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Synthesis and In Vitro Study of 17β-[*N*-Ureylene-*N*,*N*′-disubstituted]-4-methyl-4-aza-5α-Androstan-3-ones as Selective Inhibitors of Type I 5α-Reductase

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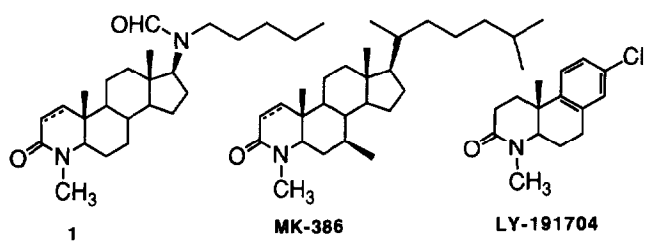
Abstract—A series of 17β-(*N*-ureylene-*N*,*N*′-disubstituted)-4-azasteroids as inhibitors of human type I 5α-reductase (5α-Re) were prepared from 17β-*N*-alkyl-4-methyl-4-aza-5α-androstan-3-ones and various isocyanates. For the measurement of 5α-Re activity, 293 cells transfected with human type I 5α-Re, cDNA were used. Azasteroids with an *N*-cyclopropyl ring exhibited potent inhibitory activity against type I 5α-Re. As the chain length increased, from the *N*′-ethyl to the *N*′-butyl chain, activity of compounds also increased and azasteroids with the *N*′-butyl chain showed strong inhibitory activity (IC_{50}=5.3 nM). Branching of alkyl chains decreased the potency of compounds. Introduction of the 1,2-double bond significantly reduced the activity of azasteroids. Replacement of the *N*′-alkyl chain with the phenyl moiety gave the most active compound of this series (IC_{50}=1.3 nM). Other variations such as the replacement of a *N*-cyclopropyl ring with the *N*-methyl or the *N*-butyl chain decreased the activity of compounds (compounds were less active compared with above). The IC_{50} values of *N*-methyl-*N*′-cyclohexyl- and *N*-butyl-*N*′-phenyl-ureylenes were 31.5 and 11.5 nM, respectively. In general, all azasteroids were poor inhibitors of Type II 5α-Re.

Introduction

Steroid 5α-reductase (EC 1.3.99.5)[1] catalyses the irreversible reduction of the C-4—C-5 double-bond of testosterone (T) to dihydrotestosterone (DHT),[2] the most active androgen known to be essential for male differentiation[3] and in the pathophysiology of many diseases, especially those relating to benign prostatic hyperplasia (BPH), prostate cancer,[4] acne,[5] hirsutism,[6] and androgenic alopecia (male-pattern baldness).[7] Two isozymes (type I and II) of 5α-Re have been isolated and characterized from the cDNA libraries.[8] The isozymes differ in their pattern of tissue distribution and with respect to biochemical and pharmacological properties. Type II is associated with the formation of DHT in the prostate which appears to be necessary, but perhaps not sufficient, for the pathogenesis of benign prostatic hyperplasia (BPH) and prostate cancer.[9] On the other hand, type I is related to skin disorders such as acne, hirsutism and male pattern baldness. Selective inhibition of type I isozyme could be one of the logical ways to treat androgen related skin diseases.

Recently, synthesis and in vitro evaluation of a wide variety of inhibitors of 5α-reductases were summarized in two review articles.[10,11] Finasteride[12] (ty I, IC_{50}=500 nM; ty II, IC_{50}=4.2 nM) and epristeride[13] (ty I, IC_{50}=410 nM; ty II, IC_{50}=0.2 nM) are the selective inhibitors of human type II isozyme. Finasteride is more effective in lowering DHT in humans than epristeride, and is currently used for the treatment for BPH.[14] Finasteride is also a slow and potent inhibitor of human type I 5α-reductase.[15] Recent studies have shown that the selectivity of inhibitors can be increased against the type I isozyme by making the correct choice of substituents at the C-17 position. For example, introduction of hydrophobic chains at C-17 position of 4-methyl-4-azasteroid gave compound **1** (ty I, IC_{50}=0.9 nM; ty II, IC_{50}>100 nM)[16] and MK-386 (ty I, IC_{50}=0.9 nM; ty II, IC_{50}=154 nM),[17] which are selective inhibitors of type I isozyme (Fig. 1). Structural similarity and the nature of the hydrophobic chain appear to be responsible for the similar activity against type I. The nonsteroidal benzoquinolinone LY-191704, which has a rigid tricyclic structure with the A-ring as a lactam, also exhibits high selectivity for the type I isozyme (ty I, K_{is}=9, 10 nM for (+)- and (−)-isomers).[18] Another class of inhibitors, e.g. 6-azasteroids, are equally potent against both isozymes.[19] However, potency against type I can be increased via the introduction of proper substituents at the C-17 position.[19] Our interest in the functionalization[20] of steroids has led to the development of another series of type I 5α-Re inhibitors. Thus, herein, we report the synthesis and activity of 17β-(*N*-ureylene-*N*,*N*′-disubstituted)-4-methyl-4-aza-5α-



1 **MK-386** **LY-191704**

Figure 1.

androstan-3-ones as selective and potent inhibitors of human type I 5α-Re.

