Synthesis of 11-substituted androstenediones and testosterones as human decidual cell growth inhibitors

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*11α-Hydroxytestosterone (**1a**), 11β-hydroxytestosterone (**1b**), 11α-methoxytestosterone (**1c**), 11β-methoxytestosterone (**1d**), 11-ketotestosterone (**1e**), and $\Delta^{9(11)}$-testosterone (**1f**) were synthesized from hydrocortisone (**4b**) or 11-epi-hydrocortisone (**4a**). The six target compounds, together with 11α-methoxyandrostenedione (**2c**), 11β-methoxyandrostenedione, (**2d**) and their lead compound, testosterone (**1**), were found to effectively inhibit the growth and differentiation of human decidual cells in culture. There is no observable binding of these compounds to estrogen receptor of rabbit uterus. The introduction of a polar group (e.g., hydroxyl and carbonyl) to C-11 of androstenes decreases both the relative binding affinities to progesterone receptor and the inhibitory effects on human decidual cell growth, while the methylation of 11-hydroxyl group minimizes these effects. The similar effects of a polar group at C-11 of testosterone (**1**) on the inhibitory effects on human decidual cell growth and the relative binding affinities to progesterone receptor of rabbit uterus may suggest that one of the mechanisms of human decidual cell growth inhibition by these compounds is the anti-progestational activity of these androgens.* (*Steroids* **59**:190–195, 1994)

Keywords: synthesis; testosterone derivatives; progesterone receptor; human decidual cell

Introduction

The development of safer and more effective contraceptives and abortifacients is attracting more and more interest in both developing and developed countries. Testosterone propionate (17β-propionyloxyandrost-4-en-3-one) has been successfully used as an adjuvant to prostaglandin[1,2] and trichosanthin[3,4] for interruption of early pregnancy in China since 1978. The mechanisms of its action are not fully known. At present, it is considered that the effect is due to its inhibition on the growth of decidual cells in early pregnancy.[5,6] It has also been reported that the plasma androsterone level of sterile women with Stein-Leventhal syndrome[7] and women suffering habitual abortion[8] is significantly higher than normal. In order to find safer and more powerful agents for the termination of early pregnancy and investigate the mechanisms of pregnancy interrupting effect of testosterone (17β-hydroxyandrost-4-en-3-one, **1**), chemical modifications of testosterone (**1**) and biological studies of its derivatives were carried out.

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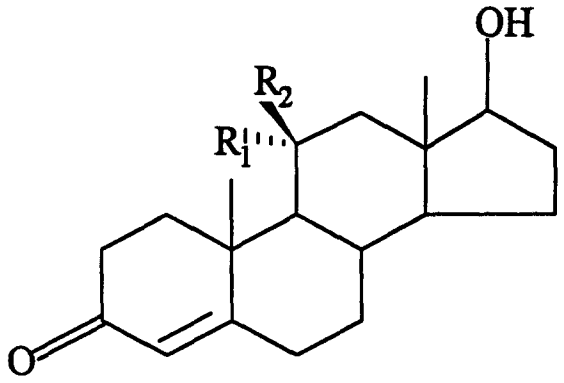
Received April 8, 1993; accepted August 6, 1993.

11-Substituents in estrogens have significant effects on the steroid conformation and thus on the biological activities of 11-substituted steroids.[9–12] In some cases, 11β-substituted derivatives are estrogens, while their 11α-epimers are anti-estrogens.[13–15] New antiprogestin, RU 38486 (11β-[4-(dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one) was screened out from a series of 11-aryl substituted estranes.[16–18] However, the structure-activity relationships of 11-substituted androstanes have not been well studied, particularly with respect to their antifertility activities. Since 11β-hydroxyl substituted androstenedione and testosterone are normal metabolites in human,[19–22] we aimed our modifications of testosterone at the 11-oxygenated substituents in order to ascertain how differently these 11-oxygenated derivatives act as anti-progestins. This will shed light on the issue of whether testosterone or its metabolites are responsible for in vivo anti-progestational activity. This also assures that these compounds can be metabolized in the body through normal metabolic pathways, in case some of them could be developed into drugs. A series of 11-substituted testosterone derivatives were designed, including 11α-hydroxytestosterone (**1a**), 11β-hydroxytestosterone (**1b**), 11α-methoxytestosterone (**1c**), 11β-methoxytestosterone (**1d**), 11-ketotestosterone (**1e**), and $\Delta^{9(11)}$-testosterone (**1f**).



