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Potent and Selective Steroidal Inhibitors of 17β-Hydroxysteroid Dehydrogenase Type 7, an Enzyme That Catalyzes the Reduction of the Key Hormones Estrone and Dihydrotestosterone

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17β-Hydroxysteroid dehydrogenase type 7 (17β-HSD7) catalyzes the reduction of estrone (E_1) into estradiol (E_2) and of dihydrotestosterone (DHT) into 5α-androstane-3β,17β-diol (3β-diol), therefore modulating the level of mitogenic estrogens and androgens in humans. By classical and parallel chemistry, we generated several 4-methyl-4-aza-5α-androstane derivatives differing in their C-17 substituent: 17β-formamide, 17β-benzamide, and 17β-tertiary amine. Best candidates in each category had demonstrated good inhibitory potency toward the conversion of E_1 into E_2 (IC_{50} = 189−451 nM) and also toward the conversion of DHT into 3β-diol (69−91% at 3 μM). Inhibition assays with 17β-HSD1, 17β-HSD5, 5α-reductase (5α-R) 1 and 5α-R2 revealed that 17β-HSD7 inhibitors with a 4-methyl-4-aza nucleus were also able to inhibit 5α-Rs but not the other enzymes tested. Two 4-aza-5α-androstane inhibitors were, however, selective and still showed good inhibition of 17β-HSD7. First selective and efficient inhibitors of 17β-HSD7 are now available for additional mechanistic and therapeutic studies.

Introduction

17β-Hydroxysteroid dehydrogenases (17β-HSDs[a]) play a crucial role in the biosynthesis of active androgens and estrogens in both steroidogenic and peripheral target tissues. They operate the conversion of 17-keto steroids to their active 17β-hydroxy-forms or vice versa, each member of the 17β-HSDs family showing different tissular distributions and having a preferred cofactor (NAD^+ or NADPH) and preferred substrates.[1] 17β-HSD7 was originally cloned in a rat corpus luteum cDNA library and identified as the prolactin receptor-associated protein[2] and was then cloned in mouse mammals gland epithelial cells and recognized as a 17β-HSD isoform.[3] The rodent enzyme was proven to efficiently reduce estrone (E_1) into estradiol (E_2), and its tissue-specific expression pattern suggests an important function in sustaining pregnancy, as well as a role in tissues prone to develop hormone-related cancers.[4] In humans, 17β-HSD7 is expressed in typical steroidogenic tissues such as testis and nonpregnant women's ovaries but also in the uterus, placenta, mammary glands, prostate, liver, kidney as well as in neural tissues[5] and in some cancerous cell lines, like CAMA-1, MCF-7, ZR-75-1, DU-145, and LNCaP.[5d,5e] It converts E_1 into the estrogen E_2, the most potent female hormone, and to the same extent also deactivates the powerful androgen dihydrotestosterone (DHT) into 5α-androstane-3β,17β-diol (3β-diol),[5c] an estrogen-receptor (ER) ligand (Figure 1).[6] 17β-HSD7 also functions as a zymosterone reductase and is thus involved in postsqualene cholesterogenesis.[7] Contrary to other mammalians in which 17β-HSD7 is obviously part of the pregnancy process (namely, in the rabbit[8] and marmoset monkey[9]), the precise role of human 17β-HSD7 is not clear. Because of its dual enzymatic activity and widespread distribution, the human enzyme seems to act as an intracrine regulator of steroid metabolism, increasing the concentration of estrogens in its surroundings. The impact of E_2 on the development of certain hormone-sensitive cancers is well-known, and the therapeutic use of an inhibitor of its biosynthesis represents a relevant strategy to counteract their proliferative effects.[10] Design of inhibitors targeting 17β-HSD7 is of interest, since it could help to better modulate the in situ formation of E_2 and thus better regulate its proliferative effect in ER^+ breast cancer cells. A 17β-HSD7 inhibitor could also help to maintain the level of DHT, an androgenic hormone with an antiproliferative effect on ER^+ cells.[11] Because of its localization at the end of the metabolic pathway of sex hormone formation, inhibiting 17β-HSD7 would not deplete the organism in any other family of steroids such as mineralocorticoids and glucocorticoids. Moreover, a selective 17β-HSD7 inhibitor would be a useful tool to better understand the biological role of this new steroidogenic enzyme.

A previous screening done with a series of 150 compounds belonging to different classes (natural hormones, anti-hormones, phytoestrogens, known inhibitors of other steroidogenic enzymes) permitted us to point out four C-19 steroids

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[a] Abbreviations: 17β-HSDs, 17β-hydroxysteroid dehydrogenases; 5α-Rs, 5α-reductases; NAD^+, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate reduced form; ER, estrogen receptor; E_1, estrone; E_2, estradiol; DHT, dihydrotestosterone; 3β-diol, 5α-androstane-3β,17β-diol; Δ^4-dione, 4-androstene-3,17-dione; A-dione, 5α-androstane-3,17-dione; T, testosterone; SAR, structure−activity relationship; IC_{50}, the half maximal inhibitory concentration; K_m, Michaelis−Menten constant; K_{cat}/K_m, the rate of catalytic efficiency; RT-PCR, reverse transcriptase polymerase chain reaction; HEK, human embryonic kidney; MEM, minimum essential medium; rt, room temperature.

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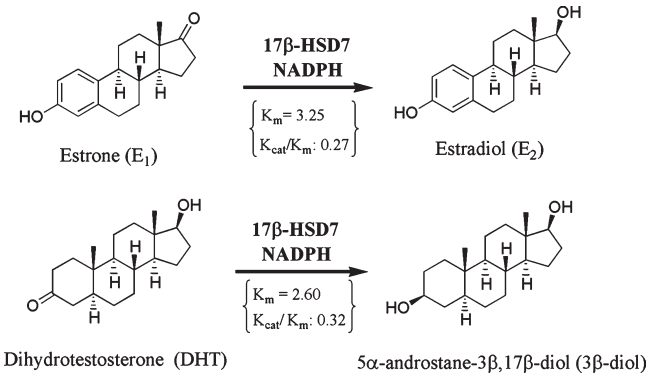


Figure 1. Principal reactions performed by human 17β-HSD7 in the presence of cofactor NADPH. The K_m value is expressed in μM, while the enzymatic efficiency (K_{cat}/K_m) is expressed in U mg^{-1} μM^{-1} (data from ref 5c).

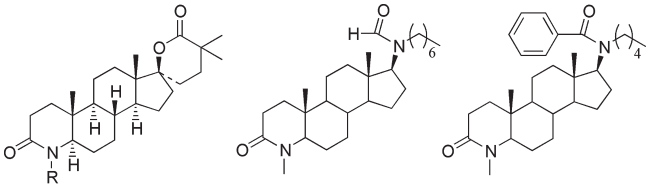


Figure 2. Lead compounds identified from a preliminary screening as inhibitors of 17β-HSD7 (E_1 to E_2 transformation). The stereochemistry of carbons 5, 8, 9, and 14 is shown only for compounds **1a** and **1b** but is the same for all other steroids.

(compounds **1a**, **1b**, **2**, and **3**) that were able to decrease the transformation of E_1 into E_2 in intact h17β-HSD7-transfected HEK-293 cells (Figure 2). Our preliminary study seems to demonstrate that a 4-aza-5α-androstane nucleus is an important structural feature and that its inhibitory potency is greatly improved by introducing a long alkylamide side chain (compounds **2** and **3**) or a dimethylated spiro-δ-lactone nucleus (compounds **1a** and **1b**) at position 17β.[12] This latter nucleus had been previously introduced on a C-18 steroid and proven to be an excellent inhibitor of human 17β-HSD5,[13] which is responsible for the transformation of androstenedione (Δ^4-dione) into testosterone (T) in peripheral tissues.[14] Furthermore, compound **2** is known as a good inhibitor of the conversion of T into DHT and Δ^4-dione into 5α-androstane-3,17-dione (A-dione) by both type 1 and type 2 5α-reductases (5α-Rs).[15] On the basis of these structural similarities between known inhibitors of steroidogenic enzymes and our lead compounds, our challenge will consist of developing efficient and selective inhibitors of 17β-HSD7. Efficiency will first be optimized by following various combinations of alkyl side chain length (7−12 carbons), amide, or amine moieties and also through the investigation of the inhibitory potency of substituted benzamide (derivatives of compounds **2** and **3**). Selectivity of 17β-HSD7 inhibitors will be assessed toward other steroidogenic enzymes, like 17β-HSD5 and 5α-Rs, but also toward 17β-HSD1 that catalyzes the conversion of E_1 into E_2 as well.

Results and Discussion

Chemical Synthesis. The preliminary structure−activity relationship (SAR) data concerning 17β-(*N*-alkylamido) derivatives seemed to converge toward an important parameter that is the length of the aliphatic side chain.[12] We therefore decided to further investigate the potential as inhibitors of 17β-HSD7 of steroid **2** analogues by determining the optimal length of the *N*-alkyl moiety. Compounds bearing five to eight side chain carbon atoms had already been synthesized as inhibitors of 5α-reductases by Li et al.,[15] whereas more hydrophobic analogues **10** and **11** were synthesized from commercially available testosterone (Scheme 1). The Rasmusson et al. method[16] afforded the 4-methyl-4-aza-5α-androstane-3,17-dione (**4**), which was further oxidized by pyridinium chlorochromate (PCC) to give the key intermediate **5** in moderate yield. The 17-keto steroid was next submitted to reductive amination by generating the imine that was then reduced by either sodium cyanoborohydride ($NaBH_3CN$) in a slightly acidic milieu or sodium borohydride ($NaBH_4$) to afford the 17β-amino steroids **6**−**9**. Because of the proximity of the angular methyl C-18, it was not possible to bring this reaction to completion, regardless of the reaction time or an excess of amine added. Furthermore, purification of compounds **6**−**9** by silica gel chromatography was difficult, resulting in moderate yields (44−75%) for this two-step sequence of reactions. Compounds **10** and **11** were next obtained by formylation of their precursors, compounds **7** and **8**, respectively, after previous activation of formic acid with dicyclohexylcarbodiimide (DCC) following a standard procedure.[15]

Further indications from our preliminary SAR study suggested that a benzamido derivative such as **3** could constitute an interesting family of 17β-HSD7 inhibitors.[12] To confirm our hypothesis, we proceeded with the synthesis of 17β-[(*N*-heptyl)arylamido] steroids **12**−**14** as well as 17β-[(*N*-heptyl)alkylamido] steroids **15**−**18**. The amine precursor **6** was either reacted with the corresponding acyl chloride or *O*-acylurea to provide compounds **12**−**18**. Both methods gave yields ranging between 66% and 80% except for compounds **15** and **18** where the bulky group was added less successfully in 51% and 41% yield, respectively.

To extend our SAR study, additional arylamido derivatives were obtained by parallel synthesis. A first library containing 27 members (compounds **19**−**45**) was obtained using peptide bond formation between amines **6**, **8**, and **9**, bearing 7, 10, and 12 carbon atoms, respectively, and a selection of 9 acyl chlorides (Table 1). Briefly, each steroid dissolved in dry THF was evenly distributed in nine wells of a 96 solid-phase reaction block (ACT Labtech apparatus). Piperidinomethylpolystyrene resin and each acyl chloride were added and mixtures kept under argon for 3 h at room temperature (rt). Aminomethylpolystyrene resin was next added to quench all excess acyl chloride, and the reaction mixture was filtered to get rid of polymers. Collected filtrates were evaporated and the residues dissolved in ethyl acetate to finally be quickly purified on a silica gel pad. Since enzymatic assay results indicated that para-substituted benzoyl groups and fluoro atoms were prone to inhibit the conversion of E_1 into E_2 by 17β-HSD7, a second library containing 22 members (compounds **46**−**67**) was synthesized (Table 2). Eleven new para-substituted or fluoro-substituted benzoyl chlorides were then chosen and reacted with amines **6** and **9**, affording amides **46**−**67** in moderated to good yields. Reactions with 2-fluoro-5-trifluoromethylbenzoyl chloride and 2-chloro-4-fluorobenzoyl failed to afford the desired products **56**, **57**, **60**, and **61**.

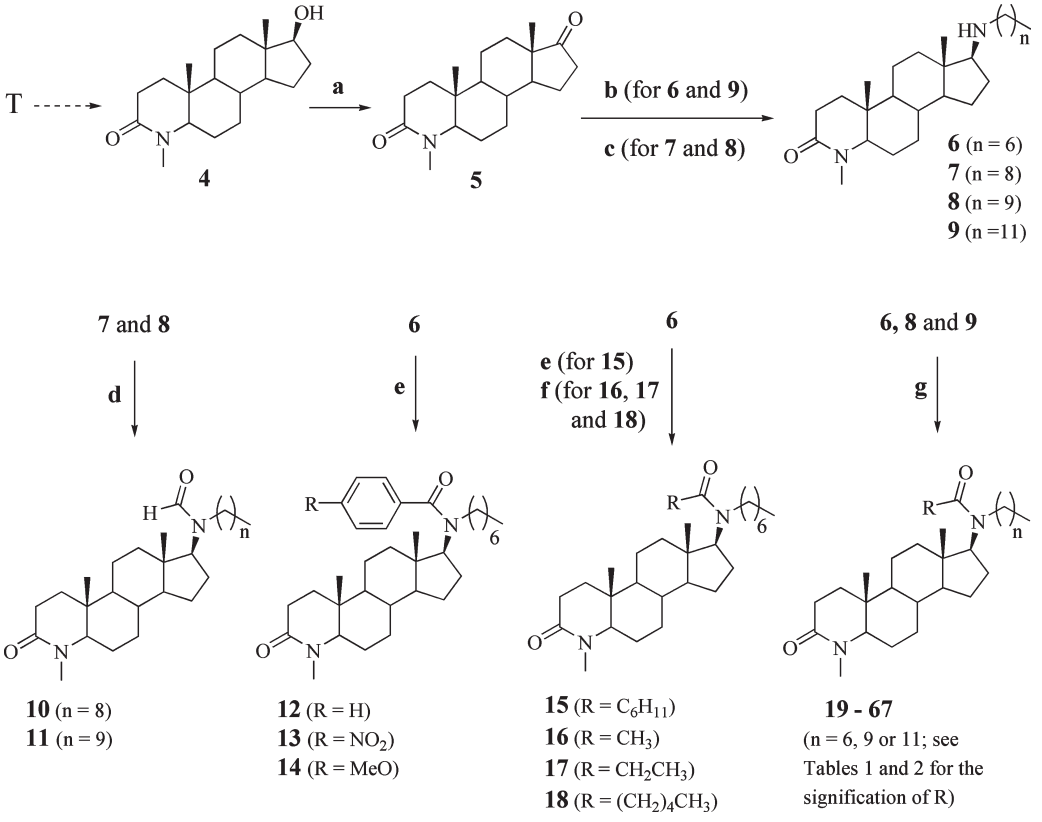
In addition to the 4-methyl-4-aza-5α-androstane (C-19 steroid) nucleus, the estrane (C-18 steroid) nucleus was also

Table 1. First Library of 17β-[(*N*-Alkyl)arylamido] Derivatives **19**−**45** Obtained by Parallel Synthesis from Amines **6**, **8**, and **9** and the Percentages of 17β-HSD7 Inhibition (E_1 to E_2 Transformation) at 0.3 μM[a]

	group A (n = 6)		group B (n = 9)		group C (n = 11)	
R	compd	inhibition, %	compd	inhibition, %	compd	inhibition, %
4-Br-Ph	**19**	68 ± 1	**20**	52 ± 2	**21**	52 ± 9
2-Cl-Ph	**22**	37 ± 1	**23**	37 ± 1	**24**	46 ± 2
3-CF_3-4-MeO-Ph	**25**	59 ± 7	**26**	46 ± 3	**27**	51 ± 1
4-Cl-Ph	**28**	65 ± 5	**29**	58 ± 17	**30**	40 ± 4
2,6-di-Cl-Ph	**31**	28 ± 3	**32**	36 ± 1	**33**	18 ± 3
4-F-Ph	**34**	84 ± 1	**35**	71 ± 2	**36**	47 ± 1
3-($ClCH_2$)-Ph	**37**	24 ± 4	**38**	30 ± 5	**39**	45 ± 6
4-($ClCH_2$)-Ph	**40**	50 ± 1	**41**	37 ± 1	**42**	33 ± 11
4-CN-Ph	**43**	56 ± 6	**44**	49 ± 2	**45**	51 ± 4
Ph	**12**	56 ± 2[b]				
H	**2**	94 ± 2				

[a] See Scheme 1 for the chemical structures. [b] Data obtained from another experiment using the same experimental conditions.

