(1-Benzylindole-3-yl)alkanoic Acids; Novel Nonsteroidal Inhibitors of Steroid 5α-Reductase (I)

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A novel series of indole-3-alkanoic acids with varied *N*-benzyl substituents were synthesized as nonsteroidal inhibitors of steroid 5α-reductase. The structure–activity relationships in this series were studied and the optimum carboxylic acid side chain was butyric acid. Furthermore, compounds with a diaryl substituent at the 1-position of the indole ring displayed strong inhibitory activities *in vitro*. Amongst these derivatives, 4-[1-(6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-3-yl)methylindol-3-yl]butyric acid (FR119680) displayed very high inhibitory activity *in vitro* against rat prostatic 5α-reductase (IC_{50}=5.0 nM) and good *in vivo* activity in the castrated young rat model.

Key words 5α-reductase inhibitor; FR119680; nonsteroidal; indole-3-alkanoic acid; benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) is a common disorder in aging males. Approximately 50% to 75% of all males over the age of 50 are known to develop this condition.[4] This disorder is characterized by a progressive enlargement of the prostate gland, leading to an increase in pressure on the urethra and results in obstruction of urinary flow. In light of the high incidence of this condition, it is obvious that some form of chemical therapy would be of immense potential importance in treating BPH.[5]

It is well known that growth of the prostate is dependent on tissue androgen contents, and that 5α-dihydrotestosterone (DHT)[6] is the most active agonist for the androgen receptor. DHT is produced enzymatically by steroid 5α-reductase from testosterone, thus therapy with a 5α-reductase inhibitor would be expected to lead to a decrease in DHT concentration within the prostate gland, and may be an extremely useful agent for treatment of BPH.

Many laboratories are developing, or have investigated 5α-reductase inhibitors, but these efforts have predominantly concentrated on compounds with a steroidal structure,[7] for example finasteride (Fig. 1). However, due to the presence of a steroidal structure, there is the strong possibility of unwanted side-effects.[8] Therefore we have undertaken efforts to discover nonsteroidal 5α-reductase inhibitors.[9]

Two compounds (**1**, **2**) based on the indole nucleus were discovered by random screening *in vitro* against the rat prostatic enzyme in our laboratory (Fig. 1). Their structures are quite similar, differing only in the positions of the acidic and lipophilic substituents. Compound **2** was chosen for structural modification with a view to obtaining a nanomolar level inhibitor for examination of *in vivo* efficacy. Stronger inhibitory activity, and greater synthetic accessibility of the requisite indole-3-alkanoic acids led to selection of **2** as our lead structure. We employed two types of modification, 1) altering the length of the acid carbon chain, and 2) changing the benzyl substituent.

Results and Discussion

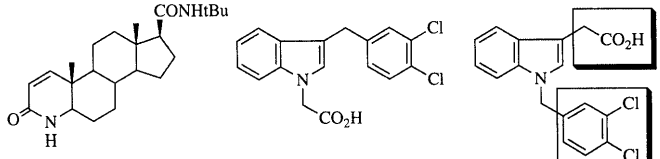
Optimum Carbon Chain Length at the Indole 3-Position The prepared compounds were evaluated for their ability to inhibit rat prostatic 5α-reductase and inhibitory activity was expressed as the IC_{50} value.

Concerning the optimum carbon chain length at the indole 3-position, it can be deduced from the data summarized in Table 1 (**3**—**5**) that while there is only a small difference in activity between the propionic and butyric derivatives, they both offer a clear advantage over the acetic derivative. Thus, in the early stages of our studies, further modifications were made using indole-3-propionic acid.

Modification of the *N*-benzyl Group The second site for structural modification that we identified in **2** is the *N*-benzyl group. A variety of substituted benzyl groups were thus introduced to the indole moiety, examples of which are shown in Table 1 (**4**—**14**). Compounds with benzyl groups bearing electron-donating substituents, for example methyl and methoxy (**7**, **8**), showed weaker activities than compounds with electron-withdrawing groups *e.g.* Cl, diCl, CF_3 (**4**, **11**, **12**). Another point worthy of comment is the position of the substituent in the benzene ring; inspection of the data for *o*-, *m*-, and *p*-Cl (**9**, **10**, **4**) indicates that the optimum position is *para* at this stage.