(1) $R_1 = R_2 = H$
(1a) $R_1 = OH$, $R_2 = H$
(1b) $R_1 = H$, $R_2 = OH$
(1c) $R_1 = OCH_3$, $R_2 = H$
(1d) $R_1 = H$, $R_2 = OCH_3$
(1e) $R_1R_2 = O$
(1f) R_1 or $R_2 = H$, $\Delta^{9(11)}$

These compounds were synthesized from hydrocortisone or 11-*epi*-hydrocortisone according to Schemes 1 and 2. The six target compounds, together with 11α-methoxyandrostenedione (**2c**), 11β-methoxyandrostenedione (**2d**) and their lead compound, testosterone (**1**), were studied for their inhibitory effects on the growth and differentiation of human decidual cells in culture and their relative binding affinities to progesterone receptor and estrogen receptor of rabbit uterus.

Experimental

Synthesis

Melting points were determined with the capillary method and are uncorrected. ^1H NMR were recorded on JOEL FX-90Q (90 MHz) FT-NMR spectrometer. $CDCl_3$ was used as solvent, while tetramethylsilane served as internal standard. IR (KBr) spectra were measured using a Perkin-Elmer 983 FT-IR spectrophotometer. MS (EI, 100 eV) were taken on a VG-25-255 spectrometer. Microanalyses were carried out with a Perkin-Elmer 240-C element analyzer. The 40–63 μm (230–400 mesh) microspherical silica gel (similar to Merck Silica Gel 60, according to the manufacturer) used for flash chromatography and silica gel GF_{254} for thin-layer chromatography (TLC) were purchased from Shandong Jime Chemical Factory (Qingdao, Shandong, China). Hydrocortisone and 11-*epi*-hydrocortisone were purchased from Tianjin Pharmaceutical Factory (Tianjin, China). All other chemicals and solvents were purchased from Beijing Chemical Factory, Beijing, China.

The synthetic routes for the target compounds are shown in Schemes 1 and 2. The experimental procedures and the characteristics of the new compounds (**1c**, **1d**, **2c**, **2d**, **3c**, **3d**, and **3f**) are detailed in the following sections, while the mp, the supporting spectra obtained, and yields of known compounds, as well as the recrystallization solvents and starting compounds for their preparation, are tabulated in Table 1.

Preparation of 11α-methoxy derivatives

3,3:17,17-Bis(ethylenedioxy)androst-5-en-11α-ol (*3a*). The mixture of 3.50 g (0.012 mol) compound **2a**, 35 mL ethylene glycol, 30 mL triethyl orthoformate, 180 mg 4-toluenesulfonic acid and 224 mL benzene was refluxed for 5.5 h. Water (11 mL) and 100 ml ether were added to the mixture after cooling. Organic phase was washed to neutral with saturated $NaHCO_3$ solution and water, concentrated to dryness under vacuum. Crystallization in cyclohexane/acetone afforded **3a** as white crystals.

3,3:17,17-Bis(ethylenedioxy)-11α-methoxyandrost-5-ene (*3c*). The mixture of 1.0 g (80%, 33.3 mmol) NaH and 50 mL dimethyl sulfoxide was stirred at 60–70 C for 60 min. To this mixture, the solution of 1.0 g (2.6 mmol) compound **3a** in 20 mL dimethyl sulfoxide was added. The resulting mixture was stirred at 60–70 C for another 60 min, before it was allowed to cool down to ambient temperature. CH_3I (7 mL, 112.4 mmol) was added dropwise to the reaction mixture while stirring and the resulting reaction mixture was stirred for 3.5 h at room temperature. TLC showed the completion of methylation [**3a**: $R_f = 0.55$; **3c**: $R_f = 0.71$ developed with cyclohexane/acetone (4:1)]. The reaction mixture was poured into ice-water, and extracted with ethyl acetate. After washing with water and drying over Na_2SO_4, ethyl acetate was evaporated with a rotavapor under vacuum to dryness. Crystallization and

Table 1 Physical properties and yields of the known compounds[a]

