OCH_2Ar), 6.72 (1H, d, $J=2.7$ Hz, C-4-H), 6.80 (1H, dd, $J=8.6$ Hz and $J=2.7$ Hz, C-2-H), 7.21 (1H, d, $J=8.6$ Hz, C-1-H) and 7.30–7.44 (5H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 14.1, 16.6 (all q), 22.5, 25.6, 25.8, 27.7, 29.2, 29.7, 33.7, 33.8 (all t), 38.7 (d), 40.1 (t), 40.3 (d), 41.5 (s), 42.5 (d), 70.0 (t), 112.5, 114.5, 126.1, 127.3 (2×), 127.8, 128.4 (2×) (all d), 131.5, 137.0, 137.2, 156.8, 171.4 and 178.4 (all s). MS *m/z* (FAB+) 460.2 [78, $(M+H)^+$], 91.1 [100, $(CH_2Ar)^+$]. HRMS *m/z* (FAB+) calcd for $C_{30}H_{38}NO_3$: 460.2852. Found: 460.2845. Anal. calcd for $C_{30}H_{37}NO_3$: C, 78.40; H, 8.11; N, 3.05. Found: C, 78.20; H, 8.08; N, 3.01.

3-Benzyloxy-*N*-hexyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (15). White solid (575 mg, 94%). For analysis, a sample was recrystallized from EtOH to give white needles: mp 108–111 °C. IR (KBr) ν_{max} 2960–2860, 1720, 1665, 1615–1500 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, t, $J=6.6$ Hz, C-6′-H_3), 1.16 (3H, s, C-18-H_3), 1.28–2.98 (19H, m), 2.84–2.89 (2H, m, C-6-H_2), 3.74 (2H, m, N–CH_2), 5.04 (2H, s, OCH_2Ar), 6.72 (1H, d, $J=2.7$ Hz, C-4-H), 6.81 (1H, dd, $J=8.6$ Hz and $J=2.7$ Hz, C-2-H), 7.22 (1H, d, $J=8.6$ Hz, C-1-H) and 7.29–7.44 (5H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 14.1, 16.6 (all q), 22.6, 25.6, 25.8, 26.7, 28.0, 29.8, 31.6, 33.7, 33.8 (all t), 38.7 (d), 40.1 (t), 40.4 (d), 41.5 (s), 42.5 (d), 70.0 (t), 112.6, 114.5, 126.1, 127.3 (2×), 127.8, 128.4 (2×) (all d), 131.6, 137.0, 137.2, 156.8, 171.4 and 178.4 (all s). MS *m/z* (FAB+) 474.3 [68, $(M+H)^+$], 91.0 [100, $(CH_2Ar)^+$]. HRMS *m/z* (FAB+) calcd for $C_{31}H_{40}NO_3$: 474.3008. Found: 473.2988. Anal. calcd for $C_{31}H_{39}NO_3$: C, 78.61; H, 8.30; N, 2.96. Found: C, 78.10; H, 8.16; N, 2.98.

3-Benzyloxy-*N*-(4′-bromobutyl)-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (16). White solid (569 mg, 84%). For analysis, a sample was recrystallized from EtOH to give white crystals: mp 113–116 °C. IR (KBr) ν_{max} 2935–2860, 1720, 1670, 1605–1500 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.17 (3H, s, C-18-H_3), 1.30–3.00 (15H, m), 2.84–2.90 (2H, m, C-6-H_2), 3.42 (2H, t, $J=6.8$ Hz, C-4′-H_2), 3.79 (2H, m, N–CH_2), 5.04 (2H, s, OCH_2Ar), 6.72 (1H, d, $J=2.7$ Hz, C-4-H), 6.81 (1H, dd, $J=8.6$ Hz and $J=2.7$ Hz, C-2-H), 7.21 (1H, d, $J=8.6$ Hz, C-1-H) and 7.30–7.45 (5H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) 17.0 (q), 25.9, 26.1, 27.1, 30.1, 30.5, 33.5, 33.9, 34.1 (all t), 39.0 (d), 39.3 (t), 40.6 (d), 41.8 (s), 42.8 (d), 70.3 (t), 112.9, 114.8, 126.4, 127.6 (2×), 128.1, 128.8 (2×) (all d), 131.8, 137.3, 137.5, 157.1, 171.8 and 178.8 (all s). MS *m/z* (FAB+) 524.1 [42, $(M+H)^+$], 91.0 [100, $(CH_2Ar)^+$]. HRMS *m/z*

(FAB+) calcd for $C_{29}H_{35}BrNO_3$: 524.1800 and for $C_{29}H_{35}{}^{81}BrNO_3$: 526.1780. Found: 524.1738 and 526.1759. Anal. calcd for $C_{29}H_{34}BrNO_3$: C, 66.41; H, 6.53; N, 2.67. Found: C, 66.30; H, 6.51; N, 2.56.

3-Benzyloxy-*N*-cyclopropylmethyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (17). White solid (536 mg, 94%). For analysis, a sample was recrystallized from EtOH to give white needles: mp 96–99 °C. IR (KBr) ν_{max} 2920–2860, 1720, 1670, 1610–1495 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.29–0.34 (2H, m, C-3′-H_2), 0.40–0.45 (2H, m, C-4′-H_2), 1.15 (1H, m, C-2′-H), 1.18 (3H, s, C-18-H_3), 1.25–3.01 (11H, m), 2.85–2.90 (2H, m, C-6-H_2), 3.67 (2H, m, N–CH_2), 5.04 (2H, s, OCH_2Ar), 6.73 (1H, d, J=2.5 Hz, C-4-H), 6.81 (1H, dd, J=8.6 Hz and J=2.5 Hz, C-2-H), 7.22 (1H, d, J=8.6 Hz, C-1-H) and 7.29–7.45 (5H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 3.9, 4.0 (all t), 10.5 (d), 17.0 (q), 26.0, 26.1, 30.1, 34.0, 34.1 (all t), 39.1, 40.6 (all d), 41.9 (s), 42.9 (d), 44.6, 70.3 (all t), 112.9, 114.9, 126.4, 127.6 (2×), 128.1, 128.7 (2×) (all d), 131.9, 137.4, 137.5, 157.2, 172.0 and 179.0 (all s). MS m/z (FAB+) 887.3 [58, $(2M+H)^+$], 444.1 [98, $(M+H)^+$], 91.0 [100, $(CH_2Ar)^+$]. HRMS m/z (FAB+) calcd for $C_{29}H_{34}NO_3$: 444.2539. Found: 444.2525. Anal. calcd for $C_{29}H_{33}NO_3$: C, 78.52; H, 7.50; N, 3.16. Found: C, 78.30; H, 7.47; N, 3.18.

3-Benzyloxy-*N*-(1″-pyridin-3″-ylmethyl)-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (18). 3-Picolylamine (4.71 mL, 46.24 mmol) and **8** (600 mg, 1.47 mmol) were heated at 180 °C under an atmosphere of N_2 for 2 h. After cooling down, the resulting orange mixture was poured into water (300 mL) and acidified with HCl 5 M. The organic fractions were extracted into ethyl acetate (2×70 mL), washed with water (250 mL), brine (2×50 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was recrystallized from EtOH to give light yellow crystals (543 mg, 77%). An analytical sample was further recrystallized from EtOH to give **18** as colorless needles: mp 170–172 °C. IR (KBr) ν_{max} 2925–2870, 1720, 1670, 1610–1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.14 (3H, s, C-18-H_3), 1.28–3.04 (11H, m), 2.84–2.88 (2H, m, C-6-H_2), 4.92 (1H, d, J=13.9 Hz, N-C$H_A$$H_B$), 4.98 (1H, d, J=13.9 Hz, N–CH_AH_B), 5.03 (2H, s, OCH_2Ar), 6.71 (1H, d, J=2.7 Hz, C-4-H), 6.79 (1H, dd, J=8.6 Hz and J=2.7 Hz, C-2-H), 7.17–7.45 (7H, m, C_6H_5, C-1-H and C-5″-H), 7.69 (1H, td, J=7.8 Hz, J=1.8 Hz, C-4″-H), 8.50 (1H, dd, J=5.1 Hz, J=1.8 Hz, C-6″-H) and 8.63 (1H, d, J=1.8 Hz, C-2″-H); ^{13}C NMR ($CDCl_3$) δ 16.5 (q), 25.5, 25.8, 29.7, 33.6, 33.7 (all t), 38.5, 40.1 (all d), 40.8 (t), 41.6 (s), 42.4 (d), 69.9 (t), 112.5, 114.5, 123.2, 126.1, 127.3 (2×), 127.7, 128.4 (2×) (all d), 131.3, 132.8 (all s), 136.4 (d), 137.1 (2×s), 148.5, 150.0 (all d), 156.8, 171.4 and 178.3 (all s). MS m/z (FAB+) 481.3 [100, $(M+H)^+$], 91.1 [47, $(CH_2Ar)^+$]. HRMS m/z (FAB+) calcd for $C_{31}H_{33}N_2O_3$: 481.2491. Found: 481.2504. Anal. calcd for $C_{31}H_{32}N_2O_3$: C, 77.47; H, 6.71; N, 5.83. Found: C, 77.00; H, 6.75; N, 5.73.