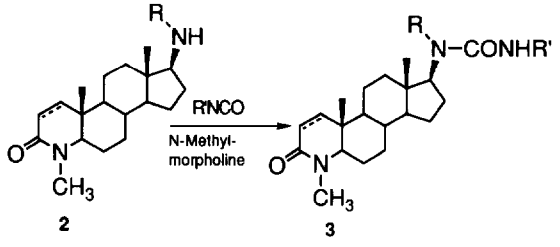
Results and Discussion

Chemistry

17β-(*N*-Alkyl)-4-methyl-4-aza-5α-androstan-3-ones (**2**) were synthesized from the commercially available testosterone.[16] Treatment of **2** with the appropriate alkyl/aryl isocyanates in the presence of *N*-methylmorpholine gave 17β-ureylene azasteroids **3** (Scheme 1).

Inhibition of human 5α-reductase (types I and II)

For the measurements of type I activity, 293 cells[20a] transfected with human type I 5α-Re cDNA were used as a source, while SW 13 cells[20a] transfected with human type II 5α-Re cDNA were used for the type II. The results are summarized in Table 1. 17β-Ureylene azasteroids having an *N*-cyclopropyl ring exhibited strong inhibitory activity against human type I isozyme. In general, activity of compounds **3b–d** increased as the chain length at the other end of the ureylene moiety increased from the *N'*-methyl to the *N'*-butyl, except for compounds **3a** and **b** which showed similar potency (IC_{50} = 21.3, 27.3 nM for **3a** and **b**). On the other hand, compound **3d** (IC_{50} = 5.3 nM) with the butyl group was fivefold more active than the compound **3b** (IC_{50} = 27.3 nM) with the ethyl group. Branching of the alkyl chain decreased the potency of the compounds **3e** and **f**. For example, azasteroid **3e** (IC_{50} = 20.5) was less active compared with **3c** (IC_{50} = 12.1 nM). Introduction of the 1,2-double bond gave another class of potent inhibitors (**3a'–f'**), which were also selective for the type I isozyme.[15,21] The structure–activity relationships suggest that the type I isozyme has preference for *N'*-straight alkyl chains of four, or perhaps bigger than four, carbon atoms. This SAR study supports our previous observation, where four to five carbon atoms of 17β-alkylformamido-chains showed high potency and selectivity for type I and activity increased as the straight chain length increased.[16] When, the alkyl group was replaced by phenyl, the most potent compound **3g** (IC_{50} = 1.3 nM) of this series was obtained. In other variations, where the *N*-cyclopropyl ring was replaced with the *N*-methyl or *N*-butyl group, activity of ureylene azasteroids decreased. For instance, with the *N*-methyl chain, compound **3h** was 22-fold less active compared with **3d**, and compound **3j** with the *N*-butyl chain was 13-fold less active. Ureylene azasteroid **3l** was also less active than phenylureylene **3g**; however, it was the most active compound (IC_{50} = 11.5 nM) of this class. In



Scheme 1.

Table 1. In vitro activity of 17β-*N*-(ureylene)-4-methyl-4-aza-androstan-3-ones[a]

Entry	C_1, C_2	R—NCON'—R'		IC_{50} (nM)[b] or % inhibition at 100 nM[c]	
				Human type I 5α-Re (transfected 293 cells)	Human type II 5α-Re (transfected SW-13 cells)
3a	Satd	Cyclopropyl	CH_3	21.3 ± 2.2	(11.6 ± 0.3)
3a'	Δ[1]	Cyclopropyl	CH_3	17.1 ± 1.7	⩾1000
3b	Satd	Cyclopropyl	C_2H_5	27.3 ± 3.4	(20 ± 3.1)
3b'	Δ[1]	Cyclopropyl	C_2H_5	(23.9 ± 3.1)	⩾1000
3c	Satd	Cyclopropyl	C_3H_7	12.1 ± 2.9	(51.5 ± 16.9)
3c'	Δ[1]	Cyclopropyl	C_3H_7	35.4 ± 4.5	⩾1000
3d	Satd	Cyclopropyl	C_4H_9	5.3 ± 1.1	(46.3 ± 1.3)
3d'	Δ[1]	Cyclopropyl	C_4H_9	24.2 ± 1	(4.9 ± 0.2)
3e	Satd	Cyclopropyl	$(CH_3)_2CH$	20.5 ± 1.9	(22.5 ± 1)
3e'	Δ[1]	Cyclopropyl	$(CH_3)_2CH$	(16.8 ± 1)	⩾1000
3f	Satd	Cyclopropyl	Cyclohexyl	(21.6 ± 0.9)	(34.6 ± 1.2)
3f'	Δ[1]	Cyclopropyl	Cyclohexyl	174.6 ± 51.4	(23.7 ± 3)
3g	Satd	Cyclopropyl	Phenyl	1.3 ± 0.64	(56.3 ± 4.5)
3h	Satd	CH_3	C_4H_9	121.5 ± 72.4	(13.05 ± 0.2)
3i	Satd	CH_3	Cyclohexyl	31.5 ± 6	(48.7 ± 4.2)
3j	Satd	C_4H_9	C_4H_9	68.1 ± 7.4	(23.8 ± 2)
3k	Satd	C_4H_9	Cyclohexyl	76.6 ± 22.4	(22.7 ± 0.8)
3l	Satd	C_4H_9	Phenyl	11.5 ± 1.9	(39.7 ± 0.4)
Finasteride[d]				262 ± 43.2	8.5 ± 0.4

[a]The results of the inhibition of 5α-reductase (type I and type II) were obtained by following standard procedures.
[b]The concentration of the compounds required to inhibit 5α-reductase activity by 50% is represented as IC_{50} values.
[c]% Inhibition is given in parentheses.
[d]Finasteride [*N*-(1,1-dimethylethyl)-3-oxo-4-aza-5α-androst-1-en-17β-carboxamide] was used as a standard reference. ^{3}H-Δ^4-Androstenedione (^{3}H-Δ^4-Dione, 5 nM) was added as the substrate.

general, all azasteroids were poor inhibitors of human type II 5α-Re.