Compound No.	Recrystallization solvent(s)	mp(lit.), C	Starting compound No.	Yield %	Spectra
3,17-dione diethylene ketals					
3a	cyclohexane/acetone	218–220(200–221[23])	**2a**	72	IR
3b	methanol	199–201(200–202[28])	**3e**	74	IR
3e	ether	184–185(185–186[23])	**2e**	74	IR
3,17-dione derivatives					
2a	ethanol	198–200(199–200[24])	**4a**	46	IR, ^1H NMR
2b	ethanol	197–199(198–200[24])	**4b**	52	IR, ^1H NMR
2e	ether	219–221(219–222[25])	**4a**	69	IR, ^1H NMR
2f	methanol	204–205(203–205[28])	**3f**	70	IR, ^1H NMR
testosterone derivatives					
1a	cyclohexane/ether	178-180(179–180[24])	**2a**	11	
1b	cyclohexane/ether	235–237(235–237[24])	**2b**	65	
1e	cyclohexane/ether	186–187(187–188[24])	**2e**	67	IR, ^1H NMR, MS
1f	cyclohexane/ether	153–154(153–155[23])	**2f**	71	IR, ^1H NMR, MS

[a] Prepared in Schemes 1 and 2.

recrystallization with methanol afforded 750 mg (72% yield) compound **3c** as colorless crystals. mp 149–151 C. IR ν_{max} 1083, 1106 (cyclic ketals) cm^{-1}, no hydroxyl or carbonyl band; ^1H NMR δ 5.36 (m, 1 H, 6-vinyl H), 3.89 (m, 8 H, two $-OCH_2CH_2O-$), 3.55 (m, 1 H, 11β-H), 3.28 (s, 3 H, 11α-OCH_3), 1.12 (s, 3 H, 19-CH_3), 0.87 (s, 3 H, 18-CH_3); MS *m/z* 404 (M^+), 372 (M^+-CH_3OH). Analysis calculated for $C_{24}H_{36}O_5$: C, 71.20; H, 9.00. Found: C, 71.40; H, 8.91.

11α-Methoxyandrost-4-ene-3,17-dione (*2c*). The mixture of 500 mg (1.24 mmol) compound **3c**, 7 mL acetic acid and 2 mL water was heated at reflux for 20 min, before it was poured into 30 mL saturated $NaHCO_3$ solution. After the general work-up with ethyl acetate as above, the residue was transferred to a flash column using 6:1 to 4:1 cyclohexane/acetone as gradient eluant for purification. Crystallization with cyclohexane/ether afforded 307.4 mg (79% yield) **2c**. mp 131.5–132.5 C. IR ν_{max} 1742 (17-C=O), 1671 (3-C=O), 1612 (shoulder peak, Δ^4) cm^{-1}, no hydroxyl band; ^1H NMR δ 5.72 (s, 1 H, 4-vinyl H), 3.50 (td, 1 H, 11β-H, $J_{11\beta,9\alpha}$ = 10 Hz, $J_{11\beta,12\alpha}$ = 10 Hz, $J_{11\beta,12\beta}$ = 5 Hz), 3.28 (s, 3 H, 11α-OCH_3), 1.28 (s, 3 H, 19-CH_3), 0.92 (s, 3 H, 18-CH_3); MS *m/z* 316 (M^+), 284 (M^+-CH_3OH). Analysis calculated for $C_{20}H_{28}O_3$: C, 75.90; H, 8.86. Found: C, 75.70; H, 8.54.

17β-Hydroxy-11α-methoxyandrost-4-en-3-one (*1c*).[26] The mixture of 300 mg (0.95 mmol) compound **2c**, 3 mL benzene, and 2 mL pyridine was cooled down to 0 C. To this solution, 19 mg (0.51 mmol) $NaBH_4$ in 10 mL methanol was slowly added dropwise. Upon completion of the reaction, suitable amount of glacial acetic acid was added. After methanol was removed by evaporation under vacuum, general work-up afforded crude **1c**, which was then purified with flash chromatography using 6:1 to 4:1 cyclohexane/acetone as gradient eluant. From cyclohexane/ether 238 mg (79% yield) **1c** was crystallized. mp 173–175 C. IR ν_{max} 3437 (—OH), 1654 (C=O), 1607 (Δ^4) cm^{-1}; ^1H NMR δ 5.72 (s, 1 H, 4-vinyl H), 3.68 (t, 1 H, 17α-H, J = 8 Hz), 3.50 (td, 1 H, 11β-H, J = 10, 10, 5 Hz), 3.30 (s, 3 H, 11α-OCH_3), 1.84 (s, 1 H, disappeared/D_2O, 17β-OH), 1.28 (s, 3 H, 19-CH_3), 0.82 (s, 3 H, 18-CH_3); MS *m/z* 318 (M^+), 300 (M^+-H_2O), 286 (M^+-CH_3OH), 268 ($M^+-H_2O-CH_3OH$); Analysis calcuated for $C_{20}H_{30}O_3$. C, 75.47; H, 9.43. Found: C, 75.61; H, 9.62.