Scheme 1. Synthesis of 17β-[(*N*-Alkyl)alkyl/arylamido]-4-methyl-4-aza-5α-androstan-3-ones[a]



[a] Reagents and conditions: (a) PCC, NaOAc, CH_2Cl_2, molecular sieve, rt, 3 h (68%); (b) (i) $NH_2(CH_2)_nCH_3$ (n = 6 and 11), p-TSA, toluene, reflux in Dean−Stark apparatus, 18−24 h; (ii) $NaBH_3CN$, MeOH, pH 5, 0 °C, 1−2 h (58% and 44%, two steps); (c) (i) $NH_2(CH_2)_nCH_3$ (n = 7 and 8), p-TSA, toluene, reflux in Dean−Stark apparatus, 18−24 h; (ii) $NaBH_4$, MeOH, 0 °C, 1.5 h (75% and 62%, two steps); (d) (i) HCOOH, DCC, $CHCl_3$, 0 °C, 5 min; (ii) steroid, pyridine, 0 °C to rt (37−73%); (e) (i) K_2CO_3, THF, rt, 0.5 h; (ii) acyl/aryl chloride (RCOCl), overnight (41−74%); (f) (i) carboxylic acid (RCOOH), DCC, $CHCl_3$, 0 °C, 10 min; (ii) steroid, pyridine, K_2CO_3, 0 °C to rt, overnight (51−80%); (g) (i) piperidinomethylpolystyrene, acyl chlorides, THF, rt, 3 h; (ii) aminomethylpolystyrene, rt, 2.5 h (62−99%).

investigated with a series of two compounds synthesized from 3-methyl-*O*-estrone (**68**) (Scheme 2). The protected estrone was transformed into the 17β-(*N*-heptylamino) derivative **69** via a two-step reductive amination in the same conditions as compounds **6**−**9** and with similar yields. The intermediate **69** was also formylated to afford amide **70** in good yield. This latter compound was then deprotected with BBr_3 to provide the final compound **71** with 65% yield.

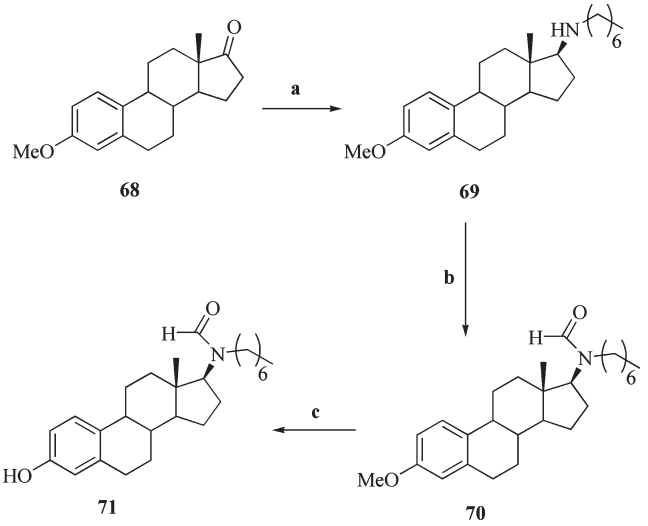
Another class of compounds tested for their inhibitory potency on 17β-HSD7 was tertiary amines (Scheme 3). Tertiary amines **72**−**75** were synthesized from amine **6** using either alkyl iodide (**72** and **73**) or alkyl bromide (**74** and **75**).[17] To achieve completion of the reaction, it was important to heat the mixture in a Schlenk tube to about 165 °C. It appears that acetonitrile (MeCN) was the best solvent for this reaction when compared to dimethylformamide (DMF) and ethylene chloride. Yields are good (76−89%) except for compound **75** that was obtained in only 20% yield even with the use of 20 equiv of cyclohexylmethyl bromide. Compound **76** failed to be obtained by this procedure because the use of methyl iodide in the presence of potassium or cesium carbonate gave rise to a quaternary ammonium salt. Reducing the

Table 2. Second Library of 17β-[(*N*-Alkyl)arylamido] Derivatives **46**−**67** Obtained by Parallel Synthesis from Amines **6** and **8** and the Percentages of 17β-HSD7 Inhibition (E_1 to E_2 Transformation) at 0.3 μM[a]

	group A (n = 6)		group B (n = 9)	
R	compd	inhibition, %	compd	inhibition, %
2,6-di-F-Ph	**46**	84 ± 5	**47**	56 ± 5
2,5-di-F-Ph	**48**	59 ± 10	**49**	56 ± 5
2,4-di-F-Ph	**50**	73 ± 5	**51**	80 ± 12
3,5-di-F-Ph	**52**	56 ± 1	**53**	38 ± 7
2,3,4,5,6-penta-F-Ph	**54**	67 ± 3	**55**	28 ± 5
3-CF_3-6-F-Ph	**56**	*b*	**57**	*b*
2-CF_3-6-F- Ph	**58**	49 ± 6	**59**	19 ± 3
2-Cl-4-F- Ph	**60**	*b*	**61**	*b*
4-^{t}Bu-Ph	**62**	29 ± 4	**63**	4 ± 5
4-Heptyl-Ph	**64**	24 ± 1	**65**	11 ± 7
4-I-Ph	**66**	60 ± 1	**67**	39 ± 2
4-F-Ph	**34**	77 ± 3		

[a] See Scheme 1 for the chemical structures. [b] Compound not obtained in suitable purity to be tested.

Scheme 2. Synthesis of 17β-[(*N*-Heptyl)formamido]estra-1,3,5(10)-trienes[a]

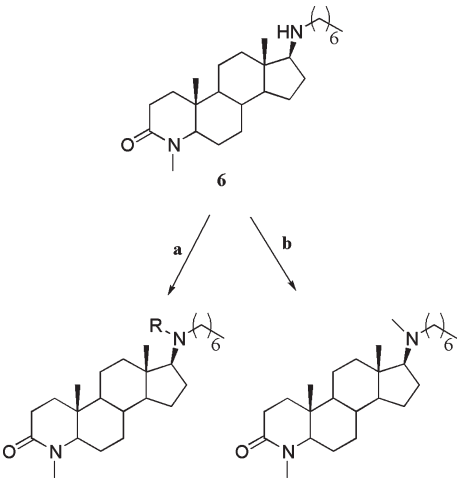


[a] Reagents and conditions: (a) (i) $NH_2(CH_2)_6CH_3$, *p*-TSA, toluene, reflux in Dean−Stark apparatus, 18−24 h; (ii) $NaBH_3CN$, MeOH, pH 5, 0 °C, 1−2 h (64%, two steps); (b) (i) HCOOH, DCC, $CHCl_3$, 0 °C, 10 min; (ii) steroid, pyridine, K_2CO_3, 0 °C to rt (84%); (c) BBr_3, CH_2Cl_2, 0 °C to rt (47−65%).

amount of methyl iodide to 1.5 equiv and lowering the reaction temperature to 50 °C gave the same result. Reduction by $NaBH_3CN$ of a methylimine, formed by the reaction between the amine **6** and formaldehyde, was then considered, but results were not convincing. However, two methods had helped us obtain the *N*-methylated compound: the Eschweiler−Clarke methylation,[18] which gave a crude yield of 77% on a chemical model, and the reduction by $NaBH_3CN$ of a methylimine resulting from the reaction of paraformaldehyde and amine **6**. The latter reaction afforded compound **76** with a 50% yield, which is a little bit lower than the typical reported yield of 66%.[19] This result was, however, found suitable considering the steric hindrance caused by the angular C-18 methyl of the steroid nucleus.

The 4-aza-5α-androstane counterparts of compounds **11** and **76**, namely, compounds **80** and **81**, were synthesized starting with 4-aza-5α-androstane-3,17-dione (**77**) (Scheme 4). This latter compound was submitted to reductive amination to

Scheme 3. Synthesis of 17β-[(*N*-Heptyl)alkyl/arylamino]-4-methyl-4-aza-5α-androstan-3-ones[a]



72 (R = $(CH_2)_4CH_3$)
73 (R = $(CH_2)_2CH_3$)
74 (R = $CH_2C_6H_5$)
75 (R = $CH_2C_6H_{11}$)

76

[a] Reagents and conditions: (a) K_2CO_3, alkyl iodide or bromide, MeCN, Schlenk tube, 165 °C, 24 h (20−89%); (b) $(CH_2O)_n$, $NaBH_3CN$, refluxing MeOH, 24 h (50%).

provide amines **78** and **79** in 54% and 30% yields, respectively. *N*-Methylation of **79**, by the method described for compound **76**, afforded compound **81** in 64% yield, but formylation of **78** was more difficult than its 4-methyl-4-aza analogue. Indeed, compound **80** showed a very similar solubility to the dicyclohexylurea side product and it was isolated with difficulty in only a 30% yield.

Biological Activity. Inhibition toward 17β-HSD7 (Transformation of E_1 into E_2). The in vitro enzymatic assays were realized in intact HEK-293 cells overexpressing 17β-HSD7, a system that offers precious advantages. First, as the molecule needs to penetrate the cell to "meet" the enzyme, working with intact cells automatically eliminates compounds that are not able to enter the cells. This methodology may discard molecules that could have been good inhibitors in the case of purified enzymes or cell homogenates, but such compounds are of less interest in a therapeutic point of view. The whole cell system also constitutes a more physiological environment than a homogenate or purified enzyme because no exogenous cofactor needs to be added. A lower concentration of the substrate than the K_m value of the enzyme was then used for the assay. Finally, the transfected HEK-293 cells overexpress the targeted enzyme activity when compared to wild type cells, which only express low levels of steroidogenic enzyme activities. For screening purposes, the assays were performed at two inhibitor concentrations and results are expressed as the inhibition (%) of the enzymatic reduction of E_1 into E_2 by 17β-HSD7.

Enzymatic assays performed with 17β-[(*N*-alkyl)formamido]-4-methyl-4-aza-5α-androstanes showed that a side chain length between 7 and 10 carbon atoms (n = 6−9) is better for inhibition than a shorter (n = 4 and 5) side chain (Figure 3). The plateau reached by long aliphatic chains may suggest that the enzyme possesses an important hydrophobic pocket. On the basis of these results, a series of 17β-[(*N*-heptyl)alkyl/arylamido] derivatives were synthesized to investigate the impact of the nature of the amide moiety

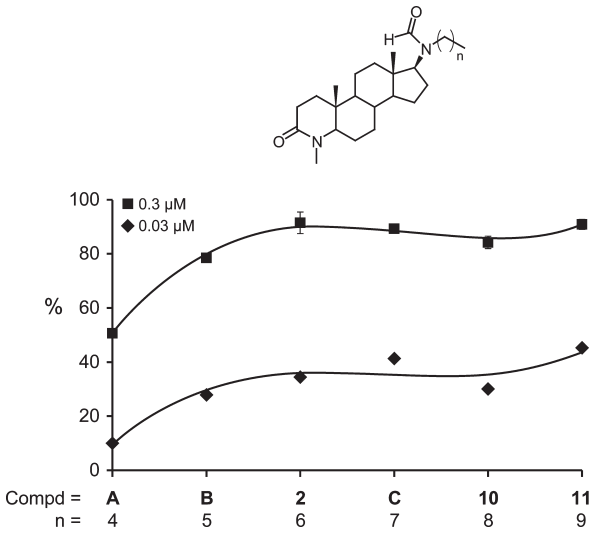
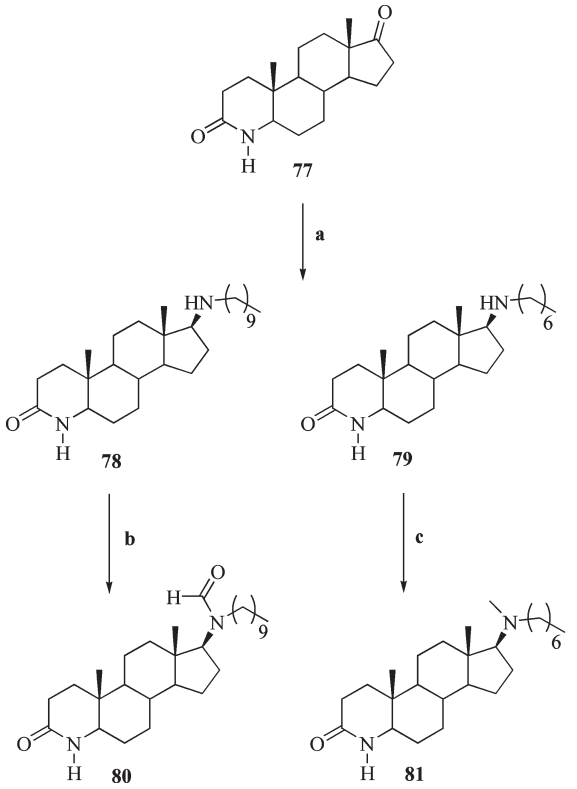


Figure 3. Optimization of the inhibitory potency (%) according to the alkylamide side chain length of various 17β-[(*N*-alkyl)formamido] derivatives. Transformation of E_1 to E_2 was by 17β-HSD7. Products were tested in triplicate at the indicated concentrations. Groups A−C compounds were available in our laboratory, and the chemical synthesis was previously reported.[15]

Scheme 4. Synthesis of 4-Aza-5α-androstane Analogues of Two Potent Inhibitors of 17β-HSD7[a]



[a] Reagents and conditions: (a) (i) $NH_2(CH_2)_nCH_3$, *p*-TSA, toluene, 4 Å molecular sieves, Schlenk tube, 18−24 h; (ii) $NaBH_3CN$, MeOH, pH 5, 0 °C, 1−2 h (30−54%, two steps); (b) (i) HCOOH, DCC, $CHCl_3$, 0 °C, 10 min; (ii) steroid, pyridine, K_2CO_3, 0 °C to rt (30%); (c) $(CH_2O)_n$, $NaBH_3CN$, refluxing MeOH, 24 h (64%).

(compounds **12**−**18**) and the importance of the 4-methyl-4-aza-5α-androstane nucleus over an estrane nucleus (compounds **70** and **71**). According to Figure 4, arylamides **12**−**14** are better inhibitors than alkylamides **15**−**18**. However, no significant difference was observed between the inhibition reached by a benzamide substituted by an electron withdrawing group (compound **13**) or an electron donating group (compound **14**) when compared to the unsubstituted benzamide **12**. A short alkyl chain is also better tolerated than one that is too long (for example, **16** vs **18**). When replaced by a C-18 estratriene nucleus, there is no doubt that the 4-methyl-4-aza-5α-androstane nucleus is an important feature that must be kept as the main structure for all future inhibitor design (Figure 5).