In conclusion, the study has shown that the 17β-*N*-ureylene disubstituted azasteroids are selective inhibitors of human type I 5α-Re. The activity of compounds increased as the hydrophobic chain length increased. The phenyl substituted ureylene gave the best activity. This, and our earlier studies, suggests that the enzyme has a hydrophobic binding pocket near the D-ring. Branched hydrophobic chains are less preferred by the type I isozyme than the straight chains.

Experimental

General

Unless otherwise mentioned, materials obtained from commercial suppliers were used without further purification. THF was distilled from sodium/benzophenone immediately prior to use. All reactions except those involving water as a reagent were conducted under argon atmosphere. Melting points were measured on a Gallenkamp capillary melting point apparatus and are uncorrected. IR spectra were determined with a Perkin–Elmer 1600 Series FT IR spectrometer. ^{1}H NMR spectra were determined on a Bruker Aspect-3000 (300 MHz) spectrometer. ^{13}C NMR spectra were measured at 75.14 MHz with a Bruker Aspect-3000 spectrometer. Low-resolution mass spectra were obtained with a Varian Model 3700 mass spectrometer. High-resolution mass spectra were measured at the Department of Chemistry, University of Montreal, Montreal, Québec. All the final products were at least 99.5% pure and the purity was determined by HPLC of Waters Model 600E (Millipore).

General procedure for the preparation of compounds 3

To 17β-(*N*-cyclopropyl)-4-methyl-4-aza-5α-androstan-3-one (**2**) in THF (21 mL) were added morpholine (3 equiv) and the corresponding alkyl isocyanate (3 equiv), and the mixture was left stirring at rt for 16 h. The solvent was removed and the product was extracted with EtOAc. The organic phase was washed with 2% aq HCl, water, and dried over $MgSO_4$. Solvents were evaporated to give the crude residue, which was chromatographed on a silica gel column using acetone:triethylamine 32:1 as an eluent to give the pure product. Most ureylene azasteroids were recrystallized from a mixture of benzene/hexane.

17β-(Ureylene-*N*-cyclopropyl-*N'*-methyl)-4-methyl-4-aza-5α-androstan-3-one (3a). Yield 68%; mp 210 °C; IR (KBr): 3440 1654, 1507 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.67 (m, cyclopropyl), 0.71 (s, 3 H, 18-CH_3), 0.82 (s, 3 H, 19-CH_3), 2.37 (dd, 2 H, J=9.5, 4.8 Hz, 2-H_2), 2.76 (d, 3 H, J=4.5 Hz, NH—CH_3), 2.87 (s, 3 H, N—CH_3), 2.96 (dd, 1 H, J=12.4 and 2.7 Hz, 5α-H), 3.95 (t, 1 H, J=10 Hz, 17-H), 5.3 (q, 1 H, NH); ^{13}C NMR ($CDCl_3$): δ 170.7, 160.8, 67.7, 65.8, 52, 51.1, 45.1, 38, 36.3, '34.2, 32.8, 29.7, 29, 27.4, 25.2, 23.3, 22.9, 20.7, 13.6, 12.3, 11.4, 9.5; MS (EI): *m/z* (relative intensity) 344 (77), 329 (100), 315 (35); HRMS calcd for $C_{24}H_{39}O_2N_3$ 401.5926, found 401.5920.

17β-(Ureylene-*N*-cyclopropyl-*N'*-ethyl)-4-methyl-4-aza-5α-androstan-3-one (3b). Yield 78%; mp 194 °C; IR (KBr): 3480, 1630, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.66 (m, cyclopropyl), 0.70 (s, 3 H, 18-CH_3), 0.81 (s, 3 H, 19-CH_3), 1.08 (t, 3 H, J=7 Hz, $NHCH_2CH_3$), 2.36 (dd, 2 H, J=9.5, 4.8 Hz, 2-H_2), 2.8 (s, 3 H, N—CH_3), 3 (dd, 1 H, J=12.5, 3.4 Hz, 5α-H), 3.23 (m, 2 H, N—CH_2CH_3), 3.94 (t, 1 H, J=10 Hz, 17-H), 5.27 (t, 1 H, J=5 Hz, NH); ^{13}C NMR ($CDCl_3$): δ 170.8, 160.2, 67.7, 65.7, 52.1, 45.5, 38.1, 36.4, 35.4, 34.3, 32.9, 29.9, 29.1, 27.4, 25.3, 23.5, 23.1, 20.8, 15.6, 13.7, 12.4, 11.8, 9.7; MS (EI): *m/z* (relative intensity) 415 (13), 400 (5), 343 (70), 329 (100), 315 (36), 286 (24); HRMS calcd for $C_{25}H_{41}N_3O_2$ 415.3198, found 415.3186.