Preparation of 11β-methoxy derivatives

3,3:17,17-Bis(ethylenedioxy)androst-5-en-11β-ol (*3b*). To the solution of 700 mg (1.8 mmol) **3e** in 200 mL anhydrous ether, 150 mg (4.05 mmol) $LiAlH_4$ was added and the resulting mixture was heated at reflux for 2.5 h. After cooling, water was added carefully to destroy unreacted $LiAlH_4$ and general work-up afforded 520 mg **3b**.

Procedures for the preparation of 11β-methoxy compounds were similar to the above described procedures for 11α-methoxy derivatives. The characteristics of these compounds are listed as follows.

3,3:17,17-Bis(ethylenedioxy)-11β-methoxyandrost-5-ene (*3d*). mp 143–145 C (from methanol). yield: 60%. IR ν_{max} 1102 ($-OCH_2CH_2O-$) cm^{-1}, no hydroxyl or carbonyl band; ^1H NMR δ 5.20 (s, broad, 1 H, 6-vinyl H), 3.72 (m, 1 H, 11α-H), 3.75–4.10 (m, 8 H, two-OCH_2CH_2O-), 3.20 (s, 3 H, 11β-OCH_3), 1.20 (s, 3 H, 19-CH_3), 1.00 (s, 3 H, 18-CH_3); MS *m/z* 404 (M^+) Analysis calculated for $C_{24}H_{36}O_5$: C, 71.20; H, 9.00. Found: C, 71.00; H, 9.23.

11β-Methoxyandrost-4-ene-3,17-dione (*2d*). mp 199–200 C (from cyclohexane/ether). yield: 73%. IR ν_{max} 1731 (17-C=O), 1663 (3-C=O), 1611 (Δ^4) cm^{-1}; ^1H NMR δ 5.68 (s, 1 H, 4-vinyl H), 3.78 (m, 1H, 11α-H), 3.28 (s, 3 H, 11β-OCH_3), 1.40 (s, 3 H, 19-CH_3), 1.09 (s, 3 H, 18-CH_3); MS *m/z* 316 (M^+), 284 (M^+-CH_3OH). Analysis calculated for $C_{20}H_{28}O_3$: C, 75.90; H, 8.86. Found: C, 75.63; H, 9.16.

17β-Hydroxy-11β-methoxyandrost-4-en-3-one (*1d*). mp 157–160 C (from cyclohexane/ether). yield: 68%. IR ν_{max} 3426 (-OH), 1668 (3-C=O), 1620 (Δ^4) cm^{-1}; ^1H NMR δ 5.68 (s, 1 H, 4-vinyl H), 3.46–3.80 (m, 2 H, 11α-H and 17α-H), 3.28 (s, 3 H, 11β-OCH_3), 1.52 (s, 1 H, disappeared/D_2O, 17β-OH), 1.40 (s, 3 H, 19-CH_3), 0.93 (s, 3 H, 18-CH_3); MS *m/z* 318 (M^+), 300 (M^+-H_2O), 286 (M^+-CH_3OH), 268 ($M^+-H_2O-CH_3OH$). Analysis calculated for $C_{20}H_{30}O_3$: C, 75.47; H, 9.43. Found: C, 75.31; H, 9.35.

Elimination of 11β-OH during ketalization—preparation of $\Delta^{9(11)}$-derivatives

3,3:17,17-Bis(ethylenedioxy)androsta-5,9(11)-diene (*3f*). **3f** was obtained with the procedures for the preparation of **3a**, except that the equivalent amount of 4-toluenesulfonic acid was doubled and reflux period was extended to 8 (from 5.5) h. Compound **3f**. mp 152–154 C (from methanol). yield: 48%. IR: ν_{max} 1090 cm^{-1} (cyclic ketals), no hydroxyl or carbonyl band; ^1H NMR δ 5.38–5.60 (m, 2 H, 6- and 11-vinyl H), 3.92 (m, 8 H, two -OCH_2CH_2O-), 1.20 (s, 3 H, 19-CH_3), 0.84 (t, 3 H, 18-CH_3); MS *m/z*: 372 (M^+); Analysis calculated for $C_{23}H_{32}O_4$: C, 74.19; H, 8.60. Found: C, 74.32; H, 8.90.