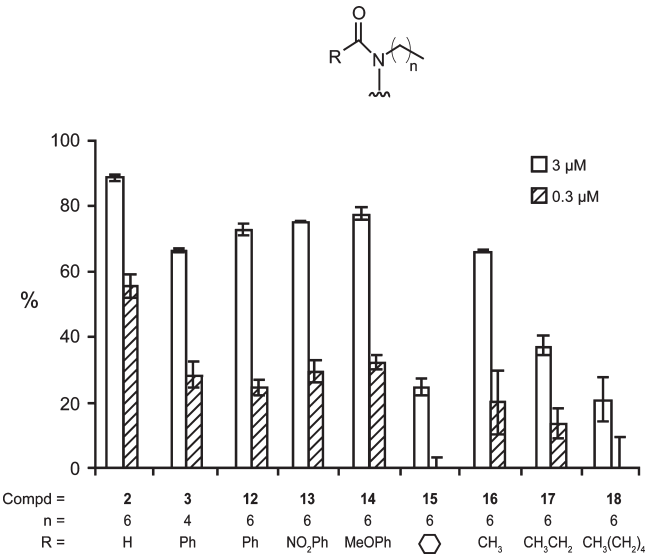


Figure 4. Comparison of the inhibitory potency (%) reached by 17β-[(*N*-alkyl)alkylamido] derivatives and 17β-[(*N*-alkyl)arylamido] derivatives for the transformation of E_1 to E_2 by 17β-HSD7. Products were tested in duplicate at the indicated concentrations. See Scheme 1 for the structures of tested compounds.

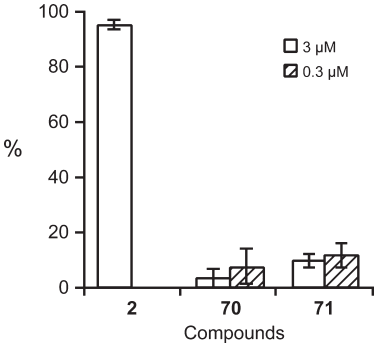


Figure 5. Inhibitory potency (%) reached by C-18 steroid derivatives for the transformation of E_1 to E_2 by 17β-HSD7. Products were tested in triplicate at the indicated concentrations. See Scheme 2 for the structures of tested compounds.

Taken together, these results directed our SAR study toward 17β-[(*N*-alkyl)arylamido]-4-methyl-4-aza-5α-androstanes. A first library containing 27 different analogue compounds divided into three groups according to the number of carbon atoms in their aliphatic side chains was prepared and is reported in Table 1. In group A (n = 6), all compounds bearing at least one para-substituent showed an inhibition value of ≥50% when tested at 0.3 μM. The best compound in this series was **34** with an inhibitory potency of 84%, which was not as good as the potency of lead compound **2** (94%) but better than lead compound **3** with 63% inhibition at the same concentration.[12] Group B compounds (n = 9) presents

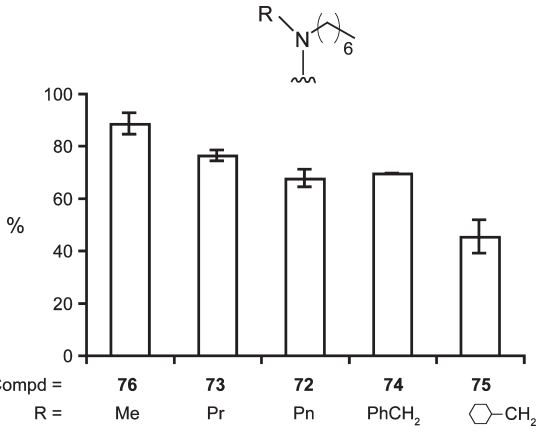


Figure 6. Inhibitory potency (%) reached by tertiary amines (E_1 to E_2 by 17β-HSD7). Products were tested in duplicate at 0.3 μM. See Scheme 3 for the structures of tested compounds.

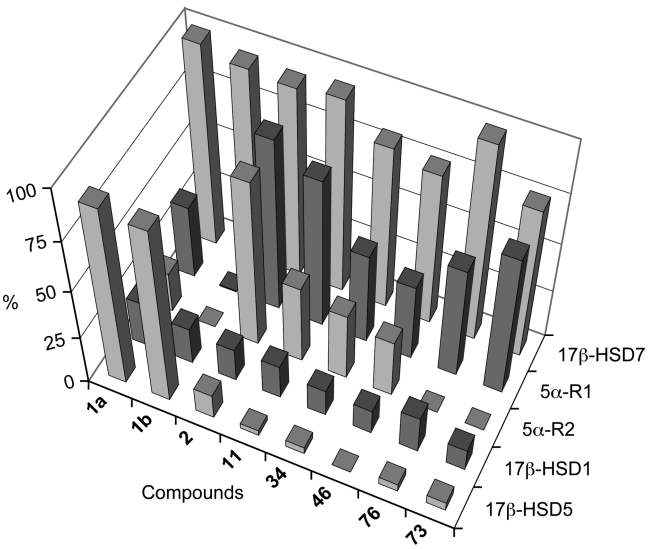


Figure 7. Selectivity of 17β-HSD7 inhibitors toward other steroidogenic enzymes. Inhibitors were assessed for their inhibitory potency (%) toward 17β-HSD1 (E_1 to E_2), 17β-HSD5 (Δ^4-dione to T), 5α-R1 (Δ^4-dione to A-dione), and 5α-R2 (Δ^4-dione to A-dione) in comparison to their potency on 17β-HSD7 (E_1 to E_2). Inhibitors were tested at 0.3 μM except for 17β-HSD1, where the concentration was 0.1 μM.

a similar profile as group A compounds (n = 6), with para-substituted benzamides being the best inhibitors when compared to other ring arrangements. Compound **35**, the para fluoro derivative, is the best inhibitor of this series with 71% inhibition at 0.3 μM. The last group (C, n = 11) has compounds that present generally lower inhibitory potency than compounds of groups A and B. Consequently, another library was then elaborated choosing only acyl chlorides bearing either a fluoro atom or a para-substituent (or both) and selecting only the heptylamine (n = 6) or decylamine (n = 9) side chain on the C-17 position of the steroid nucleus (Table 2). The maximum inhibitory potency reached by the second library members did not exceed that of the first one except for compounds **46** and **51**. Indeed, they showed 84% and 80% inhibition, respectively, when compared to compound **34** (77%) introduced as reference in the same experiment.

Focusing on *N*-heptyl derivatives, we evaluated the importance of the presence of a carbonyl group in this area of the molecule by synthesizing compounds **73**, **74**, **75**, and **76**, the tertiary amine analogues of amides **17**, **12**, **15**, and **2**. Results seem to demonstrate that the amine version is a better inhibitor than the amide one. Indeed, tertiary amines **73**, **74**, and **75** reached 76%, 69%, and 45% inhibition, respectively, at 0.3 μM, whereas their amide analogues **17**, **12**, and **15** reached 14%, 25%, and 0% at 0.3 μM (Figure 6). However, amine **76** (89% inhibition) showed similar inhibitory potency compared to its analogue **2**, with an average of 94% inhibition (data not shown) when tested at the same concentration. We will obviously need to test both tertiary amines and amides at the same concentration in a single assay to truly confirm this trend. It seems, however, that the inhibitory potency of tertiary amines drops in accordance with the elongation of the alkyl side chain (**76** vs **73** vs **72**) and the bulkiness of the substituent (**72** vs **75**). Consequently, compound **76** appears to be the best inhibitor in this series of amine derivatives.

Inhibitor Selectivity toward 17β-HSD7. To verify if the new compounds selectively inhibit 17β-HSD7, we chose the two most potent inhibitors in each category of compounds discussed above. The spiro-δ-lactones **1a** and **1b**, the formamides **2** and **11**, the arylamides **34** and **46**, and the tertiary amines **73** and **76** were tested as inhibitors of other steroidogenic enzymes (Figure 7). Because 17β-[(*N*-alkyl)formamido]-4-methyl-4-aza-5α-androstanes were proven to be good inhibitors of 5α-Rs[15] and spiro-δ-lactone, an essential pharmacophore used to block the conversion of Δ^4-dione into T by 17β-HSD5,[13] it was necessary to determine the selectivity of all compounds toward 5α-R1, 5α-R2, and 17β-HSD5. We also tested the selected inhibitors for their ability to block the conversion of E_1 into E_2 by 17β-HSD1, a cytosolic enzyme having a K_m value for E_1 3.6 times lower than 17β-HSD7.[20]

As expected, both compounds **1a** (R = Me) and **1b** (R = H) were able to inhibit 17β-HSD5 more than 90% at 0.3 μM, but all the other compounds had no effect on this enzyme. Selected inhibitors were not able to efficiently block 17β-HSD1, suggesting a very different molecular structure of the enzymatic site between 17β-HSD1 and 17β-HSD7 and this, even if they share a common substrate (E_1). It was very interesting to see that despite all 4-methyl-4-aza-5α-androstane derivatives being inhibitors of 5α-R1, compound **1b** (R = H), i.e., the only 4-aza-5α-androstane compound, did not inhibit the enzyme when tested at 0.3 μM. The same result was also obtained with 5α-R2, which was neither blocked by the 4-aza-5α-androstane nucleus nor by tertiary amines **73** and **76**. We concluded that the only way to obtain highly selective inhibitors of 17β-HSD7 was to avoid the inhibition of 5α-Rs by synthesizing the 4-aza-5α-androstane counterpart of our two best amide-type and amine-type inhibitors. As anticipated, 4-aza steroids **80** and **81** were dramatically less inhibiting 5α-Rs than their 4-methyl-4-aza analogues **11** and **76**, respectively (Figure 8). However, changing the 4-methyl-4-aza-5α-androstane nucleus for a 4-azaandrostane nucleus impaired their inhibitory potency on 17β-HSD7. This phenomenon was, however, less marked for the 17β-[(*N*-decyl)formamido] derivative **80**, whose IC_{50} passed from 195 $\pm$ 18 nM to 230 $\pm$ 15 nM, than for the 17β-[(*N*-heptyl)methylamino] derivative **81** with IC_{50} passing from 189 $\pm$ 18 nM to 458 $\pm$ 38 nM (Figure 9).

Inhibition toward 17β-HSD7 (Conversion of DHT into 3β-Diol). Selected compounds were assayed for their ability to

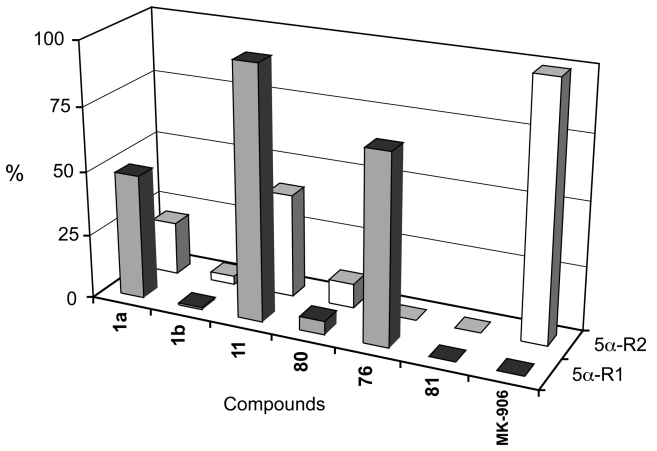


Figure 8. Inhibitory potency (%) of 4-aza-5α-androstane counterparts of two of our best 4-methyl-4-aza-5α-androstane inhibitors toward the 5α-R1 and 5α-R2 conversion of Δ^4-dione into A-dione. Products were tested in duplicate at 0.3 μM. MK-906 (finasteride) is a known inhibitor of 5α-R2.[21]

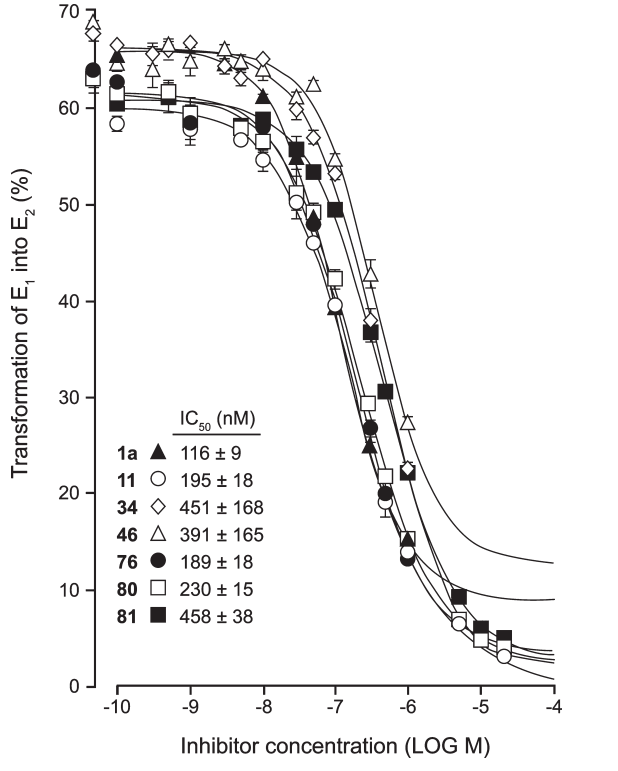


Figure 9. Determination of IC_{50} values for the transformation of E_1 to E_2 by 17β-HSD7. Inhibitors were tested in triplicate at concentrations ranging from 0.1 nM to 20 μM.

inhibit the second reaction catalyzed by 17β-HSD7, i.e., the transformation of DHT into 3β-diol (Figure 10). At 3 μM, all compounds inhibited the androgen deactivation in the range 69−92%. The best inhibitors of DHT transformation are compound **1a**, which still inhibits more than 50% of the enzyme activity at 0.3 μM, and compound **11** with 49% inhibition at the same concentration. The fact that inhibitors designed for the E_1 to E_2 transformation also inhibit the DHT to 3β-diol transformation may suggest that the catalytic site for DHT and E_1 is the same. However, since the mechanism of inhibition of these compounds is not yet understood, it is also possible that they act as noncompetitive

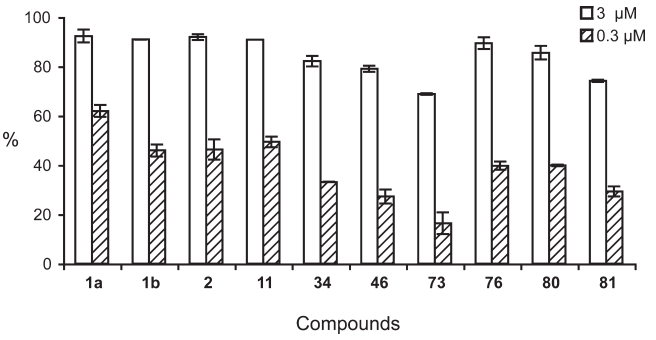


Figure 10. Inhibition (%) of the DHT into 3β-diol conversion by 17β-HSD7. Products were tested in duplicate at the indicated concentrations.

inhibitors. According to this hypothesis, they could bind the enzyme at another area than the enzymatic site and induce structural modifications that could affect two different catalytic sites at the same time. More experimentation will be necessary to clarify this hypothesis.