3-Benzyloxy-*N*-(4″-*tert*-butyl-benzyl)-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (19). White solid (667 mg, 97%): mp 199–200 °C. IR (KBr) ν_{max} 2965–2870, 1720, 1670, 1605–1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.16 (3H, s, C-18-H_3), 1.28 (9H, s, $C(CH_3)_3$), 1.30–3.01 (11H, m), 2.84–2.90 (2H, m, C-6-H_2), 4.88 (1H, d, J=13.9 Hz, N-C$H_A$$H_B$), 4.94 (1H, d, J=13.9 Hz, N-CH_AH_B), 5.03 (2H, s, OCH_2Ar), 6.72 (1H, d, J=2.7 Hz, C-4-H), 6.80 (1H, dd, J=8.6 Hz and J=2.7 Hz, C-2-H), 7.21 (1H, d, J=8.6 Hz, C-1-H) and 7.24–7.44 (9H, m, C_6H_5, C-2″-H, C-3″-H, C-5″-H and C-6″-H); ^{13}C NMR ($CDCl_3$) δ 16.6 (q), 25.6, 25.8, 29.7 (all t), 31.4 (3×q), 33.7, 33.8 (all t), 34.5 (s), 38.6, 40.1, 41.5 (all s), 42.5 (d), 42.9 (t), 69.9 (t), 112.5, 114.5, 125.2 (2×), 126.1, 127.3 (2×), 127.8, 128.0 (2×), 128.4 (2×) (all d), 131.5, 134.2, 137.0, 137.2, 149.9, 156.8, 171.4 and 178.4 (all s). MS m/z (FAB+) 1071.5 [32, $(2M+H)^+$], 536.2 [80, $(M+H)^+$], 91.0 [100, $(CH_2Ar)^+$]; MS m/z (FAB−) 534.3 [72, $(M-H)^-$], 195.0 [100], 276.0 [100]. HRMS m/z (FAB+) calcd for $C_{36}H_{42}NO_3$: 536.3165. Found: 536.3150. Anal. calcd for $C_{36}H_{41}NO_3.(H_2O)_{1/4}$: C, 80.04; H, 7.74; N, 2.59. Found: C, 80.10; H, 7.51; N, 2.61.

3-Benzyloxy-*N*-benzyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (20). Benzylamine (6.25 mL, 57.22 mmol) and **8** (500 mg, 1.22 mmol) were heated at 180 °C under an atmosphere of N_2 for 3 h. After cooling down, the resulting brown mixture was poured into water (250 mL) and acidified with HCl 5 M. The organic fractions were extracted into ethyl acetate (2×50 mL), washed with water (2×25 mL), brine (3×25 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. Fractionation of the crude product by flash chromatography with chloroform/hexane (8:2) as eluent gave **20** as a creamy powder (385 mg, 65%). For analysis, a sample was recrystallized from MeOH to give colorless needles: mp 144–146 °C. IR (KBr) ν_{max} 3100, 2940–2850, 1720, 1670, 1615–1560 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.15 (3H, s, C-18-H_3), 1.25–3.01 (11H, m), 2.84–2.89 (2H, m, C-6-H_2), 4.91 (1H, d, J=13.7 Hz, N-C$H_A$$H_B$), 4.98 (1H, d, J=13.7 Hz, N-CH_AH_B), 5.03 (2H, s, OCH_2Ar), 6.72 (1H, d, J=2.7 Hz, C-4-H), 6.80 (1H, dd, J=8.4 Hz and J=2.7 Hz, C-2-H), 7.21 (1H, d, J=8.4 Hz, C-1-H) and 7.24–7.43 (10H, m, 2×C_6H_5); ^{13}C NMR ($CDCl_3$) δ 16.5 (q), 25.6, 25.8, 29.7, 33.7 (2×) (all t), 38.6, 40.2 (all d), 41.5 (s), 42.5 (d), 43.2, 69.9 (all t), 112.5, 114.5, 126.1, 127.2, 127.3 (2×), 127.8, 128.3 (2×), 128.4 (2×), 128.4 (2×) (all d), 131.5, 137.0, 137.2 (2×), 156.8, 171.4 and 178.3 (all s). MS m/z (FAB+) 480.2 [52, $(M+H)^+$], 91.1 [100, $(CH_2Ar)^+$]. HRMS m/z (FAB+) calcd for $C_{32}H_{34}NO_3$: 480.2539. Found: 480.2522. Anal. calcd for $C_{32}H_{33}NO_3$: C, 80.14; H, 6.94; N, 2.92. Found: C, 80.10; H, 6.91; N, 2.94.

3-Hydroxy-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (21). White solid (246 mg, 91%). For analysis, a sample was recrystallized from chloroform/hexane (2:1) to give white crystals: mp 297–300 °C [lit.[18] (MeOH) 294–296 °C]. IR (KBr) ν_{max} 3410, 3180–3085, 2955–2870, 1715, 1680, 1615–1500 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.09 (3H, s, C-18-H_3), 1.15–2.66 (11H, m), 2.69–2.73 (2H, m, C-6-H_2), 6.44 (1H, d, J=2.7 Hz, C-4-H), 6.52 (1H, dd, J=8.5 Hz and J=2.7 Hz, C-2-H), 7.07 (1H, d, J=8.5 Hz, C-1-H), 9.05 (1H, s, OH) and 10.63 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ 16.2 (q), 25.2, 25.4, 29.2, 32.4, 32.8 (all t), 38.0, 40.4 (all d), 40.5 (s), 41.4, 112.7,

114.5, 125.9 (all d), 129.5, 136.7, 154.8, 172.2 and 179.0 (all s). MS *m/z* (FAB+) 300.0 [100, $(M+H)^+$], 111.1 [36], 97.1 [60]; MS *m/z* (FAB−) 605.4 [20, $(M+2NBA)^-$], 451.3 [58, $(M-H+NBA)^-$], 298.2 [100, $(M-H)^-$], 188.1 [25]. HRMS *m/z* (FAB+) calcd for $C_{18}H_{22}NO_3$: 300.1600. Found: 300.1585. Anal. calcd for $C_{18}H_{21}NO_3.(CHCl_3)_{1/2}$ requires: C, 61.88; H, 6.04; N, 3.90. Found: C, 61.80; H, 5.85; N, 3.86.

3-*tert*-Butyl-dimethylsilyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (22). Imidazole (96 mg, 1.40 mmol) and *tert*-butyl-dimethylsilyl chloride (194 mg, 1.29 mmol) were added to a stirred solution of **21** (350 mg, 1.17 mmol) in DMF (20 mL) at room temperature, under an atmosphere of N_2. Evolution of the reaction was followed by TLC and after 2 h an additional 2 equivalents of imidazole and TBDMSCl were added. The resulting mixture was stirred for another 2 h and poured into water (150 mL). The organic layer was extracted with ethyl acetate (150 mL), washed with water (4×80 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **22** as a white solid. This was recrystallized from EtOH/H_2O to give white crystals (376 mg, 78%): mp 261–264 °C. IR (KBr) ν_{max} 3210, 3090, 2950–2860, 1730, 1680, 1610–1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.19 (6H, s, $Si(CH_3)_2$), 0.97 (9H, s, $C(CH_3)_3$), 1.23 (3H, s, C-18-H_3), 1.31–2.96 (11H, m), 2.80–2.87 (2H, m, C-6-H_2), 6.57 (1H, d, *J* = 2.5 Hz, C-4-H), 6.64 (1H, dd, *J* = 8.6 Hz and *J* = 2.5 Hz, C-2-H), 7.13 (1H, d, *J* = 8.6 Hz, C-1-H) and 7.72 (1H, s, NH); ^{13}C NMR ($CDCl_3$) δ −4.2 (2×q), 16.5 (q), 18.3 (s), 25.4 (t), 25.8 (3×q), 26.1, 29.5, 32.8, 32.9 (all t), 38.5 (d), 41.2 (s), 41.6, 42.7, 117.5, 119.7, 126.0 (all d), 131.5, 136.9, 153.5, 171.6 and 178.4 (all s). MS *m/z* (FAB+) 827.6 [50, $(2M+H)^+$], 414.2 [100, $(M+H)^+$], 356.2 [45, $(M-C(CH_3)_3)^+$], 72.9 [50]; MS *m/z* (FAB−) 412.2 [100, $(M-H)^-$]. HRMS *m/z* (FAB+) calcd for $C_{24}H_{36}NO_5Si$: 414.2464. Found: 414.2453. Anal. calcd for $C_{24}H_{35}NO_5Si$ requires: C, 69.69; H, 8.53; N, 3.39. Found: C, 69.60; H, 8.46; N, 3.40.