Biological studies

Materials. [^{3}H]R5020(17α-[^{3}H]methyl-,17α,21-dimethyl-19-norpregna-4,9-diene-3,20-dione, 79 Ci/mmol) and [^{3}H]estradiol (2,4,6,7-[^{3}H]-, 93 Ci/mmol) were purchased from New England Nuclear (Boston, MA, USA). Unlabeled steroids were either purchased from Roussel-UCLAF (France) or gifts from Shanghai Research Institute of Family Planning (Shanghai, China). Stock solutions were prepared in absolute ethanol and kept at −20 C. Rabbit uterine cytosol and human decidual tissue (45–50 days from last menstruation) were prepared by The Center of Gynecology & Obstetrics at The First Hospital of Beijing Medical University. All other chemicals were purchased from Beijing Chemical Factory, Beijing, China.

Determination of Relative Binding Affinities to Progesterone and Estrogen Receptors. The procedures of receptor assay used were similar to the procedures reported by Ho and Callard.[27] The relative binding affinities of androstenes to progesterone receptor were assessed by their ability to displace [^{3}H]R5020, a highly specific synthetic progestin, and its relative binding affinity to progesterone receptor was arbitrarily set to 100. In case of estrogen receptor, [^{3}H]estradiol was used as radioactive ligand and diethylstilbestrol was used as reference compound (relative binding affinity: 100). All the experiments were performed at 4 C. Aliquots of the cytosol preparation from rabbit uterus were incubated with 0.5 nM [^{3}H]R5020 and with/without unlabeled test androstenes in Tris-EDTA buffer for 5 h at 4 C. After incubation, free [^{3}H]R5020 was extracted with dextran-coated charcoal[27] from the bound ligand, and the amount of [^{3}H]R5020 bound to the receptor was determined by liquid scintillation spectrometry. The concentration of the test compounds corresponding to 50% replacement of total [^{3}H]R5020 without competitor (IC_{50}) was used to derive the relative binding affinities of the test androstenes to progester-

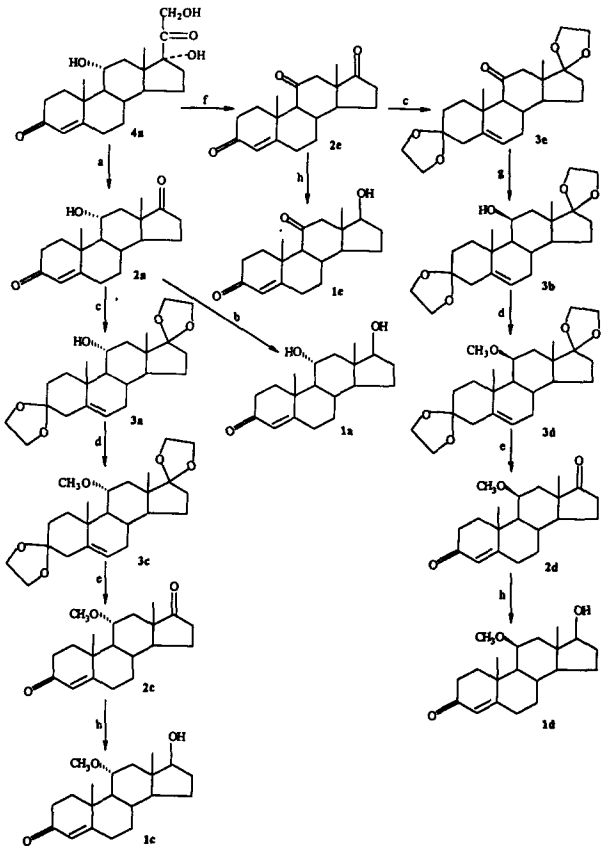
one receptor. The relative binding affinity of each steroid was calculated by dividing the IC_{50} of R5020 (0.5 nM) by the IC_{50} of the test steroids (1.9–5.5 nM).

Like the above procedures, 0.4 nM of [^{3}H]estradiol was used in the incubation with diethylstilbestrol or the test steroids (up to 400 nM) at 4 C for 24 h. Scintillation counting was used to determine the bound [^{3}H]estradiol, in order to measure the binding affinities of the test steroids to rabbit uterine estrogen receptor.