Conclusion

Despite the fact that the exact role of 17β-HSD7 in the human organism is not well understood, it is believed that it could be implicated in the growth, or at least in the maintenance, of estrogen-dependent tumors. Greater exposure of an ER^+ tumor to estrogens will result in its proliferation and increase of its aggressiveness.[22] Moreover, a recent study demonstrated that when prostatic LNCaP cancer cells pass from an androgen-dependent to an androgen-independent state, the production of estrogens increases significantly, especially via the augmentation of E_1 into E_2 conversion and DHT into 3β-diol conversion. RT-PCR analysis further demonstrated that 17β-HSD7 expression was 1.7 times greater in this situation and that it was responsible for this estrogen's synthesis pattern.[23] In our paper, development of the first selective 17β-HSD7 inhibitors was achieved through a typical SAR study, in which a preliminary screening had highlighted that the 4-methyl-4-aza-5α-androstan-3-one nucleus had a potential lead compound. Further investigation, aiming at the improvement of the 17β-substituent, allowed us to identify 17β-formamido, 17β-benzamido, and 17β-amino derivatives that efficiently inhibit the conversion of E_1 into E_2 and of DHT into 3β-diol by 17β-HSD7. According to their IC_{50} values, the best inhibitors for E_1 into E_2 conversion are the spiro-δ-lactone **1a** (116 ± 9 nM), the 17β-(*N*-decylformamido) derivative **11** (195 ± 18 nM), and the tertiary amine **76** (189 ± 18 nM). When their selectivity over 17β-HSD7 was tested, it appears that compound **1a** was inhibiting 17β-HSD5 but not compounds **11** and **76**, whereas the 4-methyl-4-aza-5α-androstane nucleus was always able to block the enzymatic activity of 5α-R1, irrespective of the nature of the 17β-substituent. Inhibitors **1a** and **11** also proved themselves as good inhibitors of the 5α-R2 activity but not the tertiary amine **76**. A full selectivity for 17β-HSD7 was then achieved by synthesizing compounds **80** and **81**, the 4-aza-5α-androstane analogues of compounds **11** and **76**, respectively. As anticipated, compounds **80** and **81** are no more able to inhibit 5α-Rs (Δ^4-dione into A-dione) and, as they do not bear 17β-spiro-δ-lactone, did not inhibit 17β-HSD5. Compound **80** still presents a good inhibitory potency toward 17β-HSD7 for both enzymatic reactions (E_1 conversion, IC_{50} = 230 ± 15 nM; DHT conversion, inhibition of 40% at 0.3 μM and

86% at 3 μM) when compared to compound **11**. However, compound **81**, although selective, is slightly less potent (E_1 conversion, $IC_{50} = 458 \pm 38$ nM; DHT conversion, inhibition of 29% at 0.3 μM and 74% at 3 μM) than its analogue, compound **76**.

Compounds **80** and **81** represent the only known selective inhibitors of 17β-HSD7 able to efficiently block both enzymatic reactions performed by this steroidogenic enzyme. This discovery will no doubt contribute to broaden our knowledge about the role of 17β-HSD7 in humans. Moreover, these compounds did not show androgenic or estrogenic effects on androgen-sensitive Shionogi and estrogen-sensitive CAMA-1 cells (data not reported), which means that our inhibitors do not generate mitogenic effects via the transactivation of the androgenic or estrogenic receptor. This major characteristic could ultimately open the door to therapeutic use of these kinds of compounds in the treatment of hormone-sensitive diseases.

Experimental Section

General Methods for Chemical Synthesis. Chemical reagents were purchased from Sigma-Aldrich Canada Ltd. (Oakville, Ontario, Canada) except aminomethylpolystyrene (1% DVB, ≃100−200 mesh, 1.05 mequiv/g), which was obtained from Richelieu Biotechnologies (Montréal, Québec, Canada), and piperidinomethyl polystyrene (3.5 mmol/g), obtained from Matrix Innovation (Montréal, Québec, Canada). Testosterone was purchased from Steraloids (Wilton, NH). HPLC and ACS solvent grades were from Fisher Scientific (Québec, Canada), and anhydrous solvents were from VWR (Ville Mont-Royal, Québec, Canada). Pyridine and THF for anhydrous reactions were distilled prior to use, and reactions were run under inert (argon) atmosphere in oven-dried glassware. Thin-layer chromatography (TLC) was performed with (60 Å) silica gel plates (Fisher Scientific), and 4-methyl-4-aza-steroids were visualized using Dragen−Dorf reagent, while other types of molecules were visualized using cerium ammonium molybdate. Flash column chromatography was performed with 40−63 μm (60 Å) Silicycle silica gel (Québec, Canada). The steroid derivative libraries were realized with an ACT LabTech manual synthesizer (Advance ChemTech, Louiseville, KY). Infrared spectra (IR) were recorded on a Perkin-Elmer 1600 (series FTIR) spectrophotometer (Norwalk, CT), and only the most significant bands are reported in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded at 300 MHz (^{1}H) and 75.5 MHz (^{13}C) on a Bruker AC/F300 spectrometer (Billerica, MA) or at 400 MHz (^{1}H) and 100.6 MHz (^{13}C) on a Bruker Avance 400 digital spectrometer, and the chemical shifts are reported in ppm. The $CHCl_3$ ^{1}H and ^{13}C NMR signals (7.26 and 77.00 ppm, respectively, for 300 or 400 MHz apparatus) were used as internal references. Low-resolution mass spectra (LRMS), ESI or APCI, were recorded on a Perkin-Elmer Sciex API-150 ex apparatus (Foster City, CA) equipped with a turbo ion-spray source. High-performance liquid chromatography (HPLC) analyses were carried out for new synthesized and tested compounds **10**−**18**, **34**, **46**, **70**−**76**, **80**, and **81** using a Waters system (Milford, MA) equipped with a UV detector and a reverse-phase column (Luna Phenyl/Hexyl or Ace 3 C18-HL) and using an appropriate gradient of solvents (methanol and water with or without 0.1% of HCOOH). The purity was found to be ≥95% except when otherwise specified at the end of the description of its synthesis.

4-Methyl-4-aza-5α-androstane-3,17-dione (5). To a stirred solution of compound **4**[15] (500 mg, 1.64 mmol) in dry CH_2Cl_2 (18 mL) was added pyridinium chlorochromate (PCC) (4.1 mmol, 2.5 equiv), NaOAc (4.92 mmol, 3.0 equiv), and activated molecular sieves (4 Å) (10% w/w of the alcohol). The mixture was stirred at rt for 3 h and then filtered through a Celite 521 pad to remove the precipitate and molecular sieves. The precipitate was washed with acetone and the combined filtrate was evaporated to give a dark-brown foam, which was further purified by flash column chromatography (CH_2Cl_2/MeOH, 97:3 to 90:10, and then acetone/hexanes, 30:70) to give compound **5** (6.0 g, 68%). IR (film on NaCl): 1738 (C=O, ketone), 1642 (C=O, lactam). ^{1}H NMR 400 MHz ($CDCl_3$): 0.87 (s, 18-CH_3), 0.90 (s, 19-CH_3), 0.80−2.20 (residual CH and CH_2), 2.45 (m, 2-CH_2 and 1H of 16-CH_2), 2.93 (s, 4-NCH_3), 3.05 (dd, J = 3.5 and 12.6 Hz, 5α-CH). ^{13}C NMR, 100 MHz ($CDCl_3$): 12.39, 13.82, 20.38, 21.65, 25.15, 29.01, 29.05, 29.16, 31.36, 32.88, 33.93, 35.75, 36.53, 47.76, 50.93, 52.01, 65.62, 170.61, 220.37. LRMS: calcd for $C_{19}H_{30}NO_2$ $[M + H]^+$ 304.2, found 304.4.

17β-(*N*-Alkylamino)-4-methyl-4-aza-5α-androstan-3-ones (6−9). First Method (Synthesis of 6 and 9). A round flask filled with dry toluene (25 mL), compound **5** (1.0 g, 3.29 mmol), *n*-heptylamine (4.94 mmol, 1.5 equiv), and *p*-TSA (38 mg) was equipped with a Dean−Stark trap and a condenser. The mixture was refluxed 18−24 h, and the formation of the corresponding imine was followed by TLC. The reaction mixture was cooled and the solvent removed under reduced pressure. The resulting residue was dissolved in dry methanol (11 mL) and cooled to 0 °C. The pH was lowed around pH 5 with concentrated HCl, and a $NaBH_3CN$ solution (6.59 mmol, 2 equiv, in 4 mL of methanol) was added dropwise. The mixture was stirred at 0 °C for 1.5−2 h and the solvent evaporated in vacuo. The residue was dissolved in water, and the solution was basified to pH 13 with 2 N KOH and extracted three times with CH_2Cl_2. The organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude oil was purified by flash column chromatography (CH_2Cl_2/MeOH, 97:3, and CH_2Cl_2/acetone, 85:15).

17β-(*N*-Heptylamino)-4-methyl-4-aza-5α-androstan-3-one (6). 774 mg, 58% yield. IR (film on NaCl): 3250 (NH, weak), 1649 (C=O, lactam). ^{1}H NMR 400 MHz ($CDCl_3$): 0.70 (s, 18-CH_3), 0.87 (t, J = 7.0 Hz, 7′-CH_3), 0.88 (s, 19-CH_3), 0.75−2.10 (residual CH and CH_2), 2.44 (dd, J = 4.7 and 9.5 Hz, 2-CH_2), 2.53 (t, J = 8.7 Hz, 17α-CH), 2.59 (m, 1′-CH_2), 2.92 (s, 4-NCH_3), 3.02 (dd, J = 3.5 and 12.6 Hz, 5α-CH). ^{13}C NMR 100 Hz ($CDCl_3$): 11.92, 12.41, 14.08, 20.90, 22.61, 23.61, 25.33, 27.38, 29.08, 29.10, 29.24, 29.78, 30.00, 30.62, 31.82, 32.95, 34.37, 36.44, 38.05, 42.93, 48.88, 52.16, 52.88, 65.78, 69.06, 170.76. LRMS: calcd for $C_{26}H_{47}N_2O$ $[M + H]^+$ 403.4, found 403.4.

17β-(*N*-Dodecylamino)-4-methyl-4-aza-5α-androstan-3-one (9). 762 mg, 44% yield. IR (film on NaCl): 3400 (NH, weak), 1650 (C=O, lactam). ^{1}H NMR 300 MHz ($CDCl_3$): 0.73 (s, 18-CH_3), 0.87 (t, J = 6.9 Hz, 12′-CH_3), 0.88 (s, 19-CH_3), 0.75−2.10 (residual CH and CH_2), 2.44 (dd, J = 4.7 and 9.5 Hz, 2-CH_2), 2.60 (m, 17α-CH and 1′-CH_2), 2.92 (s, 4-NCH_3), 3.02 (dd, J = 3.4 and 12.5 Hz, 5α-CH). ^{13}C NMR 75 MHz ($CDCl_3$): 11.95, 12.33, 14.07, 20.72, 22.61, 23.47, 25.20, 27.26, 29.00, 29.06, 29.28, 29.41, 29.54 (6x), 29.85, 31.83, 32.80, 34.16, 36.31, 37.72, 42.81, 48.69, 51.92, 52.69, 65.64, 68.60, 170.65. LRMS: calcd for $C_{31}H_{57}N_2O$ $[M + H]^+$ 473.4, found 473.5.

Second Method (Synthesis of 7 and 8). A round flask filled with dry toluene (25 mL), compound **5** (500 mg, 1.65 mmol), *n*-decylamine (1.92 mmol, 1.2 equiv), and *p*-TSA (20 mg) was equipped with a Dean−Stark trap and a condenser. The mixture was refluxed 18−24 h, and the formation of the corresponding imine was followed by TLC. The reaction mixture was cooled and the solvent removed under reduced pressure. The resulting residue was dissolved in dry methanol (10 mL) and the solution cooled to 0 °C. A $NaBH_4$ solution (2.47 mmol, 1.5 equiv, in 2 mL of methanol) was added dropwise. The mixture was stirred at 0 °C for 1.5 h and the solvent evaporated in vacuo. The residue was dissolved in water, and the solution was basified to pH 13 with 2 N KOH and extracted three times with CH_2Cl_2. The organic phase was washed with brine, dried ($MgSO_4$), filtered,

and concentrated under vacuum. The crude oil was purified by flash column chromatography (CH_2Cl_2/MeOH, 97:3 to 95:5, and CH_2Cl_2/MeOH/Et_2NH, 94:5:1).

17β-(*N*-Nonylamino)-4-methyl-4-aza-5α-androstan-3-one (7). 530 mg, 75% yield. IR (film on NaCl): 3310 (NH, weak), 1648 (C=O, lactam). ^{1}H NMR 400 MHz ($CDCl_3$): 0.72 (s, 18-CH_3), 0.87 (t, J = 7.0 Hz, 9′-CH_3), 0.88 (s, 19-CH_3), 0.75−2.10 (residual CH and CH_2), 2.44 (dd, J = 4.5 and 9.6 Hz, 2-CH_2), 2.55 (t, J = 8.7 Hz, 17α-CH), 2.60 (m, 1′-CH_2), 2.91 (s, 4-NCH_3), 3.01 (dd, J = 3.5 and 12.6 Hz, 5α-CH). ^{13}C NMR 75 MHz ($CDCl_3$): 12.07, 12.41, 14.11, 20.51, 20.81, 22.66, 23.55, 25.29, 26.81, 27.34, 29.11, 29.27, 29.50, 29.55, 29.93, 31.85, 32.91, 33.97, 34.26, 36.40, 37.82, 42.90, 48.75, 52.02, 52.79, 65.73, 68.65, 170.73. LRMS: calcd for $C_{28}H_{51}N_2O$ $[M + H]^+$ 431.4, found 431.4.

17β-(*N*-Decylamino)-4-methyl-4-aza-5α-androstan-3-one (8). 454 mg, 62% yield. IR (film on NaCl): 3307 (NH, weak), 1650 (C=O, lactam). ^{1}H NMR 300 MHz ($CDCl_3$): 0.69 (s, 18-CH_3), 0.85 (t, J = 7.1 Hz, 10′-CH_3), 0.86 (s, 19-CH_3), 0.75−2.10 (residual CH and CH_2), 2.42 (dd, J = 4.7 and 9.5 Hz, 2-CH_2), 2.53 (m, 17α-CH and 1′-CH_2), 2.90 (s, 4-NCH_3), 3.01 (dd, J = 3.5 and 12.5 Hz, 5α-CH). ^{13}C NMR 75 MHz ($CDCl_3$): 11.86, 12.34, 14.07, 20.80, 23.53, 25.24, 27.35, 29.05, 29.26, 29.50 (4×) 29.64, 29.90, 30.47, 31.83, 32.83, 34.26, 36.34, 37.95, 42.84, 48.98, 52.03, 52.77, 65.71, 68.94, 170.69. LRMS: calcd for $C_{29}H_{53}N_2O$ $[M + H]^+$ 445.7, found 445.5.

17β-[(*N*-Alkyl)formamido]-4-methyl-4-aza-5α-androstan-3-ones (10 and 11). 17β-[(*N*-Nonyl)formamido]-4-methyl-4-aza-5α-androstan-3-one (10). To a 0.2 M solution of formic acid (0.58 mmol, 2 equiv) in chloroform (1 mL) was added dropwise a solution of dicyclohexylcarbodiimide (DCC) (0.58, 2 equiv) in chloroform (2 mL). The mixture was stirred under argon at 0 °C for 5 min and then slowly added to an ice-cold solution of compound **7** (125 mg, 0.29 mmol) in pyridine (2.5 mL). After 0.5 h, the temperature was allowed to rise to rt and the mixture stirred for 1 h. Evaporation of the solvent in vacuo followed by addition of Et_2O precipitated dicyclohexylurea which was removed by filtration. The combined filtrate was concentrated under reduced pressure and the resulting oil purified by flash column chromatography (acetone/hexanes, 15:85 to 25:75) to give **10** as a white solid (98 mg, 73% yield). IR (film on NaCl): 1668 (C=O, amide), 1652 (C=O, lactam). ^{1}H NMR 400 MHz ($CDCl_3$): 0.71 (s, 18-CH_3), 0.88 (t, J = 7.0 Hz, 9′-CH_3), 0.90 (s, 19-CH_3), 0.80−2.10 (residual CH and CH_2), 2.48 (dd, J = 4.2 and 9.2 Hz, 2-CH_2), 2.94 (s, 4-NCH_3), 3.05 (dd, J = 3.5 and 12.5 Hz, 5α-CH), 3.28 (m, 2.8 H of 1′-CH_2 and 17α-CH), 4.16 (t, J = 9.7 Hz, 0.2 H of 1′-CH_2), 8.18 (s, 0.8 H of HCON), 8.24 (s, 0.2 H of HCON). ^{13}C NMR 75 MHz ($CDCl_3$): 12.38, 12.80, 14.10, 20.54, 22.63, 22.89, 23.12, 23.27, 24.34, 25.18, 26.73, 27.05, 28.57, 28.98, 29.17, 29.35, 29.50, 29.69, 31.80, 32.55, 32.83, 34.09, 36.38, 36.78, 37.25, 44.25, 44.35, 45.71, 46.74, 51.26, 51.68, 51.95, 61.92, 65.65, 68.57, 163.04, 164.56, 170.66. LRMS: calcd for $C_{29}H_{51}N_2O_2$ $[M + H]^+$ 459.4, found 459.5.