3-*tert*-Butyl-dimethylsilyl-*N*-allyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (23). Sodium hydride (60% dispersion in mineral oil, 35 mg, 870 μmol) was added to a stirred solution of **22** (300 mg, 725 μmol) in anhydrous DMF (15 mL) at 0 °C under an atmosphere of N_2. After evolution of hydrogen had ceased, allyl bromide (126 μL, 1.45 mmol) was added. The reaction mixture was stirred at room temperature for 7 h and poured into water (50 mL). The resulting solution was extracted into ethyl acetate (2×50 mL) and the organic layer washed with brine (4×25 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was purified by flash chromatography using chloroform as eluent to give **23** as a creamy oil (302 mg, 92%): IR (KBr) ν_{max} 2930–2860, 1725, 1676, 1610–1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.19 (6H, s, $Si(CH_3)_2$), 0.98 (9H, s, $C(CH_3)_3$), 1.19 (3H, s, C-18-H_3), 1.29–3.02 (11H, m), 2.80–2.86 (2H, m, C-6-H_2), 4.37 (2H, m, N–CH_2), 5.13 (1H, m, C-3′-Ha), 5.17 (1H, m, C-3′-Hb), 5.74–5.85 (1H, m, C-2′-H), 6.56 (1H, d, *J* = 2.7 Hz, C-4-H), 6.64 (1H, dd, *J* = 8.3 Hz and *J* = 2.7 Hz, C-2-H) and 7.13 (1H, d, *J* = 8.3 Hz, C-1-H). MS *m/z* (FAB+) 454.3 [100, $(M+H)^+$], 396.2 [35, $(M+H-C(CH_3)_3)^+$], 72.9 [54]; MS *m/z* (FAB−) 606.3 [32, $(M+NBA)^-$], 452.2 [100, $(M-H)^-$], 412.2 [56, $(M-H-C_3H_4)^-$]. HRMS *m/z* (FAB+) calcd for $C_{27}H_{40}NO_5Si$: 454.2777. Found 454.2760.

3-Hydroxy-*N*-ethyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (25). White solid (183 mg, 50%), washed in acetone to give a white powder (121 mg, 33%): mp 306–308 °C. IR (KBr) ν_{max} 3450, 2915–2860, 1715, 1655, 1610–1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.11 (3H, t, *J* = 7.0 Hz, C-2′-H_3), 1.16 (3H, s, C-18-H_3), 1.22–2.98 (11H, m), 2.81–2.87 (2H, m, C-6-H_2), 3.82 (2H, m, N–CH_2), 4.62 (1H, s, OH), 6.57 (1H, d, *J* = 2.7 Hz, C-4-H), 6.66 (1H, dd, *J* = 8.6 Hz and *J* = 2.7 Hz, C-2-H) and 7.17 (1H, d, *J* = 8.6 Hz, C-1-H). MS *m/z* (FAB+) 328.2 [100, $(M+H)^+$]. HRMS *m/z* (FAB+) calcd for $C_{20}H_{26}NO_3$: 328.1913. Found: 328.1906. Anal. calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 72.90; H, 7.68; N, 4.09.

3-Hydroxy-*N*-propyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (26). White solid (256 mg, 81%). For analysis, a sample was recrystallized from MeOH to give colorless crystals: mp 183–186 °C. IR (KBr) ν_{max} 3445, 3050, 2940–2860, 1725, 1655, 1585–1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.90 (3H, t, *J* = 7.4 Hz, C-3′-H_3), 1.17 (3H, s, C-18-H_3), 1.30–2.98 (13H, m), 2.82–2.86 (2H, m, C-6-H_2), 3.64–3.80 (2H, m, N–CH_2), 4.73 (1H, s, OH), 6.58 (1H, d, *J* = 2.7 Hz, C-4-H), 6.66 (1H, dd, *J* = 8.6 Hz and *J* = 2.7 Hz, C-2-H) and 7.17 (1H, d, *J* = 8.6 Hz, C-1-H); ^{13}C NMR ($CDCl_3$) δ 11.4, 16.6 (all q), 21.3 (t), 25.6 (d), 25.8, 29.6, 33.6, 33.7 (all t), 38.7, 40.3 (all d), 41.5 (s), 41.6 (t), 42.5, 113.0, 115.0, 126.3 (all d), 131.1, 137.4, 153.7, 171.8 and 178.6 (all s). MS *m/z* (FAB+) 342.3 [100, $(M+H)^+$], 111.2 [23], 97.2 [45]; MS *m/z* (FAB−) 494.4 [43, $(M+NBA)^-$], 340.3 [100, $(M-H)^-$]. HRMS *m/z* (FAB+) calcd for $C_{21}H_{28}NO_3$: 342.2069. Found: 342.2076. Anal. calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.90; H, 7.98; N, 4.20.

3-Hydroxy-*N*-butyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (27). White solid (361 mg, 94%), recrystallized from MeOH to give colorless needles (242 mg, 63%): mp 212–214 °C [lit.[18] (MeOH) 210–212 °C]. IR (KBr) ν_{max} 3445, 2940–2870, 1715, 1655, 1585–1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.92 (3H, m, C-4′-H_3), 1.16 (3H, s, C-18-H_3), 1.26–2.99 (15H, m), 2.81–2.88 (2H, m, C-6-H_2), 3.75 (2H, m, N–CH_2), 4.75 (1H, s, OH), 6.58 (1H, d, *J* = 2.7 Hz, C-4-H), 6.66 (1H, dd, *J* = 8.6 Hz and *J* = 2.7 Hz, C-2-H) and 7.17 (1H, d, *J* = 8.6 Hz, C-1-H); ^{13}C NMR ($CDCl_3$) δ 13.7, 16.5 (all q), 20.1, 25.5, 25.7, 29.4, 30.0, 33.5, 33.7 (all t), 38.6 (d), 39.8 (t), 40.2 (d), 41.4 (s), 42.4, 112.9, 114.9, 126.2 (all d), 131.1, 137.3, 153.5, 171.5 and 178.4 (all s). MS *m/z* (FAB+) 356.2 [100, $(M+H)^+$]; MS *m/z* (FAB−) 508.2 [35, $(M+NBA)^-$], 354.2 [100, $(M-H)^-$]. HRMS *m/z* (FAB+) calcd for $C_{22}H_{30}NO_3$: 356.2226. Found: 356.2225. Anal. calcd for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.20; H, 8.21; N, 3.88.

3-Hydroxy-*N*-pentyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (28). White solid (347 mg, 83%). For analysis, a sample was recrystallized from MeOH to give

white crystals: mp 181–184 °C. IR (KBr) ν_{max} 3445, 2955–2870, 1715, 1660, 1610–1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.89 (3H, t, $J=7.4$ Hz, C-5′-H_3), 1.16 (3H, s, C-18-H_3), 1.20–2.98 (17H, m), 2.81–2.86 (2H, m, C-6-H_2), 3.65–3.82 (2H, m, N-CH_2), 4.77–4.79 (1H, m, OH), 6.58 (1H, d, $J=2.7$ Hz, C-4-H), 6.65 (1H, dd, $J=8.2$ Hz and $J=2.7$ Hz, C-2-H) and 7.17 (1H, d, $J=8.2$ Hz, C-1-H); ^{13}C NMR ($CDCl_3$) δ 14.1, 16.6 (all q), 22.5, 25.6, 25.8, 27.7, 29.1, 29.7, 33.7, 33.8 (all t), 38.7 (d), 40.2 (t), 40.3 (d), 41.5 (s), 42.5, 113.0, 115.0, 126.3 (all d), 131.2, 137.4, 153.6, 171.7 and 178.5 (all s). MS m/z (FAB+) 739.1 [50, $(2M+H)^+$], 523.0 [20, $(M+H+NBA)^+$], 370.1 [100, $(M+H)^+$]; MS m/z (FAB−) 737.6 [20, $(2M-H)^-$], 522.4 [30, $(M+NBA)^-$], 368.3 [100, $(M-H)^-$]. HRMS m/z (FAB+) calcd for $C_{23}H_{32}NO_3$: 370.2382. Found: 370.2394. Anal. calcd for $C_{23}H_{31}NO_3$: C, 74.96; H, 8.46; N, 3.79. Found: C, 74.90; H, 8.38; N, 3.73.