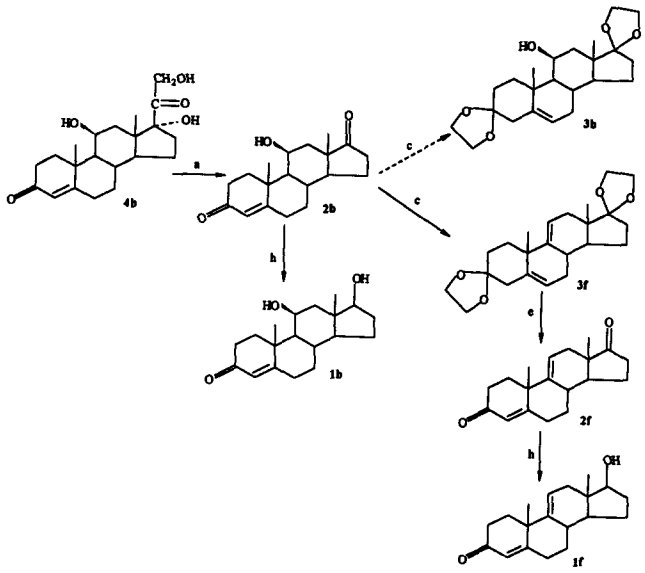
Inhibition of Human Decidual Cell Growth and Differentiation.

Culture solution: To the mixture of 10.04 g RPMI-1640, 300 mg monosodium glutamate, 2.00 g $NaHCO_3$, 200,000 IU penicillin, 100,000 IU streptomycin and few drops of 2-mercaptoethanol, double-distilled water was added to make the final volume 1000 mL (pH 7.2). After sterilized filtration, 15% (vol/vol) fetal calf serum was added. The resulting solution was stored at 4 C for later use.

Incubation with inhibitors: The incubation was carried out with a 24-hole culture plate at 37 C. After significant amount of decidual cells were observed with microscope, the compound to be tested (**1a-1f, 2c, 2d**) in physiological saline was added to each hole to make the final concentration of 69 μM. The reference group was added in the same amount of physiological saline. After 48–72 h incubation with these compounds, the shape and number of decidual cells were studied with a microscope and Giemsa staining. The culture solution containing inhibitors was removed and incubation was continued with fresh culture solution.



Scheme 1 a) active MnO_2 b) (1) $NaBH_4$/MeOH (2) active MnO_2 c) $HOCH_2CH_2OH$/4-toluenesulfonic acid d) DMSO/NaH/CH_3I (e) CH_3COOH/H_2O f) $CrO_3/H_2SO_4/CH_3COCH_3$ g) $LiAlH_4/Et_2O$ h) $NaBH_4$/MeOH/pyridine.



Scheme 2 a) active MnO_2 c) $HOCH_2CH_2OH$/4-toluenesulfonic acid e) CH_3COOH/H_2O h) $NaBH_4$/MeOH/pyridine.

Results

All the target compounds were synthesized according to Scheme 1 and 2 from hydrocortisone (**4b**) or 11-*epi*-hydrocortisone (**4a**). Like their parent compound testosterone (**1**), all of these compounds (**1a-1f, 2c, 2d**) tested can inhibit the growth and differentiation of human decidual cells in culture. It was observed that the normal decidual cells treated with inhibitors shrank into fiber-like cells and the number of cells was decreased significantly, comparing to reference group in which the same amount of sterilized saline was used. Even though it is difficult to quantitate the inhibitory effects, the differences of inhibition efficacy by different test compounds were observed. The inhibitory effects of **1a** (with 11α-hydroxyl), **1b** (with 11β-hydroxyl), and **1e** (with 11-carbonyl) are significantly less effective than their parent compound, while the other compounds have similar inhibitory effects on human decidual cell growth with their parent compound—testosterone (**1**). The inhibition was found to be reversible, since the cells started to recover after 72 h incubation from the removal of inhibitors. Complete recovery (comparing to reference) was observed after 120 h from the removal of inhibitors.

The relative binding affinities of all the compounds with rabbit uterine estrogen receptor were found to be zero. The relative binding affinities of these compounds (**1a-1f, 2c, 2d**) to progesterone receptor of rabbit uterus are listed in Table 2. For comparison reason, relative binding affinity to progesterone receptor of RU 38486 was also determined.