17β-[(*N*-Decyl)formamido]-4-methyl-4-aza-5α-androstan-3-one (11). Compound **11** (73 mg, 37% yield) was prepared from **8** (185 mg, 0.416 mmol) as described above for **10**. IR (film on NaCl): 1670 (C=O, amide), 1647 (C=O, lactam). ^{1}H NMR 400 MHz ($CDCl_3$): 0.71 (s, 18-CH_3), 0.88 (t, J = 7.0 Hz, 10′-CH_3), 0.90 (s, 19-CH_3), 0.80−2.10 (residual CH and CH_2), 2.50 (dd, J = 4.5 and 9.7 Hz, 2-CH_2), 2.94 (s, 4-NCH_3), 3.05 (dd, J = 3.5 and 12.5 Hz, 5α-CH), 3.28 (m, 2.8 H of 1′-CH_2 and 17α-CH), 4.16 (t, J = 9.7 Hz, 0.2 H of 17α-CH), 8.18 (s, 0.8 H of HCON), 8.24 (s, 0.2 H of HCON). ^{13}C NMR 75 MHz ($CDCl_3$): 12.37, 12.80, 14.10, 20.54, 22.64, 22.89, 23.12, 23.27, 24.34, 25.18, 26.73, 27.04, 28.57, 29.00, 29.13, 29.25, 29.34, 29.51, 29.69, 31.84, 32.55, 32.85, 34.10, 36.38, 36.80, 37.25, 44.25, 44.36, 45.71, 46.74, 51.27, 51.68, 51.96, 61.94, 65.64, 68.57, 163.04, 164.56, 170.63. LRMS: calcd for $C_{30}H_{53}N_2O_2$ $[M + H]^+$ 473.4, found 473.5.

17β-[(*N*-Alkyl)arylamido]-4-methyl-4-aza-5α-androstan-3-ones (12−15). 17β-[(*N*-Heptyl)benzamido]-4-methyl-4-aza-5α-androstan-3-one (12). To a solution of compound **6** (60 mg, 0.149 mmol) in dry THF (2.40 mL) was added anhydrous powdered potassium carbonate (0.448 mmol, 3 equiv), and the mixture was stirred at rt for 0.5 h. Addition of benzoyl chloride (0.448 mmol, 3 equiv) dropwise was followed by slow agitation for 3 h at rt under argon atmosphere. Solvent was removed under reduced pressure, and the resulting residue was treated with saturated $NaHCO_3$ and then extracted with three portions of CH_2Cl_2. The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude compound was purified by preparative TLC (1000 μm) (acetone/hexanes, 35:65), and the desired product was recovered from the silica gel by washing with two portions of acetone and one portion of CH_2Cl_2 over medium core filter. The combined filtrated was concentrated in vacuo to give compound **12** (56 mg, 74%). IR (film on NaCl): 1633 (C=O, amide and lactam). ^{1}H NMR 100 MHz ($CDCl_3$): 0.78 (s, 18-CH_3), 0.87 (broad s, 19-CH_3 and 7′-CH_3), 0.80−2.10 (residual CH and CH_2), 2.43 (dd, J = 4.5 and 9.2 Hz, 2-CH_2), 2.92 (s, 4-NCH_3), 3.01 (m, 5α-CH and 1 H of 1′-CH_2), 3.40 (broad, 0.8 H of 17α-CH), 3.90 (broad, 1 H of 1′-CH_2), 4.70 (broad, 0.2 H of 17α-CH), 7.36 (m, 5 H of ArH). ^{13}C NMR 300 MHz ($CDCl_3$): 12.33, 13.05, 14.04, 20.42, 22.53, 23.08, 23.94, 25.01, 26.83, 26.91, 28.22, 28.36, 28.74, 29.63, 31.63, 32.27, 33.85, 36.36, 36.80, 45.63 (2×), 51.18, 51.70, 66.07, 126.62, 128.31 (3×) 128.87, 138.17, 171.4, 173.4. LRMS: calcd for $C_{33}H_{51}N_2O_2$ $[M + H]^+$ 507.4, found 507.5.

17β-[(*N*-Heptyl)-4″-nitrobenzamido]-4-methyl-4-aza-5α-androstan-3-one (13). Compound **13** (23 mg, 67% yield) was prepared from **6** (25 mg, 0.062 mmol) as for compound **12** and was purified by a flash column chromatography (acetone/hexanes, 35:65) prior to a final preparative TLC using the same eluent. IR (film on NaCl): 1633, (C=O, amide and lactam). ^{1}H NMR 400 MHz ($CDCl_3$): 0.79 (s, 18-CH_3), 0.87 (s broad, 19-CH_3 and 7′-CH_3), 0.30−2.10 (residual CH and CH_2), 2.47 (m, 2-CH_2), 2.92 (s, 4-NCH_3), 3.10, 3.23, 3.60, 3.88, and 4.65 (5m, 5α-CH, 1′-CH_2 and 17α-CH), 7.50 (d, J = 6.7 Hz, 2 H of ArH), 8.27 (d, J = 8.2 Hz, 2 H of ArH). ^{13}C NMR 75 MHz ($CDCl_3$): 12.32, 13.09, 14.00, 20.30, 22.49, 24.01, 25.12, 27.04, 28.82, 29.24, 29.59, 31.62, 32.61, 33.73, 36.34, 36.77, 44.42, 45.19, 46.11, 47.03, 51.26, 51.56, 62.74, 65.61, 68.31, 123.36, 123.77, 127.85, 130.89, 136.62, 144.29, 147.77, 150.28, 166.39, 171.14. LRMS: calcd for $C_{33}H_{50}N_3O_4$ $[M + H]^+$ 552.4, found 552.5.

17β-[(*N*-Heptyl)-4″-methoxybenzamido]-4-methyl-4-aza-5α-androstan-3-one (14). Compound **14** (44 mg, 66% yield) was prepared from **6** (50 mg, 0.124 mmol) as for compound **12** and was purified by a flash column chromatography (acetone/hexanes, 35:65) prior to a preparative TLC using the same eluent. IR (film on NaCl): 1629 (C=O, amide and lactam). ^{1}H NMR 400 MHz ($CDCl_3$): 0.76 (s, 18-CH_3), 0.85 (t, J = 7.3 Hz, 7′-CH_3), 0.86 (s, 19-CH_3), 0.65−2.10 (residual CH and CH_2), 2.46 (dd, J = 4.3 and 8.7 Hz, 2-CH_2), 2.92 (s, 4-NCH_3), 3.00 (m, 5α-CH and 1′-CH_2), 3.68 (broad, 17α-CH), 3.83 (s, CH_3O), 6.88 (d, J = 8.6 Hz, 2 H of ArH), 7.28 (d, J = 8.5 Hz, 2 H of ArH). ^{13}C NMR 75 MHz ($CDCl_3$): 12.32, 13.03, 14.03, 20.38, 22.52, 23.03, 23.93, 25.20, 26.86, 28.87, 28.94, 29.15, 29.65, 31.64, 32.72, 33.83, 36.36, 36.72, 45.49, 51.20, 51.70, 55.25, 65.67, 113.53 (2×), 128.40 (2×), 130.47, 159.91, 170.82, 173.12. LRMS: calcd for $C_{34}H_{53}N_2O_3$ $[M + H]^+$ 537.4, found 537.5.

17β-[(*N*-Heptyl)cyclohexylamido]-4-methyl-4-aza-5α-androstan-3-one (15). Compound **15** (21 mg, 41% yield) was prepared from **6** (40 mg, 0.099 mmol) as for compound **12** and was purified by flash column chromatography (acetone/hexanes, 20:80). IR (film on NaCl): 1641 and 1632, (C=O, amide and lactame). ^{1}H NMR 400 MHz ($CDCl_3$): 0.65 and 0.72 (2s, 18-CH_3), 0.86 (s, 19-CH_3), 0.90 (t, J = 6.8 Hz, 7′-CH_3), 0.70−2.10 (residual CH and CH_2), 2.45 (m, 2-CH_2 and CHCO), 2.93 (s, 4-NCH_3), 3.05 (m, 5α-CH), 2.80, 3.08, 3.31, 3.75, and 4.54 (4m and 1t, 1′-CH_2 and 17α-CH). ^{13}C NMR 75 MHz ($CDCl_3$):

12.36, 12.74, 12.92, 14.07, 20.55, 22.54, 22.99, 23.37, 23.53, 24.80, 25.24, 25.63, 25.80, 26.42, 26.83, 28.63, 28.98, 29.16, 29.75, 30.56, 30.94, 31.34, 31.72, 31.86, 32.12, 32.77, 34.03, 36.75, 37.37, 40.82, 42.07, 44.56, 45.27, 45.71, 51.13, 51.65, 51.91, 53.42, 61.77, 65.52, 65.65, 170.89, 177.19, 177.82. LRMS: calcd for $C_{33}H_{57}N_2O_2$ $[M + H]^+$ 513.4, found 513.6.

17β-[(*N*-Alkyl)alkylamido]-4-methyl-4-aza-5α-androstan-3-ones (16−18). Compounds **16−18** were synthesized from **6** using the same method as described for compounds **10** and **11** except for the following details: (1) carboxylic acid and DCC equivalents were doubled (now 4 equiv); (2) carboxylic acid was added to DCC dissolved in chloroform; (3) the mixture was stirred for 10 min and then added to the mixture containing the steroid **6**, pyridine, and potassium carbonate (0.108 mmol, 1.5 equiv); (4) the mixture was stirred overnight.

17β-[(*N*-Heptyl)acetamido]-4-methyl-4-aza-5α-androstan-3-one (16). Compound **16** (44 mg, 80% yield) was prepared from **6** (50 mg, 0.124 mmol) and purified by flash column chromatography (acetone/hexanes, 25:75). IR (film on NaCl): 1645 (C═O, amide and lactam). ^{1}H NMR 100 MHz ($CDCl_3$): 0.67 and 0.74 (2s, 18-CH_3), 0.86 (s, 19-CH_3), 0.88 (t, J = 6.3 Hz, 7′-CH_3), 0.70−2.10 (residual CH and CH_2), 2.12 (s, 0.9 H of 2″-CH_3), 2.14 (s, 2.1 H of 2″-CH_3), 2.43 (dd, J = 4.6 and 9.4 Hz, 2-CH_2), 2.92 (s, 4-NCH_3), 3.03 (dd, J = 3.3 and 12.4 Hz, 5α-CH), 2.80, 3.12, 3.28, 3.68, and 4.50 (3m and 2t, 1′-CH_2 and 17α-CH). ^{13}C NMR 300 MHz ($CDCl_3$): 12.31, 12.80, 13.01, 14.05, 20.54, 22.38, 22.53, 22.75, 22.93, 23.25, 23.72, 24.65, 25.21, 26.93, 27.70, 28.93, 29.03, 29.19, 29.74, 31.02, 31.77, 32.71, 32.79, 33.92, 34.02, 37.11, 37.48, 44.75, 45.63, 46.73, 51.07, 51.65, 51.90, 62.32, 65.71, 67.38, 170.94, 171.38, 171.72. LRMS: calcd for $C_{28}H_{49}N_2O_2$ $[M + H]^+$ 445.4, found 445.4.

17β-[(*N*-Heptyl)propionamido]-4-methyl-4-aza-5α-androstan-3-one (17). Compound **17** (39 mg, 69% yield) was prepared from **6** (50 mg, 0.124 mmol) and purified by flash column chromatography (acetone/hexanes, 20:80). IR (film on NaCl): 1644 (C═O, amide and lactam). ^{1}H NMR 400 MHz ($CDCl_3$): 0.66 and 0.73 (2s, 18-CH_3), 0.70−2.10 (residual CH and CH_2), 0.86 (s, 19-CH_3), 0.88 (s_{app}, 7′-CH_3), 1.15 (t, J = 7.3 Hz, 3″-CH_3), 2.38 (m, 2-CH_2 and 2″-CH_2), 2.92 (s, 4-NCH_3), 3.02 (dd, J = 3.4 and 12.6 Hz, 5α-CH), 2.80, 3.08, 3.28, 3.70, and 4.51 (4m and 1t, 1′-CH_2 and 17α-CH). ^{13}C NMR 75 MHz ($CDCl_3$): 9.79, 10.31, 12.35, 12.76, 13.04, 14.04, 20.53, 22.52, 22.91, 23.27, 23.64, 24.64, 25.23, 26.97, 27.12, 27.65, 28.88, 28.96, 29.14, 29.74, 31.28, 31.76, 32.73, 34.03, 36.34, 37.30, 44.82, 45.39, 45.66, 45.77, 51.11, 51.70, 51.93, 62.36, 65.67, 66.01, 170.83, 174.56, 175.09. LRMS: calcd for $C_{29}H_{51}N_2O_2$ $[M + H]^+$ 459.4, found 459.4. HPLC purity: 87%.

17β-[(*N*-Heptyl)hexanamido]-4-methyl-4-aza-5α-androstan-3-one (18). Compound **18** (26 mg, 51% yield) was prepared from **6** (40 mg, 0.099 mmol) and purified by flash column chromatography (acetone/hexanes, 20:80). IR (film on NaCl): 1642 (C═O, amide and lactam). ^{1}H NMR 400 MHz ($CDCl_3$): 0.67 and 0.74 (2s, 18-CH_3), 0.70−2.10 (residual CH and CH_2), 0.87 (s, 19-CH_3), 0.89 and 0.90 (2s broad, 7′-CH_3 and 6″-CH_3), 2.28 and 2.43 (2m, 2-CH_2 and 2″-CH_2), 2.93 (s, 4-NCH_3), 3.04 (dd, J = 3.1 and 12.2 Hz, 5α-CH), 2.84, 3.13, 3.33, 3.73, and 4.52 (4m and 1t, 1′-CH_2 and 17α-CH). ^{13}C NMR 75 MHz ($CDCl_3$): 12.37, 12.83, 13.06, 14.03, 20.56, 22.55, 22.97, 23.31, 23.66, 25.13, 25.90, 26.94, 27.28, 28.62, 29.05, 29.50, 29.73, 31.37, 31.75, 32.46, 32.63, 33.94, 34.02, 36.36, 37.29, 44.91, 45.70, 45.94, 51.10, 51.69, 51.91, 62.36, 65.90, 66.20, 172.00, 174.50, 174.76. LRMS: calcd for $C_{32}H_{57}N_2O_2$ $[M + H]^+$ 501.4, found 501.5.

Parallel Synthesis of Compounds 19−67 (Libraries 1 and 2). Piperidinomethylpolystyrene resin (0.186 mmol, 5 equiv) and compound **6**, **8**, or **9** (0.037 mmol), previously dissolved in anhydrous THF (1 mL), were added into a 96-well solid-phase reaction block (ACT LabTech). Acyl chlorides were introduced (0.112 mmol, 3 equiv), and the reaction block was sealed and purged with argon. The reaction block was allowed to shake at 550 rpm for 3 h under a continuous argon flow. The disappearance of the starting material was confirmed by TLC and excess acyl chloride quenched by aminomethyl polystyrene resin (0.112 mmol, 3 equiv) under agitation for another 2.5 h. Reaction mixture was filtered and collected in individual vials. The solid support was washed with THF (2×) and CH_2Cl_2 (1×). The combined filtrates were evaporated to dryness and quickly purified over a small pad of silica gel (EtOAc 100% to EtOAc/acetone, 50:50). TLC and LRMS analyses were done for each member of libraries 1 and 2. A sampling of representative compounds was also analyzed by IR and ^{1}H NMR.