3-Hydroxy-*N*-hexyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (29). White solid (384 mg, 88%), recrystallized from MeOH to give white crystals (263 mg, 60%): mp 157–159 °C. IR (KBr) ν_{max} 3435, 2930–2865, 1715, 1660, 1585–1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.87 (3H, t, $J=6.8$ Hz, C-6′-H_3), 1.16 (3H, s, C-18-H_3), 1.23–2.98 (19H, m), 2.81–2.87 (2H, m, C-6-H_2), 3.74 (2H, m, N–CH_2), 4.68 (1H, s, OH), 6.58 (1H, d, $J=2.5$ Hz, C-4-H), 6.66 (1H, dd, $J=8.4$ Hz and $J=2.5$ Hz, C-2-H) and 7.17 (1H, d, $J=8.4$ Hz, C-1-H); ^{13}C NMR ($CDCl_3$) δ 14.0, 16.5 (all q), 22.5, 25.5, 25.6, 26.5, 27.8, 29.4, 31.4, 33.5, 33.6 (all t), 38.5 (d), 40.1 (t), 40.1 (d), 41.3 (s), 42.3, 112.8, 114.8, 126.2 (all d), 131.0, 137.2, 153.5, 171.6 and 178.4 (s). MS m/z (FAB+) 767.6 [48, $(2M+H)^+$], 384.3 [100, $(M+H)^+$]; MS m/z (FAB−) 382.2 [100, $(M-H)^-$]. HRMS m/z (FAB+) calcd for $C_{24}H_{34}NO_3$: 384.2539. Found: 384.2535. Anal. calcd for $C_{24}H_{33}NO_3$: C, 75.16; H, 8.67; N, 3.65. Found: C, 75.40; H, 8.65; N, 3.71.

3-Hydroxy-*N*-(4′-bromobutyl)-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (30). White solid (146 mg, 84%), recrystallized from MeOH to give white crystals (98 mg, 57%): mp 165–167 °C. IR (KBr) ν_{max} 3450, 2910–2860, 1715, 1660, 1610–1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.18 (3H, s, C-18-H_3), 1.29–3.01 (15H, m), 2.82–2.88 (2H, m, C-6-H_2), 3.42 (2H, t, $J=6.6$ Hz, C-4′-H_2), 3.72–3.87 (2H, m, N–CH_2), 4.63 (1H, s, OH), 6.58 (1H, d, $J=2.3$ Hz, C-4-H), 6.66 (1H, dd, $J=8.5$ Hz and $J=2.3$ Hz, C-2-H) and 7.17 (1H, d, $J=8.5$ Hz, C-1-H); ^{13}C NMR (DMSO-d_6) δ 17.0 (q), 25.9, 26.1, 27.1, 29.9, 30.5, 33.5, 33.9, 34.1 (all t), 39.0 (d), 39.4 (t), 40.6 (d), 41.9 (s), 42.8, 113.3, 115.3, 126.6 (all d), 131.5, 137.7, 153.9, 171.9 and 178.8 (all s). MS m/z (FAB+) 869.2 [64], 587.1 [46, $(M+H+NBA)^+$], 434.1 [100, $(M+H)^+$]. HRMS m/z (FAB+) calcd for $C_{22}H_{29}BrNO_3$: 434.1331 and for $C_{22}H_{29}{}^{81}BrNO_3$: 436.1310. Found 434.1282 and 436.1287. Anal. calcd for $C_{22}H_{28}BrNO_3$: C, 60.83; H, 6.50; N, 3.22. Found: C, 61.30; H, 6.60; N, 3.17.

3-Hydroxy-*N*-cyclopropylmethyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (31). White solid (356 mg, 89%), recrystallized from MeOH to give colorless crystals (254 mg, 64%): mp 238–240 °C. IR (KBr) ν_{max} 3440, 2940–2865, 1715, 1655, 1610–1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.29–0.34 (2H, m, C-3′-H_2), 0.40–0.45 (2H, m, C-4′-H_2), 1.13 (1H, m, C-2′-H), 1.19 (3H, s, C-18-H_3), 1.30–3.02 (11H, m), 2.82–2.89 (2H, m, C-6-H_2), 3.66 (2H, m, N–CH_2), 4.70 (1H, s, OH), 6.58 (1H, d, $J=2.7$ Hz, C-4-H), 6.66 (1H, dd, $J=8.4$ Hz and $J=2.7$ Hz, C-2-H) and 7.17 (1H, d, $J=8.4$ Hz, C-1-H); ^{13}C NMR ($CDCl_3$) δ 3.9, 4.0 (all t), 10.5 (d), 16.9 (q), 26.0, 26.1, 29.9, 31.1, 34.0 (all t), 39.0, 40.6 (all d), 41.9 (s), 42.8 (d), 44.6 (t), 113.3, 115.3, 126.6 (all d), 131.6, 137.7, 154.0, 172.2 and 179.1 (all s). MS m/z (FAB+) 707.3 [29, $(2M+H)^+$], 507.1 [72, $(M+H+NBA)^+$], 354.1 [100, $(M+H)^+$]; MS m/z (FAB−) 505.2 [32, $(M-H+NBA)^-$], 352.1 [100, $(M-H)^-$]. HRMS m/z (FAB+) calcd for $C_{22}H_{28}NO_3$: 354.2069. Found 354.2069. Anal. calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.70; H, 7.55; N, 3.88.

3-Hydroxy-*N*-(1″-pyridin-3″-ylmethyl)-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (32). Creamy solid (141 mg, 91%). For analysis, a sample was washed in hot ethyl acetate to give a white powder: mp 199–223 °C. IR (KBr) ν_{max} 3380, 2940–2865, 1720, 1670, 1610–1500 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.11 (3H, s, C-18-H_3), 1.14–2.94 (11H, m), 2.67–2.75 (2H, m, C-6-H_2), 4.82 (1H, d, $J=14.8$ Hz, N-C$H_A$$H_B$), 4.87 (1H, d, $J=14.8$ Hz, N-C$H_A$$H_B$), 6.44 (1H, d, $J=2.3$ Hz, C-4-H), 6.52 (1H, dd, $J=8.5$ Hz and $J=2.3$ Hz, C-2-H), 7.07 (1H, d, $J=8.5$ Hz, C-1-H), 7.33 (1H, dd, $J=7.8$ Hz, $J=4.7$ Hz, C-5″-H), 7.59 (1H, m, C-4″-H), 8.42–8.47 (2H, m, C-2″-H and C-6″-H) and 9.05 (1H, s, OH). MS m/z (FAB+) 391.2 [88, $(M+H)^+$], 156.1 [40], 135.1 [46], 119.1 [48], 95.1 [70]; MS m/z (FAB−) 542.3 [50, $(M-H+NBA)^-$], 389.3 [100, $(M-H)^-$], 276.1 [43], 258.1 [37], 195.1 [42], 124.1 [34], 92.0 [27]. HRMS m/z (FAB+) calcd for $C_{24}H_{27}N_2O_3$: 391.2022. Found 391.2019.

3-Hydroxy-*N*-(4″-*tert*-butyl-benzyl)-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (33). Creamy solid (550 mg), recrystallized from MeOH to give white flaky crystals (448 mg, 87%): mp 128–130 °C. IR (KBr) ν_{max} 3415, 2955–2870, 1725, 1655, 1610–1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.16 (3H, s, C-18-H_3), 1.28 (9H, s, $C(CH_3)_3$), 1.30–3.02 (15H, m), 2.81–2.87 (2H, m, C-6-H_2), 4.77 (1H, s, OH), 4.88 (1H, d, $J=14.0$ Hz, N-C$H_A$$H_B$), 4.95 (1H, d, $J=14.0$ Hz, N-C$H_A$$H_B$), 6.57 (1H, d, $J=2.7$ Hz, C-4-H), 6.65 (1H, dd, $J=8.4$ Hz and $J=2.7$ Hz, C-2-H), 7.16 (1H, d, $J=8.4$ Hz, C-1-H) and 7.24–7.32 (4H, m, C-2″-H, C-3″-H, C-5″-H and C-6″-H); ^{13}C NMR ($CDCl_3$) δ 16.9 (q), 25.9, 26.1, 29.9 (t), 31.7 (3×q), 34.0 (×2) (all t), 34.9 (s), 39.0, 40.4 (all d), 41.9 (s), 42.8 (d), 43.3 (t), 113.3, 115.3, 125.5 (2×), 126.6, 128.3 (2×) (all d), 131.4, 134.4, 137.7, 150.3, 153.9, 172.0 and 178.8 (all s). MS m/z (FAB+) 891.4 [80, $(2M+H)^+$], 599.2 [35, $(M+H+NBA)^+$], 446.2 [100, $(M+H)^+$]; MS m/z (FAB−) 889.5 [42, $(2M-H)^-$], 751.4 [87, $(M+2NBA)^-$], 598.3 [30, $(M+NBA)^-$], 444.2 [100, $(M-H)^-$]. HRMS m/z (FAB+) calcd for $C_{29}H_{35}NO_3$: 445.2617. Found 445.2618. Anal. calcd for $C_{29}H_{35}NO_3.(H_2O)_{1/4}$: C, 77.39; H, 7.95; N, 3.11. Found: C, 77.40; H, 7.67; N, 3.19.