Discussion

Relative binding affinities of androstenes to progesterone receptor

Table 2 shows that there is no difference between 17β-hydroxyl and 17-carbonyl group with respect to

Table 2 The relative binding affinities of various androstenes to progesterone receptor of rabbit uterus

Compound No.	Relative binding affinity to progesterone receptor %, (standard deviation)[a]
R5020	100 (reference)
RU38486	104 (3)
1	25 (5)
1a	9 (3)
1b	10 (2)
1c	20 (5)
1d	18 (3)
1e	9 (2)
1f	26 (4)
2c	19 (5)
2d	18 (3)

[a] All relative binding affinities are the average values of results from 3 to 5 separate determinations.

their binding to rabbit uterine progesterone receptor (i.e., **1c** versus **2c**; **1d** versus **2d**). This suggests that C-17 is not a critical site for these compounds to bind with progesterone receptor. 11-Substituents do have some effects on the binding of substituted androstenes to progesterone receptor. Introduction of a polar group to C-11 decreases the binding affinities to progesterone receptor, e.g., 11α-hydroxyl (**1a**), 11β-hydroxyl (**1b**) and 11-carbonyl (**1e**) group decreased the relative binding affinity to progesterone receptor by more than 50% (see Table 2). Methylation of 11α-hydroxyl and 11β-hydroxyl brings the relative binding affinity up to the same level with testosterone, which is consistent with the (above) observations that a low polarity at C-11 is favorable in the binding of androstenes to progesterone receptor. $\Delta^{9(11)}$-Testosterone (**1f**) possesses the highest relative binding affinity to progesterone receptor among all the compounds tested, which might be attributed to the absence of an oxygen atom at C-11. All these results are also consistent with the observation of the dramatic decrease in relative binding affinity to progesterone receptor of progesterone after 11β-hydroxyl was introduced.[29]

It is apparent that hydrophobic interaction is needed at the region of C-11 in the binding between steroids (estranes, androstanes, and pregnanes) and receptors. So we can speculate that a hydrophobic substituent, such as alkyl or aryl, at C-11 (either α- or β-face) will increase the relative binding affinity to progesterone receptor of androstenes, thus increasing the anti-progestational activity of these androgens. This might be reminiscent of the dramatic increase in relative binding affinity to progesterone receptor of estranes in the case of RU 38486, in which an aromatic substituent was introduced to C-11 of the estrane parent structure.

Inhibition of human decidual cell growth

growth of decidual tissue and there is no observable anti-estrogen activity for these compounds according to to the relative binding affinity to progesterone receptor: The three compounds (**1a**, **1b**, and **1e**) with polar substituents at C-11 are less effective than other test derivatives and they have the smallest relative binding affinities to progesterone receptor among all test compounds (*vide supra*). This may suggest that the binding to progesterone receptor (anti-progestational activity) is one of the mechanisms of the inhibition of human decidual cell growth, since it is known that progesterone and estrogen are necessary to maintain the growth of decidual tissue and there is no observable anti-estrogen activity for these compounds according to relative binding affinity to estrogen receptor.

In summary, a series of 11-substituted testosterones were synthesized and tested for their relative binding affinities to progesterone and estrogen receptor and the inhibitory effects on the growth and differentiation of human decidual cell in culture. Increase of polarity (e.g., introduction of a hydroxyl or carbonyl group) at C-11 (either α- or β-face) was found to decrease the relative binding affinity to progesterone receptor and efficiency of the inhibition of human decidual cell growth, while the decrease of polarity at C-11 (e.g., the methylation of 11α- or 11β-hydroxyl group) increases the relative binding affinity to progesterone receptor and the inhibitory effects on human decidual cell growth of testosterone derivatives. If the above in vitro results apply to the in vivo systems, the similar substituent effects at C-11 of testosterone on the relative binding affinity to progesterone receptor and the inhibitory effects on decidual cell growth may suggest that binding to progesterone receptor is one of the mechanisms for clinically observed[1–6] early pregnancy interrupting effect of testosterone derivatives.

Acknowledgments

This work was supported by Natural Science Council of China and National Family Planning Commission. The help for biological studies from Prof. Shurong Zheng, Dr. Jian Zhou, and Ms. Ying Xue of First Hospital, Beijing Medical University, is greatly acknowledged.

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