17β-(Ureylene-N-cyclopropyl-*N'*-propyl)-4-methyl-4-aza-5α-androstan-3-one (3c). Yield 80%; mp 164 °C; IR (KBr): 3480, 1630, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.67 (m, cyclopropyl), 0.70 (s, 3 H, 18-CH_3), 0.81 (s, 3 H, 19-CH_3), 0.86 (t, 3 H, J=7 Hz, $NHCH_2CH_2CH_3$), 1.46 (m, 2 H, $NHCH_2\underline{CH_2}CH_3$), 2.39 (dd, 2 H, J=9.5, 4.8 Hz, 2-H_2), 2.85 (s, 3 H, N—CH_3), 2.96 (dd, 1 H, J=12.5, 3.4 Hz, 5α-H), 3.1 (m, 2 H, N-$\underline{CH_2}CH_2CH_3$), 3.9 (t, 1 H, J=3.4 Hz, 17-H), 5.34 (t, 1 H, J=5 Hz, NH); ^{13}C NMR ($CDCl_3$): δ 170.6, 160.1, 67.5, 65.5, 51.9, 50.9, 45.3, 42.3, 37.9, 36.3, 34.1, 32.7, 29.6, 28.9, 27.2, 25.2, 23.3, 22.9, 20.7, 13.6, 12.3, 11.6, 11.3, 9.5; MS (EI): *m/z* (relative intensity) 429 (45), 414 (18), 400 (12), 344 (40), 329 (100), 315 (28), 305 (24); calcd for $C_{26}H_{43}N_3O_2$ 429.3355, found 429.3375.

17β-(Ureylene-*N*-cyclopropyl-*N'*-butyl)-4-methyl-4-aza-5α-androstan-3-one (3d). Yield 88%; mp 72 °C; IR (KBr): 3480, 1620, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.66 (m, cyclopropyl), 0.72 (s, 3 H, 18-CH_3), 0.83 (s, 3 H, 19-CH_3), 0.88 [t, 3 H, J=7 Hz, $NH(CH_2)_3CH_3$], 1.26 (m, 2 H, $NHCH_2CH_2CH_2CH_3$), 1.46 (m, 2 H, $NHCH_2CH_2\underline{CH_2}CH_3$), 2.38 (dd, 2 H, J=9.5, 4.7 Hz, C_2—H_2), 2.87 (S, 3 H, N—CH_3), 2.97 (dd, 1 H, J=12.5, 3.4 Hz, 5α-H), 3.2 (m, 2 H, $NHCH_2$-$CH_2CH_2CH_3$), 3.96 (t, 1 H, J=10 Hz, 17-H), 5.31 (t, 1 H, J=5 Hz, NH); ^{13}C NMR ($CDCl_3$): δ 170.7, 160.1, 67.6, 65.6, 52, 51, 45.3, 40.3, 38, 36.3, 34.1, 32.8, 32.3, 29.7, 29, 27.2, 25.2, 23.3, 22.9, 20.7, 20.1, 13.7, 13.6, 12.3, 11.6, 9.5; MS (EI): *m/z* (relative intensity) 443 (18), 428 (12), 360 (15), 344 (45), 329 (100), 315 (30); HRMS calcd for $C_{27}H_{45}N_3O_2$ 443.3511, found 443.3530.

17β-(Ureylene-*N*-cyclopropyl-*N'*-isopropyl)-4-methyl-4-aza-5α-androstan-3-one (3e). Yield 76%; mp 172 °C; IR (KBr): 3480, 1630, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.66 (m, cyclopropyl), 0.72 (s, 3 H, 18-CH_3), 0.83 (s, 3 H, 19-CH_3), 1.11, 1.12 [2d, 6 H, J=6.5 Hz, $CH(CH_3)2$], 2.38 (dd, 2 H, J=9.5, 4.7 Hz, 2- H_2), 2.88 (s, 3 H, N—CH_3), 2.98, (dd, 1 H, J=12.5, 3.4 Hz, 5α-H), 3.68–4.12 (m, 2H), 5.11 (d, 1 H, J=7 Hz, NH); ^{13}C NMR ($CDCl_3$): δ 170.7, 159.4, 67.4, 65.6, 53.8, 52, 51, 45.5, 42.1, 38, 36.3, 34.1, 32.8, 29.6, 29.2, 28.9, 27.1,

25.2, 23.3, 22.9, 20.7, 13.6, 12.3, 11.9, 9.7; MS (EI): *m/z* (relative intensity) 429 (7), 344 (53), 329 (100), 315 (30); HRMS calcd for $C_{26}H_{43}N_3O_2$ 429.3355, found 429.3363.

17β-(Ureylene-*N*-cyclopropyl-*N'*-cyclohexyl)-4-methyl-4-aza-5α-androstan-3-one (3f). Yield 76%; mp 100 °C; IR (KBr): 3480, 1620, 1500 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.66 (m, cyclopropyl), 0.71 (s, 3 H, 18-CH_3), 0.82 (s, 3 H, 19-CH_3), 1.4 to 1.85 (m, 10 H, cyclohexyl), 2.37 (dd, 2 H, J=9.5, 4.7 Hz, C_2—H_2), 2.86 (s, 3 H, N—CH_3), 2.96 (dd, 1 H, J=12.5, 3.5 Hz, 5α-H), 3.59 (m, 1 H, NH-cyclohexyl), 3.93 (t, 1 H, J=10 Hz, 17-H), 5.15 (t, 1 H, J=8 Hz, NH); ^{13}C NMR ($CDCl_3$): δ 170.7, 159.3, 67.5, 65.6, 52, 51, 48.9, 45.5, 38, 36.3, 34.1, 33.7, 32.7, 29.6, 29, 27.1, 25.6, 25.2, 24.9, 23.3, 23, 20.7, 13.6, 12.3, 11.8, 9.7; MS (EI): *m/z* (relative intensity) 469 (25), 454 (15), 417 (22), 344 (53), 329 (100); HRMS calcd for $C_{29}H_{47}N_3O_2$ 469.3668, found 469.3651.