First Library (Compounds 19−45). The 27 members of library 1 were obtained as described above except for compounds **25−27** and **31−33**. Indeed, reactions with 4-methoxy-3-trifluoromethylbenzoyl chloride needed an additional 0.5 equiv of acyl chloride and another hour to be completed, whereas reactions with 2,6-dichlorobenzoyl chloride needed an additional 5 equiv and an overnight reaction time to be completed. Filtration over a silica gel pad afforded amides **19−45** in yields ranging between 62% and 99%. Compound purity was found acceptable for enzymatic assay by TLC analysis, and LRMS of all library members gave satisfactory results. Representative compounds **20**, **23**, **26**, **30**, **33**, **36**, **37**, **40**, and **43** were also analyzed by IR and ^{1}H NMR. After compound **34** was identified as the best 17β-HSD7 inhibitor of this library, it was selected for additional studies, purified again, and fully characterized by IR, ^{1}H NMR, and ^{13}C NMR) and the purity assessed by HPLC.

17β-[(*N*-Decyl)-4″-bromobenzamido]-4-methyl-4-aza-5α-androstan-3-one (20). IR (film on NaCl): 1634 (C═O, amide and lactam). ^{1}H NMR 300 MHz ($CDCl_3$): 0.76 (s, 18-CH_3), 0.86 (s, 19-CH_3), 0.87 (t, J = 6.5 Hz, 10′-CH_3), 0.70−2.10 (residual CH and CH_2), 2.42 (dd, J = 4.8 and 9.4 Hz, 2-CH_2), 2.91 (s, 4-NCH_3), 3.02 (m, 5α-CH and 1′-CH_2), 3.80 (broad, 17α-CH), 7.20 (d, J = 8.1 Hz, 3″-CH and 5″-CH), 7.51 (d, J = 8.2 Hz, 4″-CH and 6″-CH). LRMS: calcd for $C_{36}H_{56}BrN_2O_2$ $[M + H]^+$ 628.4, found 628.3.

17β-[(*N*-Decyl)-2″-chlorobenzamido]-4-methyl-aza-5α-androstan-3-one (23). IR (film on NaCl): 1644 (C═O, lactam), 1634 (C═O, amide). ^{1}H NMR 400 MHz ($CDCl_3$): 076 and 0.82 (2s, 18-CH_3), 0.87 and 0.88 (2t, J = 7.2 Hz, 10′-CH_3), 0.85 and 0.89 (2s, 19-CH_3), 0.30−2.20 (residual CH and CH_2), 2.46 (m, 2-CH_2), 2.90 and 2.94 (2s, 4-NCH_3), 3.06 (m), 3.42 (t, J = 9.5 Hz), 3.88 (m) and 4.66 (t, J = 10.0 Hz) (5α-CH, 1′-CH_2 and 17α-CH), 7.30 (m, 4 H of Ar−H). LRMS: calcd for $C_{36}H_{56}ClN_2O_2$ $[M + H]^+$ 584.4, found 584.3.

17β-[(*N*-Decyl)-3″-trifluoromethyl-4″-methoxybenzamido]-4-methyl-4-aza-5α-androstan-3-one (26). IR (film on NaCl): 1640 (C═O, lactam and amide). ^{1}H NMR 300 MHz ($CDCl_3$): 0.77 (s, 18-CH_3), 0.87 (s and t, J = 6.6 Hz, 19-CH_3 and 10′-CH_3), 0.60−2.05 (residual CH and CH_2), 2.40 (dd, J = 4.9 and 9.5 Hz, 2-CH_2), 2.91 (s, 4-NCH_3), 2.98 (m, 5α-CH and 1′-CH_2), 3.65 (broad, 17α-CH), 3.94 (s, CH_3O), 7.00 (d, J = 8.5 Hz, 5″-CH), 7.51 (d, J = 8.5 Hz, 6″-CH), 7.54 (s, 2″-CH). LRMS: calcd for $C_{38}H_{58}F_3N_2O_3$ $[M + H]^+$ 647.4, found 647.4.

17β-[(*N*-Dodecyl)-4″-chlorobenzamido]-4-methyl-4-aza-5α-androstan-3-one (30). IR (film on NaCl): 1642 (C═O, lactam), 1634 (C═O, amide). ^{1}H NMR 300 MHz ($CDCl_3$): 0.76 (s, 18-CH_3), 0.86 (s, 19-CH_3), 0.87 (t, J = 6.4 Hz, 12′-CH_3), 0.65−2.10 (residual CH and CH_2), 2.42 (dd, J = 4.5 and 9.2 Hz, 2-CH_2), 2.95 (s, 4-NCH_3), 3.02 (m, 5α-CH and 1′-CH_2), 3.80 (broad, 17α-CH), 7.29 (d, J = 6.7 Hz, 3″-CH and 5″-CH), 7.38 (d, J = 8.3 Hz, 2″-CH and 6″-CH). LRMS: calcd for $C_{38}H_{60}ClN_2O_2$ $[M + H]^+$ 611.4, found 611.5.

17β-[(*N*-Dodecyl)-2″,6″-dichlorobenzamido]-4-methyl-4-aza-5α-androstan-3-one (33). IR (film on NaCl): 1644 (C═O, lactam and amide). ^{1}H NMR 400 MHz ($CDCl_3$): 0.81 and 0.83 (2s, 18-CH_3), 0.85 and 0.89 (2s, 19-CH_3), 0.88 (t, J = 6.9 Hz, 12′-CH_3), 0.40−2.10 (residual CH and CH_2), 2.58 (m, 2-CH_2), 2.93 and 2.97 (2s, 4-NCH_3), 3.08 (m), 3.34 (m), 3.73 (t, J = 8.8 Hz) and 4.60 (t, J = 10.0 Hz) (5α-CH, 1′-CH_2 and 17α-CH), 7.20−7.40

(m, Ar−H). LRMS: calcd for $C_{38}H_{59}Cl_2N_2O_2$ $[M + H]^+$ 645.4, found 645.4.

17β-[(*N*-Heptyl)-4″-fluorobenzamido]-4-methyl-4-aza-5α-androstan-3-one (34). IR (film on NaCl): 1634 (C═O, lactam and amide). ^{1}H NMR 400 MHz ($CDCl_3$): 0.76 (s, 18-CH_3), 0.86 (s broad, 19-CH_3 and 7′-CH_3), 0.60−2.10 (residual CH and CH_2), 2.44 (dd, J = 4.4 and 9.4 Hz, 2-CH_2), 2.91 (s, 4-NCH_3), 3.03 (m, 5α-CH, 1′-CH_2), 3.75 (broad, 17α-CH), 7.07 (t, J = 8.6 Hz, 3″-CH and 5″-CH), 7.32 (dd, J = 5.5 and 8.8 Hz, 2″-CH and 6″-CH. ^{13}C NMR 100 MHz ($CDCl_3$): 12.37, 13.06, 14.00, 20.46, 22.51, 23.07, 23.98, 25.24, 26.85, 28.76, 28.93, 29.20, 29.69, 31.63, 32.78, 33.93, 36.45, 36.92, 45.58, 51.32, 51.82, 65.71, 115.28, 115.50, 128.74, 134.30, 161.60, 164.07, 170.91, 172.28. LRMS: calcd for $C_{33}H_{50}FN_2O_2$ $[M + H]^+$ 525.4, found 525.3.

17β-[(*N*-Dodecyl)-4″-fluorobenzamido]-4-methyl-4-aza-5α-androstan-3-one (36). IR (film on NaCl): 1636 (C═O, lactam and amide). ^{1}H NMR 300 MHz ($CDCl_3$): 0.76 (s, 18-CH_3), 0.87 (s broad, 19-CH_3 and 12′-CH_3), 0.60−2.10 (residual CH and CH_2), 2.42 (dd, J = 4.4 and 9.3 Hz, 2-CH_2), 2.91 (s, 4-NCH_3), 3.00 (m, 5α-CH and 1′-CH_2), 3.80 (broad, 17α-CH), 7.07 (t, J = 8.5 Hz, 3″-CH and 5″-CH), 7.32 (dd, J = 5.6 and 8.1 Hz, 2″-CH and 6″-CH). LRMS: calcd for $C_{38}H_{60}FN_2O_2$ $[M + H]^+$ 595.5, found 595.5.

17β-[(*N*-Heptyl)-3″-chloromethylbenzamido]-4-methyl-4-aza-5α-androstan-3-one (37). IR (film on NaCl): 1634 (C═O, lactam and amide). ^{1}H NMR 300 MHz ($CDCl_3$): 0.78 (s, 18-CH_3), 0.86 (s broad, 19-CH_3 and 7′-CH_3), 0.60−2.10 (residual CH and CH_2), 2.42 (dd, J = 4.5 and 9.6 Hz, 2-CH_2), 2.91 (s, 4-NCH_3), 3.05 (m, 5α-CH and 1′-CH_2), 3.80 (broad, 17α-CH), 4.60 (s, CH_2Cl), 7.28 (m, 5″-CH), 7.37 (m, 2″-CH, 4″-CH and 6″-CH). LRMS: calcd for $C_{34}H_{52}ClN_2O_2$ $[M + H]^+$ 555.4, found 555.3.

17β-[(*N*-Heptyl)-4″-chloromethylbenzamido]-4-methyl-4 aza-5α-androstan-3-one (40). IR (film on NaCl): 1634 (C═O, lactam and amide). ^{1}H NMR 300 MHz ($CDCl_3$): 0.77 (s, 18-CH_3), 0.86 (s broad, 19-CH_3 and 7′-CH_3), 0.60−2.10 (residual CH and CH_2), 2.42 (dd, J = 4.7 and 9.2 Hz, 2-CH_2), 2.90 (s, 4-NCH_3), 3.02 (m, 5α-CH and 1′-CH_2), 3.80 (broad, 17α-CH), 4.59 (s, CH_2Cl), 7.31 (d, J = 8.1 Hz, 3″-CH and 5″-CH), 7.39 (d, J = 8.1 Hz, 2″-CH and 6″-CH). LRMS: calcd for $C_{34}H_{52}ClN_2O_2$ $[M + H]^+$ 555.4, found 555.3.

17β-[(*N*-Heptyl)-4″-cyanobenzamido]-4-methyl-4-aza-5α-androstan-3-one (43). IR (film on NaCl): 1633 (C═O, lactam and amide). ^{1}H NMR 300 MHz ($CDCl_3$): 0.35 and 0.70 (2m, 9-CH), 0.77 (s, 18-CH_3), 0.86 (s broad, 19-CH_3 and 7′-CH_3), 0.80−2.10 (residual CH and CH_2), 2.42 (m, 2-CH_2), 2.91 (s, 4-NCH_3), 3.07 (m, 5α-CH and 1H of 1′-CH_2), 3.24, 3.60, 3.87, and 4.60 (4m, 1H of 1′-CH_2 and 17α-CH), 7.43 (d, J = 7.6 Hz, 2″-CH and 6″-CH), 7.69 (d, J = 8.1 Hz, 3″-CH and 5″-CH). LRMS: calcd for $C_{34}H_{50}N_3O_2$ $[M + H]^+$ 532.4, found 532.3.

Second Library (Compounds 46−67). The 22 members of library 2 were obtained as described above. Filtration over a silica gel pad afforded amides **46**−**67** in yields ranging from 69% to 94%. Except compounds **56**, **57**, **60**, and **61**, which were not tested, LRMS gave satisfactory results, and TLC analyses confirmed that purities of compounds were acceptable for enzymatic assay. Representative compounds **47**, **49**, **51**, **53**, **55**, **58**, **62**, **64**, and **66** were also analyzed by IR and ^{1}H NMR. After compound **46** was identified as the best 17β-HSD7 inhibitor of this library, it was selected for additional studies, purified again, and fully characterized by IR, ^{1}H NMR, and ^{13}C NMR and the purity assessed by HPLC.

17β-[(*N*-Heptyl)-2″,6″-difluorobenzamido]-4-methyl-4-aza-5α-androstan-3-one (46). IR (film on NaCl): 1644 (C═O, lactam and amide). ^{1}H NMR 400 MHz ($CDCl_3$): 0.78 and 0.79 (2s, 18-CH_3), 0.82 and 0.89 (2t, J = 7.2 Hz, 7′-CH_3), 0.86 and 0.89 (2s, 19-CH_3), 0.30−2.10 (residual CH and CH_2), 2.48 (m, 2-CH_2), 2.91 and 2.95 (2s, 4-NCH_3), 3.10 (m), 3.47 (t, J = 9.5 Hz), 3.92 (m), 4.69 (t, J = 9.9 Hz) (4 signals of 5α-CH, 1′-CH_2 and 17α-CH), 6.95 (m, 2 H of Ar−H), 7.34 (m, 1 H of Ar−H). ^{13}C NMR 100 MHz ($CDCl_3$): 12.31, 12.36, 12.73, 13.07, 13.05, 14.07, 20.31, 20.63, 22.40, 22.59, 22.79, 23.46, 23.63, 24.31, 25.14, 25.22, 26.47, 27.24, 28.26, 28.29, 28.77, 28.83, 29.00, 29.25, 29.31, 39.58, 29.79, 30.78, 31.38, 31.81, 32.65, 33.71, 34.08, 35.59, 36.35, 36.40, 37.12, 44.72, 44.94, 46.34, 47.04, 51.13, 51.46, 51.63, 51.88, 110.98, 111.21, 111.37, 111.74, 111.99, 112.22, 115.84, 127.78, 130.37, 130.46, 130.56, 130.65, 156.64, 160.28, 162.40, 163.12, 171.16, 171.33. LRMS: calcd for $C_{33}H_{49}F_2N_2O_2$ $[M + H]^+$ 553.4, found 543.3.

17β-[(*N*-Decyl)-2″,6″-difluorobenzamido]-4-methyl-4-aza-5α-androstan-3-one (47). IR (film on NaCl): 1645 (C═O, lactam and amide). ^{1}H NMR 400 MHz ($CDCl_3$): 0.77 and 0.78 (2s, 18-CH_3), 0.86 and 0.87 (2t, J = 7.0 Hz, 10′-CH3), 0.88 and 0.89 (2s, 19-CH_3), 0.40−2.10 (residual CH and CH_2), 2.44 (m, 2-CH_2), 2.90 and 2.93 (2s, 4-NCH_3), 3.10 (m), 3.47 (t, J = 9.5 Hz), 3.90 (m) and 4.67 (t, J = 9.9 Hz) (4 signals of 5α-CH, 1′-CH_2 and 17α-CH), 6.93 (m, 2 H of Ar−H), 7.32 (m, 1 H of Ar−H). LRMS: calcd for $C_{36}H_{55}F_2N_2O_2$ $[M + H]^+$ 585.4, found 585.4.

17β-[(*N*-Decyl)-2″,5″-difluorobenzamido]-4-methyl-4-aza-5α-androstan-3-one (49). IR (film on NaCl): 1646 (C═O, lactam), 1636 (C═O, amide). ^{1}H NMR 400 MHz ($CDCl_3$): 0.76 and 0.78 (2s, 18-CH_3), 0.86 and 0.87 (2t, J = 6.9 Hz, 10′-CH_3), 0.88 and 0.89 (2s, 19-CH_3), 0.40−2.10 (residual CH and CH_2), 2.46 (m, 2-CH_2), 2.91 and 2.94 (2s, 4-NCH_3), 3.10, 3.48, 3.88, and 4.63 (4m, 5α-CH, 1′-CH_2 and 17α-CH), 7.06 (m, 3″-CH and 4″-CH), 7.13 and 7.68 (2m, 6″-CH). LRMS: calcd for $C_{36}H_{55}F_2N_2O_2$ $[M + H]^+$ 585.4, found 585.5.