3-Hydroxy-*N*-benzyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (34). White solid (170 mg, 91%), washed

with hot MeOH to give a white precipitate (122 mg, 65%): mp 298–301 °C. IR (KBr) ν_{max} 3430, 2950–2890, 1720, 1655, 1610–1505 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.12 (3H, s, C-18-H_3), 1.18–2.92 (11H, m), 2.68–2.75 (2H, m, C-6-H_2), 4.79 (1H, d, J = 14.8 Hz, N-C$H_A$$H_B$), 4.85 (1H, d, J = 14.8 Hz, N-C$H_A$$H_B$), 6.45 (1H, d, J = 2.3 Hz, C-4-H), 6.53 (1H, dd, J = 8.5 Hz and J = 2.3 Hz, C-2-H), 7.07 (1H, d, J = 8.5 Hz, C-1-H), 7.17–7.32 (5H, m, C_6H_5) and 9.05 (1H, s, OH); ^{13}C NMR (DMSO-d_6) δ 16.3 (q), 25.2 (2×), 29.1, 32.9, 33.5 (all t), 38.0, ~39 (under solvent peaks) (all d), 41.0 (s), 41.7 (d), 42.3 (t), 112.7, 114.5, 125.8, 126.6, 126.8 (2×), 128.1 (2×) (all d), 129.4, 136.7, 137.4, 154.8, 171.2 and 178.0 (all s). MS m/z (FAB+) 390.3 [30, $(M+H)^+$], 133.2 [43], 111.2 [57], 97.2 [100]. HRMS m/z (FAB+) calcd for $C_{25}H_{28}NO_3$: 390.2069. Found 390.2062. Anal. calcd for $C_{25}H_{27}NO_3.(H_2O)_{1/2}$: C, 75.35; H, 7.08; N, 3.51. Found: C,75.60; H, 7.01; N, 3.34.

3-Hydroxy-*N*-allyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (35). Tetrabutyl ammonium fluoride hydrate (183 mg, 701 μmol) was added to a stirred solution of **23** (265 mg, 584 μmol) in THF (10 mL) at room temperature, under an atmosphere of N_2. After stirring for 2 h, another 1.2 equiv of TBAF were added to enable completion of the reaction. After another 5 h, the mixture was poured into water (40 mL), acidified with HCl 5M, and the white precipitate formed was filtered, washed and air dried to give a white powder (172 mg, 87%). Purification of the crude product by recrystallization from ethyl acetate gave **35** as white crystals (114 mg, 58%): mp 246–248 °C [lit.[18] (MeOH) 238–240 °C]. IR (KBr) ν_{max} 3445, 2920–2860, 1720, 1660, 1610–1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.18 (3H, s, C-18-H_3), 1.30–3.02 (11H, m), 2.82–2.87 (2H, m, C-6-H_2), 4.37 (2H, m, N–CH_2), 4.72 (1H, s, OH), 5.13 (1H, m, C-3′-Ha), 5.17 (1H, m, C-3′-Hb), 5.75–5.85 (1H, m, C-2′-H), 6.58 (1H, d, J = 2.7 Hz, C-4-H), 6.65 (1H, dd, J = 8.3 Hz and J = 2.7 Hz, C-2-H) and 7.17 (1H, d, J = 8.3 Hz, C-1-H). MS m/z (FAB+) 340.2 [100, $(M+H)^+$]; MS m/z (FAB−) 491.1 [50, $(M-H+NBA)^-$], 338.1 [100, $(M-H)^-$]. HRMS m/z (FAB+) calcd for $C_{21}H_{26}NO_3$: 340.1913. Found 340.1916. Anal. calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 73.90; H, 7.37; N, 4.11.

3-Sulfamoyloxy-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (36). The crude product was washed with boiling acetone to give a white solid (56 mg, 44%): mp 242–244 °C. IR (KBr) ν_{max} 3250, 3090, 2940–2850, 1690, 1695, 1640–1560, 1370, 1170 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.10 (3H, s, C-18-H_3), 1.19–2.72 (11H, m), 2.81–2.85 (2H, m, C-6-H_2), 6.98 (1H, d, J = 2.3 Hz, C-4-H), 7.03 (1H, dd, J = 8.6 Hz and J = 2.3 Hz, C-2-H), 7.38 (1H, d, J = 8.6 Hz, C-1-H), 7.91 (2H, s, NH_2) and 10.65 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ 16.2 (q), 25.0 (2×), 29.0, 32.4, 32.7 (all t), 37.5, 40.3 (all d), 40.5 (s), 42.1, 119.2, 121.5, 126.4 (all d), 137.5, 137.6, 147.8, 172.1 and 178.9 (all s). MS m/z (FAB+) 379.3 [94, $(M+H)^+$], 157.2 [32], 133.2 [56], 97.2 [100]; MS m/z (FAB−) 531.2 [37, $(M+NBA)^-$], 377.2 [100, $(M-H)^-$]. HRMS m/z (FAB+) calcd for $C_{18}H_{23}N_2O_5S$: 379.1328. Found 379.1331. Anal. calcd for $C_{18}H_{22}N_2O_5S$: C, 57.13; H, 5.86; N, 7.40. Found: C, 56.80; H, 5.83; N, 7.19.

3-Sulfamoyloxy-*N*-ethyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (38). The crude product was recrystallized from ethyl acetate/hexane (1:2) to give creamy crystals (72 mg, 83%): mp 215–217 °C. IR (KBr) ν_{max} 3415, 3305, 2970–2870, 1715, 1665, 1375, 1190 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.11 (3H, t, J = 7.0 Hz, C-2′-H_3), 1.17 (3H, s, C-18-H_3), 1.24–2.99 (11H, m), 2.88–2.95 (2H, m, C-6-H_2), 3.74–3.88 (2H, m, N-CH_2), 4.89 (2H, s, NH_2), 7.06 (1H, d, J = 2.4 Hz, C-4-H), 7.12 (1H, dd, J = 8.5 Hz and J = 2.4 Hz, C-2-H) and 7.33 (1H, d, J = 8.5 Hz, C-1-H). MS m/z (FAB+) 813.2 [40, $(2M+H)^+$], 560.1 [70, $(M+H+NBA)^+$], 407.1 [100, $(M+H)^+$]; MS m/z (FAB−) 811.4 [72, $(2M-H)^-$], 712.3 [47, $(M+2NBA)^-$], 405.1 [100, $(M-H)^-$]. HRMS m/z (FAB+) calcd for $C_{20}H_{27}N_2O_5S$: 407.1641. Found 407.1645.