17β-(Ureylene-*N*-cyclopropyl-*N'*-phenyl)-4-methyl-4-aza-5α-androstan-3-one (3g). Yield 73%; mp 108 °C; IR (KBr): 3440, 1641, 1610, 1500 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.80 (s, 3 H, 18-CH_3), 0.86 (s, 3 H, 19-CH_3), 2.4 (dd, 2 H, J=9.5, 4.7 Hz, 2-H_2), 2.9 (s, 3 H, N—CH_3), 3.01 (dd, 1 H, J=12.5, 3.5 Hz, 5α-H), 4.06 (t, 1 H, J=10 Hz, 17-H), 7 (t, 1 H, J=7.3 Hz, aromatic), 7.25 (m, 2 H, aromatic), 7.37 (m, 2 H, aromatic); ^{13}C NMR ($CDCl_3$): δ 170.7, 157.2, 139.1, 128.8, 122.8, 119.5, 67.8, 65.6, 52, 51.1, 45.6, 38.1, 36.3, 34.2, 32.8, 29.7, 29, 27.8, 25.2, 23.4, 23.1, 20.7, 13.7, 12.4, 12, 9.9; MS (EI): *m/z* (relative intensity) 344 (27), 329 (26), 315 (96); HRMS calcd for $C_{29}H_{41}N_3O_2$ 463.3258, found 463.3198.

17β-(Ureylene-*N*-cyclopropyl-*N'*-methyl)-4-methyl-4-aza-5α-androst-1-ene-3-one (3a'). Yield 70%; mp 201 °C; IR (KBr): 3392, 1654, 1605, 1527 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.66 (m, cyclopropyl), 0.72 (s, 3 H, 18-CH_3), 0.86 (s, 3 H, 19-CH_3), 2.77 (d, 1 H, J=4.7 Hz, NH—CH_3), 2.9 (s, 3 H, N—CH_3), 3.05 (dd, 1 H, J=12.9, 3.6 Hz, 5α-H), 3 .96 (t, 1 H, J=9.5 Hz, 17-H), 5.31 (t, 1 H, J=5 Hz, NH), 5.78 (d, 1 H, J=10 Hz, 2-H), 6.63 (d, 1 H, J=10 Hz, 1-H); ^{13}C NMR ($CDCl_3$): δ 165.5, 160.8, 148.8, 122.9, 77.4, 77, 76.6, 67.7, 63.7, 51, 47.9, 45.2, 39.4, 37.9, 34.5, 29.4, 27.5, 27.4, 24.3, 23.3, 23, 20.9, 13.7, 12.1, 11.5, 9.5; MS (EI): *m/z* (relative intensity) 399 (4), 341 (18), 327 (27), 313 (15); HRMS calcd for $C_{24}H_{37}N_3O_2$ 399.2885, found 399.2881.

17β-(Ureylene-*N*-cyclopropyl-*N'*-ethyl)-4-methyl-4-aza-5α-androst-1-ene-3-one (3b'). Yield 72%; mp 185 °C; IR (KBr): 3416, 1654, 1604, 1518 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.68 (m, cyclopropyl), 0.73 (s, 3 H, 18-CH_3), 0.87 (s, 3 H, 19-CH_3), 1.17 (t, 3 H, J=7 Hz, $NHCH_2CH_3$), 2.91 (s, 3 H, N—CH_3), 3.20 (q, 2 H, N—CH_2CH_3), 3.25 (dd, 1 H, J=9.5 4.8 Hz, 5α-H), 3.96 (t, 1 H, J=10 Hz, 17-H), 5.3 (t, 1 H, J=5 Hz, NH), 5.80 (d, 1 H, J=10 Hz, 2-H), 6.63 (d, 1 H, J=10 Hz, 1-H); ^{13}C NMR ($CDCl_3$): δ 165.6, 160.1, 148.8, 123, 67.6, 63.7, 51, 47.9, 45.5, 39.5, 38, 35.4, 34.6, 29.5, 27.5, 27.3, 24.3, 23.4, 23, 20.9, 15.5, 13.7, 12.2, 11.7, 9.7; MS (EI): *m/z* (relative intensity) 413 (11), 398 (7), 341 (60), 327 (100), 313 (33); HRMS calcd for $C_{25}H_{39}N_3O_2$ 413.3042, found 413.3096.