17β-[(*N*-Decyl)-2″,4″-difluorobenzamido]-4-methyl-4-aza-5α-androstan-3-one (51). IR (film on NaCl): 1636 (C═O, lactam and amide). ^{1}H NMR 400 MHz ($CDCl_3$): 0.75 and 0.78 (2s, 18-CH_3), 0.85 and 0.87 (2t, J = 7.1 Hz, 10′-CH_3), 0.87 and 0.89 (2s, 19-CH_3), 0.30−2.10 (residual CH and CH_2), 2.44 (m, 2-CH_2), 2.90 and 2.94 (2s, 4-NCH_3), 3.10 (m), 3.49 (t, J = 9.5 Hz), 3.90 (m), 4.68 (m) (4 signals of 5α-CH, 1′-CH_2 and 17α-CH), 6.85 (m, 1H of Ar−H), 6.94 (t, J = 7.3 Hz, 1 H of Ar−H), 7.32 and 7.40 (2m, 6″-CH). LRMS: calcd for $C_{36}H_{55}F_2N_2O_2$ $[M + H]^+$ 585.4, found 585.4.

17β-[(*N*-Decyl)-3″,5″-difluorobenzamido]-4-methyl-4-aza-5α-androstan-3-one (53). IR (film on NaCl): 1642 (C═O, lactam) and 1632 (C═O, amide). ^{1}H NMR 400 MHz ($CDCl_3$): 0.75 (s, 18-CH_3), 0.87 (s, 19-CH_3), 0.87 (t, J = 6.9 Hz, 12′-CH_3), 0.70−2.10 (residual CH and CH_2), 2.43 (dd, J = 4.6 and 9.5 Hz, 2-CH_2), 2.92 (s, 4-NCH_3), 3.03 (m, 5α-CH and 1′-CH_2), 3.78 (broad, 17α-CH), 6.85 (m, Ar−H). LRMS: calcd for $C_{36}H_{55}F_2N_2O_2$ $[M + H]^+$ 585.4, found 585.4.

17β-[(*N*-Decyl)pentafluorobenzamido]-4-methyl-4-aza-5α-androstan-3-one (55). IR (film on NaCl): 1652 (C═O, lactam and amide). ^{1}H NMR 400 MHz ($CDCl_3$): 0.77 and 0.79 (2s, 18-CH_3), 0.86 and 0.88 (2t, J = 6.9 Hz, 10′-CH_3), 0.87 and 0.89 (2s, 19-CH_3), 0.40−2.10 (residual CH and CH_2), 2.44 (dd, J = 5.0 and 9.8 Hz, 2-CH_2), 2.91 and 2.93 (2s, 4-NCH_3), 3.10 (m), 3.35 (t, J = 9.6 Hz), 3.88 (m) and 4.60 (t, J = 9.9 Hz) (4 signals of 5α-CH, 1′-CH_2 and 17α-CH). LRMS: calcd for $C_{36}H_{52}F_5N_2O_2$ $[M + H]^+$ 639.4, found 639.4.

17β-[(*N*-Heptyl)-2″-fluoro-6″-trifluoromethylbenzamido]-4-methyl-4-aza-5α-androstan-3-one (58). IR (film on NaCl): 1646 (C═O, lactam and amide). ^{1}H NMR 400 MHz ($CDCl_3$): 0.79 and 0.81 (2s, 18-CH_3), 0.80 and 0.81 (2t, J = 7.0 Hz, 7′-CH_3), 0.85 and 0.89 (2s, 19-CH_3), 0.40−2.10 (residual CH and CH_2), 2.44 (m, 2-CH_2), 2.89 and 2.93 (2s, 4-NCH_3), 3.10 (m), 3.25 (t, J = 9.5 Hz), 3.76 (m), 4.53 (t, J = 10.0 Hz) and 4.61 (t, J = 10.0 Hz) (5 signals of 5α-CH, 1′-CH_2 and 17α-CH), 7.32 (m, 1 H of Ar−H), 7.50 (m, 2 H of Ar−H). LRMS: calcd for $C_{34}H_{49}F_4N_2O_2$ $[M + H]^+$ 593.4, found 593.3.

17β-[(*N*-Heptyl)-4″-*tert*-butylbenzamido]-4-aza-methyl-5α-androstan-3-one (62). IR (film on NaCl): 1636 (C═O, lactam and amide). ^{1}H NMR 400 MHz ($CDCl_3$): 0.78 (s, 18-CH_3), 0.84 (t, J = 7.2 Hz, 7′-CH_3), 0.87 (s, 19-CH_3), 1.32 (s, $(CH_3)_3C$), 0.70−2.1 (residual CH and CH_2), 2.48 (m, 2-CH_2), 2.93 (s, 4-NCH_3), 3.02 (m, 5α-CH and 1′-CH_2), 3.78 (broad, 17α-CH), 7.25 (d, J = 6.5 Hz, 3″-CH and 5″-CH), 7.38 (d, J = 8.3 Hz,

2″-CH and 6″-CH). LRMS: calcd for $C_{37}H_{59}N_2O_2$ [M + H]$^+$ 563.5, found 563.4.

17β-[(*N*-Heptyl)-4″-heptylbenzamido]-4-aza-methyl-5α-androstan-3-one (64). IR (film on NaCl): 1636 (C=O, lactam and amide). ^{1}H NMR 400 MHz ($CDCl_3$): 0.77 (s, 18-CH_3), 0.87 (s, 19-CH_3), 0.88 (t, J = 6.8 Hz, 7′-CH_3 and CH_3CH_2), 0.70−2.10 (residual CH and CH_2), 2.40 (m, 2-CH_2), 2.61 (t, J = 7.6 Hz, CH_2CH_2Ar), 2.91 (s, 4-NCH_3), 3.03 (m, 5α-CH and 1′-CH_2), 3.78 (broad, 17α-CH), 7.16 (d, J = 8.0 Hz, 3″-CH and 5″-CH), 7.23 (d, J = 8.2 Hz, 2″-CH and 6″-CH). LRMS: calcd for $C_{40}H_{65}N_2O_2$ [M + H]$^+$ 605.5, found 605.5.

17β-[(*N*-Heptyl)-4″-iodobenzamido]-4-methyl-4-aza-5α-androstan-3-one (66). IR (film on NaCl): 1636 (C=O, lactam and amide). ^{1}H NMR 400 MHz ($CDCl_3$): 0.77 (s, 18-CH_3), 0.87 (s broad, 19-CH_3 and 7′-CH_3), 0.60−2.10 (residual CH and CH_2), 2.43 (dd, J = 4.4 and 9.3 Hz, 2-CH_2), 2.91 (s, 4-NCH_3), 3.03 (m, 5α-CH and 1′-CH_2), 3.78 (broad, 17α-CH), 7.07 (d, J = 7.9 Hz, 3″-CH and 5″-CH), 7.72 (d, J = 8.2 Hz, 2″-CH and 6″-CH). LRMS: calcd of $C_{33}H_{50}IN_2O_2$ [M + H]$^+$ 633.3, found 633.3.

17β-(*N*-Heptylamino) and (*N*-Heptylformamido) Derivatives of Estrane Nucleus (Compounds 69−71). 17β-(*N*-Heptylamino)-3-methoxyestra-1,3,5(10)-triene (69). This compound was synthesized from **68** (2.0 g, 7.03 mmol) as described for the synthesis of compounds **6** and **9** except for the following details: (1) 5 equiv (35.16 mmol) of *n*-heptylamine was added, and (2) the aqueous phase was basified to pH 13 using 4 N NaOH. The crude oil was purified by flash column chromatography (acetone/hexanes, 3:97 to 5:95) to give compound **69** (522 mg, 64% yield). IR (film on NaCl): 3700 (weak), 1609 and 1500 (C=C, aryl). ^{1}H NMR 400 MHz ($CDCl_3$): 0.75 (s, 18-CH_3), 0.90 (t, J = 6.8 Hz, 7′-CH_3), 1.20−2.40 (residual CH and CH_2), 2.65 (m, 1′-CH_2 and 17α-CH), 2.85 (m, 6-CH_2), 3.78 (s, CH_3O), 6.64 (d, J = 2.6 Hz, 4-CH), 6.72 (dd, J = 2.7 and 8.5 Hz, 2-CH), 7.21 (d, J = 8.6 Hz, 1-CH). ^{13}C NMR 75 MHz ($CDCl_3$): 11.83, 14.10, 22.60, 23.46, 26.46, 26.73, 27.39, 29.22, 29.50, 29.82, 30.24, 31.80, 38.15, 38.74, 43.04, 43.94, 48.96, 52.30, 55.16, 69.07, 111.40, 113.71, 126.28, 132.77, 137.97, 157.35. LRMS: calcd for $C_{26}H_{42}NO$ [M + H]$^+$ 384.4, found 384.3.

17β-[(*N*-Heptyl)formamido]-3-methoxyestra-1,3,5(10)-triene (70). Compound **70** was prepared following the same method as described for compounds **16**−**18**, starting from compound **69** (50 mg, 0.130 mmol) using DCC (0.391 mmol, 3 equiv) and formic acid (0.391 mmol, 3 equiv). The resulting crude product was purified by flash column chromatography (EtOAc/hexanes, 5:95) to give a solid (45 mg, 84% yield). IR (film on NaCl): 1670 (C=O, amide), 1500 and 1615 (C=C, aryl). ^{1}H NMR 300 MHz ($CDCl_3$): 0.74 (s, 18-CH_3), 0.88 (t, J = 6.5 Hz, 7′-CH_3), 1.20−2.40 (residual CH and CH_2), 2.85 (m, 6-CH_2), 3.35 (m, 1′-CH_2 and 17α-CH), 3.77 (s, CH_3O), 6.63 (d, J = 2.7 Hz, 4-CH), 6.71 (dd, J = 2.7 and 8.6 Hz, 2-CH), 7.19 (d, J = 8.6 Hz, 1-CH), 8.23 (s, 0.8 H of HCON), 8.28 (s, 0.2 H of HCON). ^{13}C NMR 75 MHz ($(CD_3)_2CO$): 12.80, 13.19, 14.34, 23.26, 23.48, 23.74, 23.86, 24.96, 26.03, 27.36, 27.69, 28.06, 29.49, 32.57, 33.36, 37.70, 38.60, 39.54, 44.57, 45.16, 47.23, 51.70, 51.79, 55.27, ∼63, 69.07, 112.24, 114.41, 129.04, 132.91, 138.41, 158.55, 163.36, 164.77. LRMS: calcd for $C_{27}H_{42}NO_2$ [M + H]$^+$ 412.3, found 412.3.

17β-[(*N*-Heptyl)formamido]-3-hydroxyestra-1,3,5(10)-triene (71). Compound **69** (29 mg, 0.071 mmol) was dissolved in dry CH_2Cl_2 (9 mL) under an argon atmosphere. The solution was stirred, and BBr_3 (0.177 mmol, 2.5 equiv) was slowly added at 0 °C and then allowed to warm up at rt. After 4 h, HCl (10%) was added to stop the reaction and the aqueous phase was neutralized with saturated $NaHCO_3$. The unprotected steroid was extracted by three portions of CH_2Cl_2, which were collected, washed with brine, filtered over cotton wool, and evaporated under reduced pressure. The crude compound was purified by flash column chromatography (acetone/hexanes, 10:90) to give **71** as a white solid (12 mg, 47% yield). IR (film on NaCl): 3220 (OH, phenol), 1643 (C=O, amide), 1580 and 1485 (C=C, aryl). ^{1}H NMR 400 MHz ($CDCl_3$): 0.74 (s, 18-CH_3), 0.88 (t, J = 6.8 Hz, 7′-CH_3), 1.20−2.40 (residual CH and CH_2), 2.83 (m, 6-CH_2), 3.33 (m, 1′-CH_2 and 17α-CH), 6.57 (d, J = 2.7 Hz, 3-CH), 6.63 (dd, J = 2.7 and 8.5 Hz, 2-CH), 7.13 (d, J = 8.5 Hz, 1-CH), 8.22 (s, 0.85 H of HCON), 8.27 (s, 0.15 H of HCON). ^{13}C NMR 75 MHz, ($(CD_3)_2CO$): 12.85, 13.24, 14.39, 23.29, 23.52, 23.79, 23.91, 25.01, 27.01, 27.39, 27.72, 28.13, 30.27, 32.60, 33.41, 37.21, 37.76, 38.64, 39.65, 43.03, 44.60, 44.86, 45.20, 46.63, 47.27, 51.74, 51.84, 63.13, 69.13, 113.54, 115.88, 127.07, 131.77, 138.37, 155.91, 163.37, 164.79. LRMS: calcd for $C_{26}H_{40}NO_2$ [M + H]$^+$ 398.3, found 398.3. HPLC purity: 83%.

17β-[(*N*-Heptyl)alkyl/arylamino]-4-methyl-4-aza-5α-androstan-3-ones (72−75). 17β-[(*N*-Heptyl)pentylamino]-4-methyl-4-aza-5α-androstan-3-one (72). The *N*-heptylamino derivative **6** (24 mg, 0.060 mmol) was dissolved in hot anhydrous acetonitrile (2 mL) and transferred into a Schlenk tube containing potassium carbonate (0.270 mmol, 4.5 equiv). Pentyl iodide (0.240 mmol, 4 equiv) was added to the mixture, and the tube was purged with argon and closed. *Caution*: Reactions performed in closed tubes should be carried out with suitable precautions such as the use of safety shields and gloves. The mixture was heated to 165 °C over 24 h. After that, it was allowed to cool and the solvent removed under reduced pressure. The residue was dissolved in water (15 mL) and extracted with three portions of EtOAc (15 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The crude residue was purified by flash column chromatography (acetone/hexanes, 15:85) to afford compound **72** (21.6 mg, 76% yield). IR (film on NaCl): 1650 (C=O, lactam). ^{1}H NMR 400 MHz ($CdCl_3$): 0.76 (s, 18-CH_3), 0.87 (s, 19-CH_3), 0.88 (t, J = 6.8 Hz, 7′-CH_3), 0.89 (t, J = 6.6 Hz, 5″-CH_3), 0.70−2.10 (residual CH and CH_2), 2.44 (m, 17α-H and 2-CH_2), 2.48 (t, J = 7.8 Hz, 1′-CH_2 and 1″-CH_2), 2.92 (s, 4-NCH_3), 3.01 (dd, J = 3.5 and 12.5 Hz, 5α-CH). ^{13}C NMR 100 MHz ($CDCl_3$): 12.21, 12.38, 14.10, 14.16, 21.17, 22.65, 22.77, 23.14, 25.36, 25.46, 25.75, 26.73, 27.61, 29.12, 29.40, 29.70, 29.87, 29.98, 31.92, 32.92, 34.33, 36.36, 39.31, 43.63, 51.54 (2x), 51.10, 52.05, 65.79, 71.84, 170.78. LRMS: calcd for $C_{31}H_{57}N_2O$ [M + H]$^+$ 473.5, found 473.4. HPLC purity: 90%.

17β-[(*N*-Heptyl)propylamino]-4-methyl-4-aza-5α-androstan-3-one (73). Compound **73** (23 mg, 83% yield) was obtained from **6** (26 mg, 0.0636 mmol) as reported above for **72**. IR (film on NaCl): 1651 (C=O, lactam). ^{1}H NMR 400 MHz ($CDCl_3$): 0.76 (s, 18-CH_3), 0.83 (t, J = 7.3 Hz, 3″-CH_3), 0.87 (s, 19-CH_3), 0.88 (t, J = 6.8 Hz, 7′-CH_3), 0.70−2.10 (residual CH and CH_2), 2.48 (m, 17α-CH, 2-CH_2, 1′-CH_2 and 1″-CH_2), 2.92 (s, 4-NCH_3), 3.01 (dd, J = 3.7 and 12.5 Hz, 5α-CH). ^{13}C NMR 100 MHz ($CDCl_3$): 11.86, 12.17, 12.33, 14.10, 18.77, 21.20, 22.62, 23.07, 25.30, 25.64, 26.67, 27.57, 29.08, 29.37, 29.68, 29.91, 31.89, 32.83, 34.24, 36.28, 39.20, 43.56, 51.53, 51.80, 52.89, 53.45, 65.73, 71.77, 170.72. LRMS: calcd for $C_{29}H_{53}N_2O$ [M + H]$^+$ 445.4, found 445.4. HPLC purity: 91%.