3-Sulfamoyloxy-*N*-propyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (39). The crude product was purified by flash chromatography with chloroform/acetone (95:5) as eluent to give a white solid (107 mg, 87%). An analytical sample was recrystallized from acetone/hexane (1:2) to give white crystals: mp 202–204 °C. IR (KBr) ν_{max} 3365, 3255, 3095, 2965–2880, 1710, 1660, 1600–1500, 1380, 1180 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.90 (3H, t, J = 7.4 Hz, C-3′-H_3), 1.17 (3H, s, C-18-H_3), 1.32–3.00 (13H, m), 2.88–2.93 (2H, m, C-6-H_2), 3.64–3.80 (2H, m, N–CH_2), 4.90 (2H, s, NH_2), 7.06 (1H, d, J = 2.5 Hz, C-4-H), 7.11 (1H, dd, J = 8.4 Hz and J = 2.5 Hz, C-2-H) and 7.33 (1H, d, J = 8.4 Hz, C-1-H); ^{13}C NMR ($CDCl_3$) δ 11.2, 16.5 (all q), 21.2, 25.4, 25.5, 29.4, 33.6, 33.7 (all t), 38.3, 40.5 (all d), 41.4 (s), 41.5 (t), 42.7, 119.0, 121.5, 126.4 (all d), 138.0, 138.2, 148.1, 171.1 and 178.0 (all s). MS m/z (FAB+) 421.0 [100, $(M+H)^+$], 109.0 [52], 97.0 [45], 81.0 [74, $(SO_2NH_2+H)^+$], 67.0 [60]; MS m/z (FAB−) 573.3 [34, $(M+NBA)^-$], 419.3 [100, $(M-H)^-$]. HRMS m/z (FAB+) calcd for $C_{21}H_{29}N_2O_5S$: 421.1797. Found 421.1800. Anal. calcd for $C_{21}H_{28}N_2O_5S$: C, 59.98; H, 6.71; N, 6.66. Found: C, 60.00; H, 6.60; N, 6.49.

3-Sulfamoyloxy-*N*-butyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (40). The crude product was recrystallized from acetone/hexane (1:2) to give white crystals (78 mg, 71%): mp 194–196 °C. IR (KBr) ν_{max} 3335, 3250, 2940–2870, 1710, 1650, 1385, 1190 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.92 (3H, t, J = 7.2 Hz, C-4′-H_3), 1.17 (3H, s, C-18-H_3), 1.25–2.99 (15H, m), 2.88–2.92 (2H, m, C-6-H_2), 3.67–3.81 (2H, m, N–CH_2), 4.91 (2H, s, NH_2), 7.06 (1H, d, J = 2.3 Hz, C-4-H), 7.12 (1H, dd, J = 8.7 Hz and J = 2.3 Hz, C-2-H) and 7.34 (1H, d, J = 8.7 Hz, C-1-H). MS m/z (FAB+) 869.2 [78, $(2M+H)^+$], 588.1 [78, $(M+H+NBA)^+$], 435.1 [100, $(M+H)^+$]; MS m/z (FAB−) 587.2 [32, $(M+NBA)^-$], 433.2 [100, $(M-H)^-$]. HRMS m/z (FAB+) calcd for $C_{22}H_{31}N_2O_5S$: 435.1954. Found 435.1960. Anal. calcd for $C_{22}H_{30}N_2O_5S$: C, 60.81; H, 6.96; N, 6.45. Found: C, 60.50; H, 6.86; N, 6.26.

3-Sulfamoyloxy-*N*-pentyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (41). The crude product was purified by flash chromatography with chloroform/acetone (95:5) as eluent to give a white foam (111 mg, 92%). An analytical sample was recrystallized from ethyl acetate/hexane (1:2) to give white crystals: mp 159–161 °C. IR (KBr) ν_{max} 3345, 3255, 3095, 2930–2870, 1720, 1655,

1600–1500, 1385, 1190 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.89 (3H, t, $J=7.4$ Hz, C-5′-H_3), 1.17 (3H, s, C-18-H_3), 1.21–2.98 (17H, m), 2.90–2.94 (2H, m, C-6-H_2), 3.66–3.81 (2H, m, N–CH_2), 4.94 (2H, s, NH_2), 7.06 (1H, d, $J=2.5$ Hz, C-4-H), 7.11 (1H, dd, $J=8.6$ Hz and $J=2.5$ Hz, C-2-H) and 7.33 (1H, d, $J=8.6$ Hz, C-1-H); ^{13}C NMR ($CDCl_3$) δ 13.9, 16.4 (all q), 22.3, 25.3 (2×), 27.5, 29.0, 29.3, 33.5 (2×) (all t), 38.1 (d), 40.0 (t), 40.2 (d), 41.2 (s), 42.5, 119.0, 121.6, 126.5 (all d), 138.0, 138.1, 147.8, 171.3 and 178.1 (all s). MS *m/z* (FAB+) 449.0 [100, $(M+H)^+$], 97.0 [46]; MS *m/z* (FAB−) 447.3 [100, $(M-H)^-$]. HRMS *m/z* (FAB+) calcd for $C_{23}H_{33}N_2O_5S$: 449.2110. Found 449.2111. Anal. calcd for $C_{23}H_{32}N_2O_5S$: C, 61.58; H, 7.19; N, 6.24. Found: C, 61.70; H, 7.30; N, 6.22.

3-Sulfamoyloxy-*N*-hexyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (42). The crude product was purified by flash chromatography with chloroform/acetone (9:1) as eluent to give a white foam (127 mg, 81%). This was recrystallized from ethyl acetate/hexane (1:2) to give colorless crystals (77 mg, 49%): mp 112–115 °C. IR (KBr) ν_{max} 3310, 3190, 2925–2860, 1720, 1655, 1390, 1185 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, $J=6.6$ Hz, C-6′-H_3), 1.19 (3H, s, C-18-H_3), 1.24–2.99 (19H, m), 2.88–2.94 (2H, m, C-6-H_2), 3.66–3.82 (2H, m, N-CH_2), 4.91 (2H, s, NH_2), 7.06 (1H, d, $J=2.5$ Hz, C-4-H), 7.11 (1H, dd, $J=8.6$ Hz and $J=2.5$ Hz, C-2-H) and 7.33 (1H, d, $J=8.6$ Hz, C-1-H); ^{13}C NMR ($CDCl_3$) δ 14.1, 16.6 (all q), 22.6, 25.5, 26.7, 27.9, 29.5, 31.5 (2×), 33.6, 33.7 (all t), 38.2 (d), 40.2 (t), 40.3 (d), 41.4 (s), 42.6, 119.2, 121.7, 126.6 (all d), 138.1, 138.3, 147.9, 171.5 and 178.2 (all s). MS *m/z* (FAB+) 925.3 [64, $(2M+H)^+$], 463.1 [100, $(M+H)^+$]; MS *m/z* (FAB−) 1077.5 [70, $(2M+NBA)^-$], 615.3 [70, $(M+NBA)^-$], 462.2 [100, M^-]. HRMS *m/z* (FAB+) calcd for $C_{24}H_{35}N_2O_5S$: 463.2267. Found 463.2263. Anal. calcd for $C_{24}H_{34}N_2O_5S$: C, 62.31; H, 7.41; N, 6.06. Found: C, 62.60; H, 7.43; N, 6.20.

3-Sulfamoyloxy-*N*-(4′-bromobutyl)-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (43). The crude product was purified by flash chromatography with chloroform/acetone (9:1) as eluent to give a white foam (154 mg, 100%). This was recrystallized from ethyl acetate/hexane (1:2) to give white crystals (125 mg, 81%): mp 162–165 °C. IR (KBr) ν_{max} 3380, 3260, 2945–2870, 1720, 1650, 1565–1495, 1388, 1180 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.18 (3H, s, C-18-H_3), 1.22–3.00 (15H, m), 2.86–2.97 (2H, m, C-6-H_2), 3.42 (2H, t, $J=6.6$ Hz, C-4′-H_2), 3.79 (2H, m, N-CH_2), 4.89 (2H, s, NH_2), 7.06 (1H, d, $J=2.5$ Hz, C-4-H), 7.12 (1H, dd, $J=8.6$ Hz and $J=2.5$ Hz, C-2-H) and 7.33 (1H, d, $J=8.6$ Hz, C-1-H); ^{13}C NMR ($CDCl_3$) δ 16.6 (q), 25.4, 25.5, 26.7, 29.4, 30.1, 33.2, 33.5, 33.7 (all t), 38.2 (d), 39.1 (t), 40.3 (d), 41.4 (s), 42.6, 119.2, 121.7, 126.6 (all d), 138.1, 138.2, 147.9, 171.4 and 178.2 (all s). MS *m/z* (FAB+) 513.1 [100, $(M+H)^+$], 435.2 [46, $(M-Br+H)^+$]. HRMS *m/z* (FAB+) calcd for $C_{22}H_{30}BrN_2O_5S$: 513.1059 and for $C_{22}H_{30}{}^{81}BrN_2O_5S$: 515.1038. Found 513.1038 and 515.1038.