Stronger electron-withdrawing substituents were not so active (*e.g.* *p*-F, **13**, IC_{50}=650 nM). Introduction of substituents having greater electron density were next examined. As a result of these modifications, the compound with a 4-phenyl substituent (**14**) proved to have the highest activity (IC_{50}= 280 nM) of the propionic acid derivatives.

Since the diaryl substituent had potent activity, the length of the carboxylic acid side chain was further examined, keeping the biphenyl moiety constant. Table 1 (**14**—**18**) shows



	Finasteride	1	2
IC_{50}[a]	5.9 nM	710 nM	240 nM

Fig. 1. Finasteride and Indole-Based Inhibitors of 5α-Reductase

a) Inhibition of rat prostate 5α-reductase.

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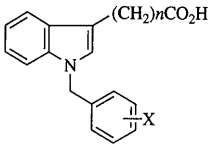
Table 1. Inhibition of Rat Prostate 5α-Reductase by *N*-Benzylindole-3-alkanoic Acids



Compd. No.	*n*	X	IC_{50} (nM)
3	1	*p*-Cl	600
4	2	*p*-Cl	450
5	3	*p*-Cl	430
6	2	H	2000
7	2	*p*-Me	1800
8	2	*p*-OMe	2100
9	2	*o*-Cl	12000
10	2	*m*-Cl	1500
11	2	3,4-diCl	360
12	2	*p*-CF_3	520
13	2	*p*-F	650
14	2	*p*-Ph	280
15	1	*p*-Ph	180
16	3	*p*-Ph	54
17	4	*p*-Ph	680
18	5	*p*-Ph	5000

that the strongest compound was the butyric acid derivative (**16**), with an IC_{50} value 54 nM.

Modification of the Diaryl Substituent Since the previous data showed that a diaryl substituent, *p*-biphenyl, had particularly strong activity, several compounds containing other diaryl substituents were prepared from indole-3-butyric acid. The activity of most of the resulting compounds was indeed high (Table 2, **19**—**23**). The most important result to come from these studies was the nanomolar level inhibitory activity of the compound with a diaryl ester substituent (**23**); the IC_{50} value was 2.8 nM.

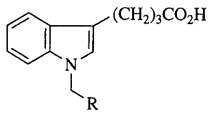
However, since phenyl esters are well known to be prone to hydrolysis under basic conditions, the design of a potentially more stable compound was initiated. Compounds with a tricyclic substituent were prepared since hydrolytic cleavage of such a moiety was proposed to be slow.

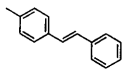
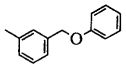
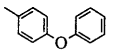
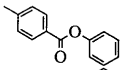
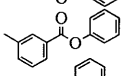
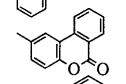
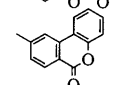
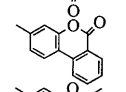
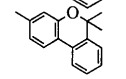
Among these compounds (Table 2, **24**—**26**), **26** in addition to being much more chemically stable, also had nanomolar level inhibitory activity *in vitro*, however it did not display significant *in vivo* inhibitory activity in the castrated young rat model. In this model the growth of ventral prostate was induced by the subcutaneous injection of testosterone propionate (TP) to castrated young rats and was reduced by administration of the inhibitor.[10] We considered that reduction of polarity of **26** was necessary to improve pharmacokinetics and examined the introduction of more lipophilic *N*-substituents. By introduction of a dimethyl cyclic ether moiety, we then arrived at the very strongly active and chemically stable compound, FR119680, which displayed excellent *in vivo* inhibitory activity at 10 mg/kg (s.c.).

Chemistry

All indole derivatives were synthesized by reactions of a benzyl halide (bromide or chloride) with a dianion of the indolealkanoic acid, which was conveniently prepared from the corresponding carboxylic acid and sodium hydride in *N*,*N*-dimethylformamide (DMF) (Chart 1).