17β-(Ureylene-*N*-cyclopropyl-*N'*-propyl)-4-methyl-4-aza-5α-androst-1-ene-3-one (3c'). Yield 72%; mp 165 °C; IR (KBr): 3427, 1653, 1604, 1512 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.69 (m, cyclopropyl), 0.73 (s, 3 H, 18-CH_3), 0.87 (s, 3 H, 19-CH_3), 0.85 (t, 3 H, J=7 Hz, $NHCH_2CH_2CH_3$), 1.49 (m, 2 H, $NHCH_2CH_2CH_3$), 2.91 (s, 3 H, N—CH_3), 3.15 (m, 2 H, $NHCH_2CH_2CH_3$), 3.28 (dd, J=12.5, 3.4 Hz, 5α-H), 3.97 (t, 1 H, J=10 Hz, 17-H), 5.36 (t, 1 H, J=5 Hz, NH), 5.79 (d,1 H, J=10 Hz, 2-H), 6.62 (d, 1 H, J=10 Hz, 1-H); ^{13}C NMR ($CDCl_3$): δ 165.6, 160.2, 148.8, 123, 67.6, 63.7, 51, 47.9, 45.5, 42.3, 39.5, 38, 34.6, 29.5, 27.5, 27.3, 24.3, 23.4, 23, 21, 13.7, 12.1, 11.6, 11.4, 9.6; MS (EI): *m/z* (relative intensity) 427 (12), 412 (5), 341 (58), 327 (100); 313 (33); HRMS calcd for $C_{26}H_{41}N_3O_2$ 427.3198, found 427.3196.

17β-(Ureylene-*N*-cyclopropyl-*N'*-butyl)-4-methyl-4-aza-5α-androst-1-ene-3-one (3d'). Yield 98%; mp 76 °C; IR (KBr): 3428, 1654, 1624, 1542 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.71 (m, cyclopropyl), 0.75 (s, 3 H, 18-CH_3), 0.89 (s, 3 H, 19-CH_3), 0.91 (t, 3 H, J=7 Hz, $NHCH_2CH_2CH_2CH_3$), 1.33 (m, 2 H, $NHCH_2CH_2\underline{CH_2}$ CH_3), 1.47 (m, 2H, $NHCH_2\underline{CH_2}CH_2CH_3$), 2.9 (s, 3 H, N—$CH_3$), 3.2 (m, 2 H, $NH\underline{CH_2}CH_2CH_2CH_3$), 3.33 (dd, 1 H, J=12.5, 3.4 Hz, 5α-H), 3.99 (t, 1 H, J=10 Hz, 17-H), 5.34 (t, 1 H, J=7 Hz, NH), 5.81 (d, 1 H, J=10 Hz, 1 H, 2-H), 6.65 (d, 1 H, J=10 Hz, 1-H); ^{13}C NMR ($CDCl_3$): δ 165.7, 160.4, 148.9, 123.1, 67.7, 63.8, 51.1, 48, 45.5, 40.5, 39.6, 38, 34.7, 32.4, 29.5, 27.6, 27.4, 24.4, 23.5, 23.1, 21, 20.1, 13.8, 13.8, 12.2, 11.7, 9.7; MS (EI): *m/z* (relative intensity) 441 (22), 426 (25), 442 (58), 327 (76), 313 (63); HRMS calcd for $C_{27}H_{43}N_3O_2$ 441.3355, found 441.3355.

17β-(Ureylene-*N*-cyclopropyl-*N'*-isopropyl)-4-methyl-4-aza-5α-androst-1-ene-3-one (3e'). Yield 98%; mp 118 °C; IR (KBr): 3429, 1620, 1500 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.67 (m, cyclopropyl), 0.75 (s, 3 H, 18-CH_3), 0.88 (s, 3 H, 19-CH_3), 1.14, 1.15 [2d, 6 H, J=6.5 Hz, $CH(CH_3)_2$], 2.93 (s, 3 H, N—CH_3), 3.32 (dd, 1 H, J=12.5, 3.4 Hz, 5α-H), 3.93 (septet, 1 H, J=6.5 Hz, $CH(CH_3)_2$), 5.1 (t, 1 H, J=7 Hz, NH), 5.8 (d, 1 H, J=10 Hz, 2-H), 6.64 (d, 1 H, J=10 Hz, 1-H); ^{13}C NMR ($CDCl_3$): δ 165.7, 159.5, 148.9, 123.1, 67.5, 63.8, 51.1, 48, 45.7, 42.2, 39.5, 38, 34.6, 29.5, 27.6, 27.3, 24.4, 23.4, 23.1, 21, 13.8, 12.2, 12, 9.8; MS (EI): *m/z* (relative intensity) 427 (10), 412 (7), 369 (58), 342 (45), 327 (100), 313 (98); HRMS calcd for $C_{26}H_{41}N_3O_2$ 427.3198, found 427.3124.

17β-(Ureylene-*N*-cyclopropyl-*N'*-cyclohexyl)-4-methyl-4-aza-5α-androst-1-ene-3-one (3f'). Yield 97%; mp 104 °C; IR (KBr): 3480, 1650, 1594, 1500 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.70 (m, cyclopropyl), 0.76 (s, 3 H, 18-CH_3), 0.89 (s, 3 H, 19-CH_3), 1.42–1.85 (m, 10 H, cyclohexyl), 2.94 (s, 3 H, N—CH_3), 3.33 (dd, 1 H, J=12.5, 3.7 Hz, 5α-H), 3.61 (m, $N\underline{CH}C_5H_{10}$), 3.98 (t, 1 H, J=10 Hz, 17-H), 5.24 (t, 1 H, J=8 Hz, NH), 5.82

(d, 1 H, $J=10$ Hz, 2-H), 6.65 (d, 1 H, $J=10$ Hz,1-H); ^{13}C NMR ($CDCl_3$): δ 165.7, 159.4, 148.8, 123.1, 76.6, 67.6, 63.8, 51.1, 49.1, 48, 45.7, 39.6, 38.1, 34.7, 33.9, 29.5, 27.6, 27.4, 25.8, 25, 24.4, 23.5, 23.1, 21, 13.8, 12.2, 11.9, 9.8; MS (EI): *m/z* (relative intensity) 467 (4), 445 (3), 342 (56), 327 (68), 313 (62); HRMS calcd for $C_{29}H_{45}N_3O_2$ 467.3498, found 467.3570.