3-Sulfamoyloxy-N-(4′-chlorobutyl)-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (44). The crude mixture was purified by flash chromatography with chloroform/acetone (9:1) as eluent to give a white foam (66 mg) containing 58.4% of **44** and 41.6% of **43** (% area from HPLC run). The compounds were separated by preparative HPLC (elution with MeOH/H_2O 68:32) to give **44** as a white solid: mp 162–164 °C. IR (KBr) ν_{max} 3390, 3245, 2940–2865, 1720, 1645, 1560–1490, 1385, 1185 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.17 (3H, s, C-18-H_3), 1.28–3.00 (15H, m), 2.88–2.96 (2H, m, C-6-H_2), 3.54 (2H, t, $J=6.4$ Hz, C-4′-H_2), 3.79 (2H, m, N-CH_2), ~4–5 (2H, br s, NH_2), 7.06 (1H, d, J ~2 Hz, C-4-H), 7.11 (1H, dd, $J=8.5$ Hz and J~2 Hz, C-2-H) and 7.33 (1H, d, $J=8.6$ Hz, C-1-H). MS *m/z* (FAB+) 469.3 [100, $(M+H)^+$]; MS *m/z* (FAB−). 621.3 [40, $(M+NBA)^-$], 467.2 [100, $(M-H)^-$]. HRMS *m/z* (FAB+) calcd for $C_{22}H_{30}ClN_2O_5S$: 469.1564. Found 469.1540.

3-Sulfamoyloxy-*N*-cyclopropylmethyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (45). The crude product was recrystallized from acetone/hexane (1:2) to give white crystals (112 mg, 92%): mp 202–204 °C. IR (KBr) ν_{max} 3280, 2960, 1700, 1660, 1395, 1185 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.29–0.34 (2H, m, C-3′-H_2), 0.40–0.45 (2H, m, C4′-H_2), 1.08–1.16 (1H, m, C-1′-H), 1.19 (3H, s, C-18-H_3), 1.32–3.02 (11H, m), 2.88–2.96 (2H, m, C-6-H_2), 3.66 (2H, m, N–CH_2), 4.93 (2H, s, NH_2), 7.07 (1H, d, $J=2.5$ Hz, C-4-H), 7.12 (1H, dd, $J=8.6$ Hz and $J=2.5$ Hz, C-2-H) and 7.34 (1H, d, $J=8.6$ Hz, C-1-H). MS *m/z* (FAB+) 865.1 [55, $(2M+H)^+$], 586.1 [45, $(M+H+NBA)^+$], 433.0 [100, $(M+H)^+$]; MS *m/z* (FAB−) 431.2 [100, $(M-H)^-$]. HRMS *m/z* (FAB+) calcd for $C_{22}H_{29}N_2O_5S$: 433.1797. Found 433.1794. Anal. calcd for $C_{22}H_{28}N_2O_5S$: C, 61.09; H, 6.52; N, 6.48. Found: C, 61.00; H, 6.85; N, 5.91.

3-Sulfamoyloxy-*N*-(1″-pyridin-3″-ylmethyl)-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (46). The crude product was purified by flash chromatography with chloroform/acetone (8:2) as eluent to give a creamy powder (42 mg, 78%). This was recrystallized from acetone/hexane (1:2) to give colorless crystals (28 mg, 52%): mp 215–218 °C. IR (KBr) ν_{max} 3335, 3100–2850, 1720, 1675, 1590–1495, 1380, 1190 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.10 (3H, s, C-18-H_3), 1.15–2.97 (11H, m), 2.79–2.84 (2H, m, C-6-H_2), 4.81 (1H, d, $J=14.8$ Hz, N-C$H_A$$H_B$), 4.86 (1H, d, $J=14.8$ Hz, N-$CH_A$$H_B$), 6.96 (1H, d, $J=2.7$ Hz, C-4-H), 7.01 (1H, dd, $J=8.6$ Hz and $J=2.7$ Hz, C-2-H), 7.31 (1H, dd, $J=7.8$ Hz, $J=4.7$ Hz, C-5″-H), 7.36 (1H, d, $J=8.6$ Hz, C-1-H), 7.57 (1H, m, C-4″-H), 7.89 (2H, s, NH_2) and 8.41–8.44 (2H, m, C-2″-H and C-6″-H). MS *m/z* (FAB+) 470.3 [48, $(M+H)^+$], 133.2 [38], 111.2 [52], 97.1 [100]; MS *m/z* (FAB−) 622.3 [52, $(M+NBA)^-$], 468.3 [100, $(M-H)^-$], 276.2 [62], 198 [48], 139.1 [46], 93.1 [40]. HRMS *m/z* (FAB+) calcd for $C_{24}H_{28}N_3O_5S$: 470.1750. Found 470.1767. Anal. calcd for $C_{24}H_{27}N_3O_5S\cdot(H_2O)_{1/2}$: C, 60.03; H, 5.90; N, 8.78. Found: C, 60.00; H, 5.86; N, 8.57.

3-Sulfamoyloxy-*N*-(4″-*tert*-butyl-benzyl)-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (47). The crude product was recrystallized from ethyl acetate/hexane (1:2) to give white crystals (199 mg, 85%): mp 227–230 °C. IR (KBr) ν_{max} 3320, 3240, 2960–2870, 1720, 1660, 1385,

1180 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.16 (3H, s, C-18-H_3), 1.29 (9H, s, $C(CH_3)_3$), 1.30–3.02 (11H, m), 2.87–2.93 (2H, m, C-6-H_2), 4.87 (2H, s, NH_2), 4.87–4.96 (2H, m, N-CH_AH_B) 7.06 (1H, d, $J=2.5$ Hz, C-4-H), 7.11 (1H, dd, $J=8.6$ Hz and $J=2.5$ Hz, C-2-H) and 7.24–7.34 (5H, m, C-1-H, C-2″-H, C-3″-H, C-5″-H and C-6″-H); ^{13}C NMR ($CDCl_3$) δ 16.4 (q), 25.3 (2×), 29.3 (all t), 31.2 (3×q), 33.5 (2×) (all t), 34.4 (s), 38.0, 40.0 (all d), 41.3 (s), 42.5 (d), 42.8 (t), 119.0, 121.6, 125.1 (2×), 126.5, 127.8 (2×) (all d), 133.9, 137.9, 138.1, 147.8, 149.8, 171.2 and 178.1 (all s). MS *m/z* (FAB+) 1049.3 [70, $(2M+H)^+$], 525.1 [100, $(M+H)^+$]; MS *m/z* (FAB−) 1047.5 [80, $(2M-H)^-$], 523.2 [100, $(M-H)^-$]. HRMS *m/z* (FAB+) calcd for $C_{29}H_{37}N_2O_5S$: 525.2389. Found 525.2405.

3-Sulfamoyloxy-*N*-benzyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (48). The crude product was purified by flash chromatography with chloroform/acetone (9:1) as eluent to give a white powder (151 mg, 84%). This was recrystallized from acetone/hexane (1:2) to give white crystals (133 mg, 74%): mp 208–210 °C. IR (KBr) ν_{max} 3340, 3230, 3100–3050, 2950–2870, 1715, 1655, 1610–1495, 1385, 1195 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.13 (3H, s, C-18-H_3), 1.17–2.96 (11H, m), 2.81–2.87 (2H, m, C-6-H_2), 4.80 (1H, d, $J=14.6$ Hz, N-C$H_A$$H_B$), 4.86 (1H, d, $J=14.6$ Hz, N-$CH_A$$H_B$), 6.99 (1H, d, $J=2.3$ Hz, C-4-H), 7.04 (1H, dd, $J=8.4$ Hz and $J=2.3$ Hz, C-2-H), 7.19–7.40 (6H, m, C_6H_5 and C-1-H) and 7.92 (2H, s, NH_2). MS *m/z* (FAB+) 469.2 [100, $(M+H)^+$]; MS *m/z* (FAB−) 621.3 [38, $(M+NBA)^-$], 467.2 [100, $(M-H)^-$]. HRMS *m/z* (FAB+) calcd for $C_{25}H_{29}N_2O_5S$: 469.1797. Found 469.1789. Anal. calcd for $C_{25}H_{28}N_2O_5S$: C, 64.08; H, 6.02; N, 5.98. Found: C, 63.90; H, 6.12; N, 5.86.