Table 2. Inhibition of Rat Prostate 5α-Reductase and the Growth of Ventral Prostate in the Castrated Young Rat Model by 3-Indolebutyric Acids with Diaryl and Tricyclic Substitutents



Compd. No.	R	*In vitro* (rat) IC_{50} (nM)	*In vivo* (rat)[a] (10 mg/kg, s.c.)
19		350	N.T.[b]
20		70	N.T.
21		49	N.T.
22		24	N.T.
23		2.8	N.T.
24		24	N.T.
25		29	N.T.
26		4.5	4.7%
27 (FR119680)		5.0	44.1%
Finasteride		5.9	N.T.

a) *In vivo* effects of **26** and FR119680 on ventral prostate weight of castrated rats (TP-treated). Prepubertal male rats were castrated, subcutaneously injected with 300 mg/kg of TP (except castrated control), and subcutaneously administered with drug suspension for 5 d. Data are expressed as percent reduction in prostate weight which was calculated as follows: 100[(prostate weight of test comp+TP group)−(prostate weight of castrated control group)]/[(prostate weight of vehicle+TP group)−(prostate weight of castrated control group)] *b*) Not tested.

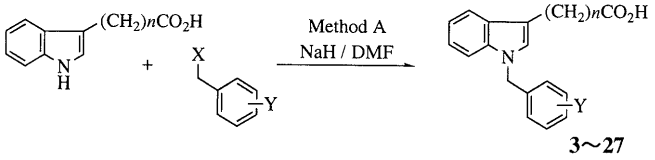


Chart 1. Synthesis of Indole Derivatives

The tricyclic bromides (**31**, **36**, **38**, **41**) used for the synthesis of **24**, **25**, **26** and **27** were prepared as shown in Chart 2. The tricyclic lactone **29** was obtained from the reaction between *p*-cresol and ethyl 2-cyclohexanonecarboxylate (**28**). **29** was converted to the bromide **31** by dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) followed by bromination with *N*-bromosuccinimide (NBS). However, reaction between phenol and ethyl 4-methyl-2-cyclohexanonecarboxylate (**32**) did not afford the tricyclic lactone **35**. This suggests that the cyclization reaction requires an additional electron-donating group on the phenol ring. Coupling of resorcinol with **32** proceeded smoothly to give **33**, which was converted to the triflate **34** with triflic anhydride and reduced by reaction with formic acid and palladium acetate in the presence of 1,1′-bis(diphenylphosphino)ferrocene (DPPF) to afford **35**. The conversion of **35** to the bromide **36**

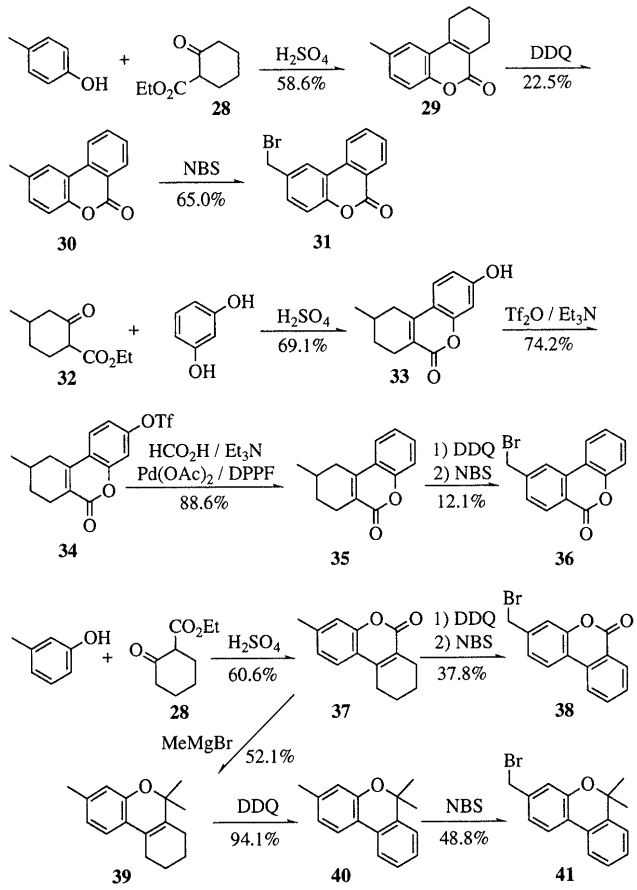


Chart 2. Synthesis of the Tricyclic Bromides (**31**, **36**, **38**, **41**)

involved the methods described as for **31**.