17β-(Ureylene-*N*-methyl-*N'*-butyl)-4-methyl-4-aza-5α-androstan-3-one (3h). Yield 85%; mp 85 °C; IR (KBr): 3376, 1630, 1529 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.66 (s, 3 H, 18-CH_3), 0.83 (s, 3 H 19-CH_3), 0.87 (t, 3 H, $J=7$ Hz, $NHCH_2CH_2CH_2CH_3$), 1.33 (m, 2 H, $NHCH_2CH_2CH_2CH_3$), 1.47 (m, 2 H, $NHCH_2CH_2$ CH_2CH_3), 2.78 (s, 3 H, N—CH_3), 2.88 (s, 3 H, N—CH_3), 2.99 (dd, 1 H, $J=12.5$, 3.4 Hz, 5α-H), 3.18 (m, 2 H, $NHCH_2CH_2CH_2CH_3$), 4.15 (t, 1 H, $J=10$ Hz, 17-H), 4.42 (t, 1 H, $J=7$ Hz, NH); ^{13}C NMR ($CDCl_3$): δ 170.6, 159.1, 65.6, 63.6, 51.9, 51.1, 44.8, 40.7, 37.2, 36.3, 33.9, 32.8, 32.4, 31.1, 29.7, 29.2, 29, 25.2, 23.1, 22.9, 20.5, 20.1, 13.8, 13, 12.3; MS (EI): *m/z* (relative intensity) 417 (13), 318 (25), 288 (10), 249 (22); HRMS calcd for $C_{25}H_{43}N_3O_2$ 417.3117, found 417.3098.

17β-(Ureylene-*N*-methyl-*N'*-cyclohexyl)-4-methyl-4-aza-5α-androstan-3-one (3i). Yield 90%; mp 164 °C; IR (KBr): 3374, 1636, 1522 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.66 (s, 3 H, 18-CH_3), 0.84 (s, 3 H 19-CH_3), 1.4–1.85 (m, 10 H, cyclohexyl), 2.39 (dd,2 H, $J=9.5$ Hz, 4.7 Hz, 2-H_2), 2.77 (s, 3 H, N—CH_3), 2.88 (s, 3 H, N—CH_3), 2.99 (dd, 1 H, $J=12.5$, 3.5 Hz, 5α-H), 3.6 (m, 1 H, $NCHC_5H_{10}$), 4.12 (t, $J=10$ Hz, 17-H), 4.42 (t, $J=7$ Hz, NH); ^{13}C NMR ($CDCl_3$): δ 170.7, 158.4, 65.6, 63.7, 52, 51.1, 49, 44.9, 37.4, 36.4, 34, 32.8, 31.2, 29.7, 29, 25.7, 25.2, 25, 23.1, 23, 20.5, 13, 12.3; MS (EI): *m/z* (relative intensity) 443 (45), 417 (7), 318 (15), 249 (14); HRMS calcd for $C_{27}H_{45}N_3O_2$ 443.3511, found 443.3513.

17β-(Ureylene-*N,N'*-dibutyl)-4-methyl-4-aza-5α-androstan-3-one (3j). Yield 98%; mp 84 °C; IR (KBr): 3025, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.62 (s, 3 H, 18-CH_3), 0.81 (s, 3 H 19-CH_3), 0.86 (t, 6 H, $J=7$ Hz, $NHCH_2CH_2CH_2CH_3$), 2.36 (dd, 2 H, $J=9.5$, 4.6 Hz, 2-H_2), 2.86 (s, 3 H, N—CH_3), 2.96 (dd, 1 H, $J=12.1$, 3.1 Hz, 5α-H), 2.95 [m, 4H, $CONHCH_2(CH_2)_2CH_3$], 4.01 (t, 1 H, $J=7$ Hz); 4.4 (t, 1 H, $J=5$ Hz); ^{13}C NMR ($CDCl_3$): δ 170.7, 158.5, 65.7, 64, 52, 51.2, 45.2, 44.5, 40.7, 37.5, 36.4, 34.1, 32.8, 32.4, 32, 29.7, 29.1, 29, 25.3, 24.2, 23.1, 20.6, 20.2, 20.1, 13.8 (2C), 12.7, 12.4; MS: (EI): *m/z* (relative intensity) 459 (18), 444 (5), 317 (25), 249 (5), 112 (100); HRMS calcd for $C_{28}H_{49}N_3O_2$ 459.3810, found 459.3871.