3-Sulfamoyloxy-*N*-allyl-16,17-*seco*-estra-1,3,5(10)-triene-16,17-imide (49). The crude product was purified by flash chromatography with chloroform/acetone (9:1) as eluent to give a white foam (85 mg, 99%). This was recrystallized from acetone/hexane (1:2) to give white crystals (75 mg, 87%): mp 210–213 °C. IR (KBr) ν_{max} 3385, 3275, 2935–2870, 1715, 1670, 1600–1495, 1385, 1185 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.13 (3H, s, C-18-H_3), 1.25–2.89 (11H, m), 2.81–2.87 (2H, m, C-6-H_2), 4.23 (2H, m, N–CH_2), 5.01 (1H, m, C-3′-Ha), 5.05 (1H, m, C-3′-Hb), 5.69–5.79 (1H, m, C-2′-H), 6.99 (1H, d, $J=2.5$ Hz, C-4-H), 7.04 (1H, dd, $J=8.6$ Hz and $J=2.5$ Hz, C-2-H), 7.38 (1H, d, $J=8.6$ Hz, C-1-H) and 7.91 (2H, s, NH_2); ^{13}C NMR (DMSO-d_6) δ 16.3 (q), 24.8, 25.0, 29.0, 32.8, 33.5 (all t), 37.4, ∼39 (under solvent peaks) (all d), 40.9 (s), 41.1 (t), 42.0 (d), 115.6 (t), 119.2, 121.5, 126.4, 132.7 (all d), 137.5, 137.6, 147.8, 170.8 and 177.6 (s). MS *m/z* (FAB+) 837.4 [48, $(2M+H)^+$], 572.2 [68, $(M+H+NBA)^+$], 419.1 [100, $(M+H)^+$]; MS *m/z* (FAB−) 571.1 [30, $(M+NBA)^-$], 417.1 [100, $(M-H)^-$]. HRMS *m/z* (FAB+) calcd for $C_{21}H_{27}N_2O_5S$: 419.1641. Found 419.1635. Anal. calcd for $C_{21}H_{26}N_2O_5S$: C, 60.27; H, 6.26; N, 6.69. Found: C, 60.30; H, 6.32; N, 6.56.

3-Hydroxy-16,17-*seco*-estra-1,3,5(10)-triene-16,17-dioic acid (50). A solution of 3-benzyloxy-16,17-*seco*-estra-1,3,5(10)-triene-16,17-dioic acid **8** (270 mg, 661 μmol) in methanol (30 mL) was stirred in the presence of Pd/C (10%, 270 mg) under an atmosphere of hydrogen at 20 psi overnight. After filtration and evaporation of the filtrate, the crude product was recrystallized from ethyl acetate/toluene (1:20) to give **50** as creamy crystals (71 mg, 34%): mp 218–220 °C [lit.[19] (EtOH), 223–224 °C]. ^1H NMR (DMSO-d_6) 1.02 (3H, s, C-18-H_3), 1.1–2.7 (13H, m), 6.42 (1H, d, $J=2.4$ Hz, C-4-H), 6.51 (1H, dd, $J=8.7$ Hz and $J=2.4$ Hz, C-2-H), 7.06 (1H, d, $J=8.7$ Hz, C-1-H), 9.02 (1H, s, OH) and 12.12 (2H, br s, 2×CO_2H); ^{13}C NMR (acetone-d_6) 15.9 (q), 27.1, 27.8, 30.8, 36.6, 37.4 (all t), 42.4, 43.1, 43.9 (all d), 47.6 (s), 113.9, 115.7, 127.3 (all d), 131.2, 138.3, 156.2, 174.8 and 179.7 (all s). MS *m/z* (FAB+) 318.1 [100, M^+], 301.1 [75, $(M-OH)^+$], 272.1 [60, $(M-H-CO_2H)^+$], 213.1 [35, $(M-H-CO_2H-CH_2CO_2H)^+$]; MS *m/z* (FAB−) 317.2 [100, $(M-H)^-$].

3-Sulfamoyloxy-16,17-*seco*-estra-1,3,5(10)-triene-16,17-dioic acid anhydride (51). A concentrated solution of sulfamoyl chloride (10 equiv) in toluene was added to a solution of 3-hydroxy-16,17-*seco*-estra-1,3,5(10)-triene-16,17-dioic acid **50** (380 mg, 1.19 mmol) and imidazole (244 mg, 3.58 mmol) in anhydrous DMF (5 mL) at 0 °C under an atmosphere of N_2. The resulting mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with ethyl acetate (70 mL) and washed with brine (100 mL, then 4×50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo (water bath temperature ≤40 °C) to give a slightly wet white residue. This crude product was left to recrystallize from ethyl acetate/ether (1:3) in the refrigerator for a week to give some beige crystals (126 mg, 28%): mp 186–199 °C. An analytical sample was further recrystallized from ethyl acetate/ether (1:15) to give **51** as creamy crystals. ^1H NMR (DMSO-d_6) 1.0–3.5 (16H, m), 6.99 (1H, d, $J=2.4$ Hz, C-4-H), 7.04 (1H, dd, $J=8.5$ Hz and $J=2.4$ Hz, C-2-H), 7.38 (1H, d, $J=8.5$ Hz, C-1-H) and 7.92 (2H, s, NH_2). MS *m/z* (FAB+) 255.1 [55, $(M-OSO_2NH_2-CO)^+$], 173.1 [76], 97.0 [100, $(OSO_2NH_2+H)^+$], 58.9 [66]; MS *m/z* (FAB−) 532.1 [44, $(M+NBA)^-$], 378.0 [100, $(M-H)^-$]. HRMS *m/z* (FAB−) calcd for $C_{18}H_{20}NO_6S$: 378.1011. Found 378.1006. Anal. calcd for $C_{18}H_{21}NO_6S$: C, 56.98; H, 5.58; N, 3.69. Found: C, 57.00; H, 5.67; N, 3.68.

3-Sulfamoyloxy-16,17-*seco*-estra-1,3,5(10)-triene-16,17-dioic acid (52). A concentrated solution of sulfamoyl chloride (5 equiv) in toluene was added to a solution of 3-hydroxy-16,17-*seco*-estra-1,3,5(10)-triene-16,17-dioic acid **50** (334 mg, 1.05 mmol) and triethylamine (0.44 mL, 3.15 mmol) in anhydrous DMF (5 mL) at 0 °C under an atmosphere of N_2. The resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with brine (100 mL, then 4×50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo (water bath temperature ≤40 °C) to give a yellow syrup. This crude product was further purified by flash chromatography (ethyl acetate/hexane with 2% acetic acid, 1:1 to 4:1, gradient) to give **52** as a white residue (171 mg, 41%): IR (KBr) ν_{max} 3800–2500, 1710, 1500, 1390, 1190 cm^{-1}. ^1H NMR (DMSO-d_6) 1.03 (3H, s, C-18-H_3),

1.1–2.9 (13H, m), 6.95 (1H, d, $J=2.6$ Hz, C-4-H), 7.02 (1H, dd, $J=8.6$ Hz and $J=2.6$ Hz, C-2-H), 7.36 (1H, d, $J=8.6$ Hz, C-1-H), 7.90 (2H, s, NH_2) and 12.16 (2H, br s, $2\times CO_2H$). MS m/z (FAB+) 420.2 [90], 398.1 [98, $(M+H)^+$], 380.1 [100, $(M-OH)^+$]; MS m/z (FAB−) 396.2 [100, $(M-H)^-$]. HRMS m/z (FAB−) calcd for $C_{18}H_{24}NO_7S$: 398.1273. Found 398.1275.

3-Sulfamoyloxy-16,17-*seco*-estra-1,3,5(10)-triene-16,17-dioic acid dimethyl ester (53). Diazomethane generated from Diazald (217 mg, 1 mmol) in a Mini Diazald apparatus under standard conditions was allowed to condense onto a solution of **52** (50 mg, 0.13 mmol) in THF (10 mL). After 30 min of mixing at room temperature, the reaction mixture was evaporated to give **53** as a light yellow residue (50 mg, 93%): mp ~45 °C; IR (KBr) ν_{max} 3360, 3280, 3000–2860, 1730, 1500, 1390, 1190 cm^{-1}. ^1H NMR (DMSO-d_6) 1.08 (3H, s, C-18-H_3), 1.2–2.9 (13H, m), 3.59 (3H, s, CO_2Me), 3.60 (3H, s, CO_2Me), 6.96 (1H, d, $J\sim2$ Hz, C-4-H), 7.04 (1H, dd, $J=8$ Hz and $J\sim2$ Hz, C-2-H), 7.35 (1H, d, $J=8.7$ Hz, C-1-H) and 7.94 (2H, br s, NH_2). MS m/z (FAB+) 73.0 [100, $(CH_2CO_2Me)^+$]; MS m/z (FAB−) 438.1 [35], 424.1 [100, $(M-H)^-$], 297.0 [66, $(M-H-OMe-OSO_2NH_2)^-$], 269.0 [38, $(M-H-CO_2Me-OSO_2NH_2)^-$], 223.0 [95, $(M-2H-OMe-CO_2Me-OSO_2NH_2)^-$]. HRMS m/z (FAB+) calcd for $C_{20}H_{28}NO_7S$: 426.1586. Found 426.1572.

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