17β-[(*N*-Heptyl)benzylamino]-4-methyl-4-aza-5α-androstan-3-one (74). Compound **74** (28 mg, 89% yield) was prepared from **6** (26 mg, 0.0643 mmol) as reported above for **72**. IR (film on NaCl): 1651 (C=O, lactam), 1500 (C=C, aryl). ^{1}H NMR 400 MHz ($CDCl_3$): 0.83 (s, 18-CH_3), 0.85 (t, J = 7.0 Hz, 7′-CH_3), 0.88 (s, 19-CH_3), 0.70−2.10 (residual CH and CH_2), 2.45 (m, 2-CH_2 and 1′-CH_2), 2.61 (t, J = 9.1 Hz, 17α-CH), 2.92 (s, 4-NCH_3), 3.01 (dd, J = 3.4 and 12.5 Hz, 5α-CH), 3.68 (s, 1″-CH_2), 7.21 (t, J = 7.2 Hz, 1 H of Ar−H), 7.29 (t, J = 7.2 Hz, 2 H of Ar−H), 7.36 (d, J = 7.0 Hz, 2 H of Ar−H). ^{13}C NMR 75 MHz ($CDCl_3$): 12.33, 12.42, 14.06, 21.01, 22.56, 23.13, 24.68, 25.27, 25.65, 27.32, 29.06, 29.25, 29.87, 31.80, 32.81, 34.17, 36.28, 39.05, 40.38, 43.83, 51.84, 51.95, 52.64, 56.16, 65.71, 71.54, 126.30, 127.95 (2×), 128.23 (2×), 141.46, 170.72. LRMS: calcd for $C_{33}H_{53}N_2O$ [M + H]$^+$ 493.4, found 493.4. HPLC purity: 93%.

17β-[(*N*-Heptyl)cyclohexylmethylamino]-4-methyl-4-aza-5α-androstan-3-one (75). Compound **75** (4.2 mg, 20% yield) was prepared from **6** (17 mg, 0.0422 mmol) as reported above for compound **72**, but 20 equiv (0.844 mmol) of cyclohexylmethyl bromide and 5 equiv (0.211 mmol) of potassium carbonate were used instead. IR (film on NaCl): 1649 (C=O, lactam). ^{1}H NMR 400 MHz ($CDCl_3$): 0.72 (s, 18-CH_3), 0.87 (s, 19-CH_3), 0.88 (t, J = 6.9 Hz, 7′-CH_3) 0.75−2.10 (residual CH and CH_2), 2.23 (m, 1″-CH_2), 2.43 (2-CH_2, and 1′-CH_2), 2.52 (m, 17α-CH), 2.92 (s, 4-NCH_3), 3.01 (dd, J = 3.4 and 12.6 Hz, 5α-CH). ^{13}C NMR 75 MHz ($CDCl_3$): 12.41, 12.87, 14.05, 20.37, 20.98, 21.65, 22.52, 24.74, 25.14, 25.38, 25.76, 26.88, 29.01, 29.12, 29.69, 30.96, 31.33, 31.60, 32.08, 32.88, 33.93, 35.78, 36.34, 40.26, 43.36, 47.78, 50.89, 51.38, 53.61, 58.00, 65.50, 73.57, 170.56. LRMS: calcd for $C_{33}H_{59}N_2O$ $[M + H]^+$ 499.4, found 499.5.

17β-[(*N*-Heptyl)methylamino]-4-methyl-4-aza-5α-androstan-3-one (76). Compound **6** (67 mg, 0.167 mmol) was dissolved in anhydrous methanol (1.5 mL), and paraformaldehyde (0.184 mmol, 1.1 equiv) and sodium cyanoborohydride (0.200 mmol, 1.2 equiv) were added. The mixture was refluxed for 24 h, and 0.5 equiv of both reactants was added. The mixture was refluxed for an additional 6 h. The mixture was then allowed to cool, brine was added, and steroid was extracted with EtOAc (3×). The combined organic phase was washed with brine, dried over $MgSO_4$, and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (CH_2Cl_2, 100% to MeOH/CH_2Cl_2, 5:95) to afford compound **76** (35 mg, 50%). IR (film on NaCl): 1649, (C=O, lactam). ^{1}H NMR 300 MHz ($CDCl_3$): 0.88 (s broad, 18-CH_3, 19-CH_3 and 7′-CH_3), 0.70−2.10 (residual CH and CH_2), 2.25 (s broad, 1″-CH_3), 2.15−2.70 (broad, 1′-CH_2 and 17α-CH), 2.45 (dd, J = 4.6 and 9.6 Hz, 2-CH_2), 2.94 (s, 4-NCH_3), 3.03 (dd, J = 3.4 and 12.5 Hz, 5α-CH). ^{13}C NMR 75 MHz ($CDCl_3$): 12.22, 12.36, 14.10, 21.10, 22.62, 23.13, 25.29, 27.51, 29.11, 29.28, 29.90, 31.82, 32.87, 34.20, 36.28, 39.59, 41.26, 43.37, 51.58, 53.35, 56.46, 65.70, 74.65, 170.72. LRMS: calcd for $C_{27}H_{49}N_2O$ $[M + H]^+$ 417.4, found 417.3.

17β-(*N*-Alkylamino)-4-aza-5α-androstan-3-ones (78−81). 17β-(*N*-Decylamino)-4-aza-5α-androstan-3-one (78). Compound **78** was prepared from **77**[15,16] (150 mg, 0.518 mmol) as described for compounds **6** and **9** except that the formation of the imine was performed in a Schlenk tube containing molecular sieves, 4 Å, instead of a refluxing apparatus. The crude product was purified by flash column chromatography (MeOH/CH_2Cl_2, 3:97 to 15:85) to give a white solid (120 mg, 54% yield). IR (film on NaCl): 3188 and 3065 (NH), 1682 (C=O, lactam). ^{1}H NMR 400 MHz ($CDCl_3$): 0.78 (s, 18-CH_3), 0.87 (t, J = 7.3 Hz, 10′-CH_3), 0.89 (s, 19-CH_3), 0.75−2.15 (residual CH and CH_2), 2.38 (m, 2-CH_2), 2.61 (t, J = 8.7 Hz, 17α-CH), 2.66 (m, 1′-CH_2), 3.03 (dd, J = 3.5 and 12.2 Hz, 5α-CH), 6.52 (s broad, NH). ^{13}C NMR 75 MHz ($CDCl_3$): 11.36, 12.04, 14.13, 20.85, 22.69, 23.62, 27.33, 28.60, 29.30, 29.47, 29.58, 31.89, 33.35, 34.94, 35.78, 37.67, 42.92, 48.72, 51.30, 52.74, 60.73, 68.60, 172.05. LRMS: calcd for $C_{28}H_{51}N_2O$ $[M + H]^+$ 431.4, found 431.4.

17β-(*N*-Heptylamino)-4-aza-5α-androstan-3-one (79). Compound **79** (120 mg, 30% yield) was prepared from **77** (300 mg, 1.037 mmol) as reported above for **78**. IR (film on NaCl): 3200 and 3068 (NH), 1682 (C=O, lactam). ^{1}H NMR 400 MHz ($CDCl_3$): 0.70 (s, 18-CH_3), 0.87 (t, J = 7.0 Hz, 7′-CH_3), 0.87 (s, 19-CH_3), 0.70−2.05 (residual CH and CH_2), 2.35 (m, 2-CH_2), 2.51 (t, J = 8.7 Hz, 17α-CH), 2.58 (m, 1′-CH_2), 3.01 (dd, J = 3.7 and 12.3 Hz, 5α-CH), 6.52 (NH). ^{13}C NMR 75 MHz ($CDCl_3$): 11.36, 11.95, 14.10, 20.92, 22.62, 23.68, 27.38, 27.45, 28.63, 29.24, 29.33, 29.56, 30.44, 31.83, 33.37, 35.05, 35.84, 37.92, 42.95, 49.03, 51.40, 52.83, 60.77, 69.00, 172.03. LRMS: calcd for $C_{25}H_{45}N_2O$ $[M + H]^+$ 389.4, found 389.3.

17β-(*N*-Decylformamido)-4-aza-5α-androstan-3-one (80). Compound **80** (15 mg, 30% yield) was prepared from **78** (46 mg, 0.107 mmol) according to the method used for compound **16**. IR (film on NaCl): 3176 (NH), 1682 (C=O, lactam and amide). ^{1}H NMR 400 MHz ($CDCl_3$): 0.71 (s, 18-CH_3), 0.87 (t, J = 7.0 Hz, 10′-CH_3), 0.91 (s, 19-CH_3), 0.75−2.05 (residual CH and CH_2), 2.41 (m, 2-CH_2), 3.08 (d, J = 8.7 Hz, 5α-CH), 3.28 (m, 2.80 H of 1′-CH_2 and 17α-CH), 4.15 (t, J = 9.7 Hz, 0.2 H of 17α-CH), 5.65 (broad, NH), 8.18 (s, 0.8 H of HCON), 8.23 (s, 0.2 of HCON). ^{13}C NMR, 100 MHz ($CDCl_3$): 11.37, 12.40, 14.08, 20.66, 22.65, 23.00, 24.38, 27.08, 27.35, 28.62 (2x), 29.11, 29.27, 29.36, 29.51, 29.56, 31.86, 33.43, 34.88, 35.88, 36.86, 44.37, 44.43, 51.37, 51.76, 60.69, 68.66, 162.94, 164.84. LRMS: calcd for $C_{29}H_{51}N_2O_2$ $[M + H]^+$ 459.4, found 459.4.

17β-[(*N*-Heptyl)methylamino]-4-aza-5α-androstan-3-one (81). Compound **81** (30 mg, 64% yield) was prepared from **79** (45 mg, 0.116 mmol) according to the method used for compound **76** and purified by flash column chromatography (MeOH/CH_2Cl_2, 1:99 to 4:96). IR (film on NaCl): 3410 and 3210 (NH), 1652 (C=O, lactam). ^{1}H NMR 400 MHz ($CDCl_3$): 0.80 (s, 18-CH_3), 0.88 (t, J = 6.8 Hz, 7′-CH_3), 0.89 (s, 19-CH_3), 0.75−2.15 (residual CH and CH_2), 2.22 (s, 1″-CH_3), 2.40 (dd, J = 4.0 and 10.0 Hz, 2-CH_2), 2.30−2.60 (broad, 1′-CH_2 and 17α-CH), 3.04 (dd, J = 4.7 and 11.4 Hz, 5α-CH), 5.36 (s, NH). ^{13}C NMR 100 MHz ($CDCl_3$): 11.32, 12.62, 14.02, 20.93, 22.51, 22.82, 26.92, 27.21, 28.54, 28.92, 28.99, 31.60, 33.30, 34.65, 35.66, 39.10, 43.39, 50.67, 53.31, 60.54, 74.18, 171.82. LRMS: calcd for $[M + H]^+$ $C_{26}H_{47}N_2O$ 403.4, found 403.4.

General Methods for Biological Assay. 17β-HSD7 Inhibition Assays. Human embryonic kidney (HEK)-293 cells (American Type Culture Collection, Rockville, MD) were previously transfected with 17β-HSD7 DNA as reported by Lui et al.[5e] Essentially, pCMV-neo-h17β-HSD7 plasmids were transfected using the lipofectin transfection kit and grown under G-418 until resistant colonies were observed. HEK-293 cells overexpressing 17β-HSD7 were plated at 500 000 cells/well in a 6-well plate at 37 °C under a 95% air, 5% CO_2 humidified atmosphere in minimum essential medium (MEM) containing nonessential amino acids (100×, 10 mL/L), $NaHCO_3$ (2.2 g/L), glutamine, plasmocyne (5 μL/mL), pyruvic acid (0.11 g/L), and 10% (v/v) fetal calf serum. 15 000 cpm (∼150 nM) of [4-^{14}C]-estrone (51.3 mCi/mmol) or [4-^{14}C]-dihydrotestosterone (53 mCi/mmol) (Perkin-Elmer Life Sciences, inc. Boston, MA) and an ethanolic solution of inhibitor were added to freshly changed culture medium and incubated for 7 h (E_1 to E_2) or 18 h (DHT to 3β-diol). Each inhibitor was assessed in duplicate or in triplicate. After incubation time, culture medium was removed by pipeting and steroids were extracted twice with 2 mL of diethyl ether. The organic phases were pooled and evaporated to dryness under reduced pressure. Residues were dissolved in CH_2Cl_2 and dropped on silica gel 60 F_{254} thin layer chromatography plates (VWR, Ville Mont-Royal, Québec, Canada) for separation by migration in toluene/acetone (4:1) as solvent system. Substrates and metabolites were identified by comparison with reference steroids and quantified using the Storm 860 imager (Molecular Dynamics, Sunnyvale, CA). The % of transformation and the % of inhibition were calculated as follows: % transformation (E_1 to E_2) = [^{14}C]-E_2/([^{14}C]-E_1 + [^{14}C]-E_2) × 100, % transformation (DHT into 3β-diol) = [^{14}C]-3β-diol/([^{14}C]-DHT + [^{14}C]-3β-diol) × 100, and % inhibition = [(% transformation without inhibitor) − (% transformation with inhibitor)]/(% transformation without inhibitor) × 100.

For IC_{50} value determination, the HEK-293 cells overexpressing 17β-HSD7 were plated at 600 000 cells/well in the presence of 15 000 cpm of [^{14}C]-E_1 and the inhibitor in ethanolic solution (0.1 nM to 20 μM). Assessment was performed in duplicate. Cells were incubated overnight and steroids extracted as reported above. IC_{50} values were determined using a homemade program called DE_{50} 1.64 (CRCHUL, Québec, Canada).

5α-R Inhibition Assays ([4-^{14}C]-Δ^4-Dione into [4-^{14}C]-Adione). HEK-293 cells transfected with pCMV-neo-h5α-reductase type 1 or type 2 construction were plated at 500 000 cells/well in a 6-well plate at 37 °C under a 95% air, 5% CO_2 humidified atmosphere in minimum essential medium (MEM)

complemented as described above. Incubation in the presence of 15 000 cpm of [^{14}C]-4-androstene-3,17-dione (53.6 mCi/mmol) (Perkin-Elmer Life Sciences, Inc., Boston, MA) and inhibitor solution was performed in duplicate at two final concentrations of 0.3 and 3 μM (10 μL). Incubation time for 5α-R1 was 1 h, while incubation time for 5α-R2 was 3 h. After the incubation period, steroids were extracted as reported for 17β-HSD7 assay except that the TLC separation of radioactive materials (Δ^4-dione and A-dione) was achieved in toluene/EtOAc (4:1) as solvent system. Radioactivity associated with each metabolite was determined by the Storm 860 system, and the % of transformation and % of inhibition were calculated as reported above.

17β-HSD5 Inhibition Assays ([^{14}C]-Δ^4-Dione into [^{14}C]-T). HEK-293 cells transfected with pCMV-neo-h17β-HSD5 construction were plated at 500 000 cells/well and incubated in presence of 15 000 cpm of [4-^{14}C]-Δ^4-dione and appropriate concentrations (0.3 μM or 3 μM) of inhibitor in ethanol (in triplicate). Incubation time for this enzymatic reaction was 20 h at 37 °C and 5% CO_2. After incubation, steroids were extracted, separated, and quantified similarly as that reported in literature.[13]

17β-HSD1 Inhibition Assay ([^{14}C]-E_1 into [^{14}C]-E_2). The source of enzymatic activity was obtained from sonicated HEK-293 cells transfected with h17β-HSD1 gene, and the enzymatic assay was performed as previously described.[24] The inhibitor dissolved in ethanol was tested at two final concentrations of 0.1 and 1 μM.

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Supporting Information Available: Results of a preliminary screening of 150 compounds as potential inhibitors of the transformation of E_1 into E_2 by 17β-HSD7 (Table A) and HPLC purity of new synthesized compounds selected for additional studies as inhibitors of 17β-HSD7 (Table B). This material is available free of charge via the Internet at http://pubs.acs.org.

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