17β-(Ureylene-*N*-butyl-*N'*-cyclohexyl)-4-methyl-4-aza-5α-androstan-3-one (3k). Yield 90%; mp 164 °C; IR (KBr): 3320, 1620, 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.60 (s, 3 H, 18-CH_3), 0.79 (s, 3 H 19-CH_3), 0.83 (t, 3 H, $J=7$ Hz, $NCH_2CH_2CH_2CH_3$), 1.4–1.85 (m, 10 H, cyclohexyl), 2.34 (dd,2 H, $J=9.5$ Hz, 4.6 Hz, 2-H_2), 2.83 (s, 3 H, N—CH_3), 2.93 (dd, 1 H, $J=12.5$, 3.5 Hz, 5α-H), 3.49 (m, 1 H, $NCHC_5H_{10}$), 3.78 (t, $J=10$ Hz, 17-H), 4.24 (d, $J=7.6$ Hz, NH); ^{13}C NMR ($CDCl_3$): δ 170.6, 157.6, 65.6, 64, 51.9, 51.2, 49.3, 45.2, 44.4, 37.6, 36.3, 34, 34, 33.8, 32.8, 31.9, 30.8, 29.7, 29, 25.6, 25.2, 25, 24.9, 24.2, 23, 20.6, 20.2, 13.8, 12.6, 12.3; MS (EI): *m/z* (relative intensity) 485 (25), 470 (5), 360 (22), 345 (7), 317 (38), 288 (23), 249 (22), 112 (100); HRMS calcd for $C_{30}H_{51}N_3O_2$ 485.3969, found 485.3993.

17β-(Ureylene-*N*-butyl-*N'*-phenyl)-4-methyl-4-aza-5α-androstan-3-one (3l). Yield 94%; mp 225 °C; IR (KBr): 3355, 1653, 1617, 1534 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.68 (s, 3 H, 18-CH_3), 0.81 (s, 3 H 19-CH_3), 0.88 (t, 3 H, $J=7$ Hz, $NCH_2CH_2CH_2CH_3$), 2.36 (dd, 2 H, $J=9.5$, 4.7 Hz, 2-H_2), 2.86 (s, 3 H, N—CH_3), 2.96 (dd, 1 H, $J=12.5$, 3.3 Hz, 5α-H), 3.1 (m, 2 H, NCH_2CH_2 CH_2CH_3), 4.1 (t, 1 H, $J=10$ Hz, 17-H), 6.68 (s, 1 H, NH), 6.93 (t, 1 H, $J=7.3$ Hz, aromatic), 7.24 (m, 2 H, aromatic), 7.34 (m, 2 H, aromatic); ^{13}C NMR ($CDCl_3$): δ 170.7, 155.8, 139.5, 128.7 (2C), 122.5, 119.8 (2C), 65.6, 64.4, 51.9, 51.2, 45.3, 44.8, 37.5, 36.4, 34, 32.8, 32.1, 29.7, 29.1, 29, 25.3, 24.4, 23.1, 20.6, 20.2, 13.9, 12.7, 12.4; MS (EI): *m/z* (relative intensity) 479 (10), 444 (4), 360 (16), 317 (42), 288 (18), 249 (20), 119 (65), 112 (100); HRMS calcd for $C_{30}H_{45}N_3O_2$ 479.3498, found 479.3432.

Inhibition of human 5α-reductase (types I and II)

The measurements of in vitro activity of compounds **3a–l** were carried out according to the following procedures.

Type I 5α-reductase. 293 cells[20a] (ATCC CRL 1573) were transfected with the human type 1 5α-Re cDNA and were used as the source of type 1 5α-Re. After the transfection, cells were homogenized for the in vitro assay. Compounds to be tested were dissolved in ethanol and diluted with 50 mM Tris HCl buffer containing 20% glycerol and 1 mM EDTA at pH 7.5. Inhibitors were first screened at two concentrations for 5α-Re inhibitory activity: 1 and 0.1 μM. In general, compounds showing 50% or more inhibition at the 1 μM concentration were subsequently tested at 12 doses ranging from 0.1 to 1000 nM, for the precise measurement of their IC_{50} values. The compound and 5 nM ^{3}H-androstenedione, 500 μM NADPH and the homogenized cells were added to the sample wells in a final volume of 1 mL of medium. Following the 60 min incubation at 37 °C, the media were extracted twice with ether after the addition of 25 μg each of nonradioactive steroids carriers (androstanedione, androstenedione, androsterone and testosterone). Steroids were separated by TLC, and the radioactivity was counted. Results are expressed as the amount of androstanedione produced as a percentage of control values.

Type II 5α-reductase. SW-13 cells[20a] (ATCC HTB81) were transfected with the human 5α-Re type II cDNA and were used as the source of type II 5α-Re. After transfection, cells were homogenized for the in vitro assay. Compounds to be tested were dissolved in ethanol and diluted with 50 mM Tris HCl buffer containing 20% glycerol and 1 mM EDTA at pH 7.5.

Inhibitors were first screened at two concentrations for 5α-Re inhibitory activity: 1 and 0.1 μM. In general, compounds showing 50% or more inhibition at the 1 μM concentration were subsequently tested at 12 concentrations ranging from 0.1 to 1000 nM, for the measurement of the IC_{50} value. The indicated compound, 5 nM ^{3}H-androstenedione, 500 μM NADPH and the cell homogenate were added to the sample tubes to a final volume of 1 mL. Following a 60 min incubation at 37 °C, the media were extracted twice with ether after the addition of 25 μg each of nonradioactive steroid carriers (androstanedione, androstenedione, androsterone and testosterone). Steroids were separated by TLC, and the radioactivity was counted. Results are expressed as the amount of androstanedione produced as a percentage of control values.

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