Reaction between *m*-cresol and **28** afforded the tricyclic lactone **37**, which was then converted to the bromide **38**. The tricyclic ether **39** was obtained by the reaction of **37** and methylmagnesium bromide. **39** was converted to the bromide **41** by dehydrogenation with DDQ and bromination with NBS.

Conclusions

At the outset of this work, we set out to produce 5α-reductase inhibitors with a non-steroidal structure. By modification of the indole nucleus of a random screening lead, we have succeeded in producing an excellent prototype compound, which displays very high inhibitory activity against rat 5α-reductase, both *in vitro* and *in vivo*.

Experimental

Chemistry Melting points were determined on a Thomas Hoover melting point apparatus and uncorrected. Infrared (IR) spectra were obtained on a Perkin Elmer 16PC fourier transform (FT)-IR spectrometer. Proton magnetic resonance (^{1}H-NMR) spectra were obtained on a Bruker AM200 (200 MHz) spectrometer or a Varian Gemini-300 (300 Hz) spectrometer, and chemical shifts are reported in parts per million relative to tetramethyl silane as internal standard (tetramethylsilane, δ 0.00). Mass spectra (MS) were obtained on a VG Platform.

Method A. [1-(4-Chlorobenzyl)indol-3-yl]acetic Acid (**3**): To a solution of 3-indoleacetic acid (150 mg, 0.86 mmol) in DMF (1.5 ml) was added NaH (60% in mineral oil, 76 mg, 1.89 mmol, 2.2 eq) at 20 °C. The reaction mixture was stirred for 30 min at the same temperature, and 4-chlorobenzyl chloride (140 mg, 0.86 mmol, 1.0 eq) was added. After stirring for 1 h at 20 °C, the reaction was quenched by addition of water. The mixture was washed with ether, and the separated aqueous layer was acidified with 1 N HCl (pH=1) and extracted with ether. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica gel chromatography (Merck 70-230 mesh, hexane : $CHCl_3$ = 1 : 1 to $CHCl_3$) and recrystallization (ether/hexane) to give **3** (176 mg, 68.2%) as colorless crystals, mp 142—143 °C. IR (KBr) cm^{-1}: 3080, 2910, 2880, 1720, 1490, 1465, 1240, 740. ^{1}H-NMR (DMSO-d_6) δ: 3.65 (2H, s), 5.38 (2H, s), 7.02 (1H, t, J=8 Hz), 7.11 (1H, t, J=8 Hz), 7.21 (1H, d, J=8 Hz), 7.37 (1H, d, J=8 Hz), 7.39 (1H, s), 7.41 (1H, d, J=8 Hz), 7.52 (1H, d, J=8 Hz). ESI-MS *m/z*: 298 $(M-H)^-$.

3-[1-(4-Chlorobenzyl)indol-3-yl]propionic Acid (**4**): **4** (145 mg, 58.3%) was prepared from 3-indolepropionic acid (150 mg) and 4-chlorobenzyl chloride (127 mg), mp 132—134 °C. IR (KBr) cm^{-1}: 3060, 2920, 2880, 1705, 1470, 1290, 1220, 750. ^{1}H-NMR ($CDCl_3$) δ: 2.60 (2H, t, J=7 Hz), 2.93 (2H, t, J=7 Hz), 5.35 (2H, s), 7.0—7.6 (9H, m). ESI-MS *m/z*: 312 $(M-H)^-$.

4-[1-(4-Chlorobenzyl)indol-3-yl]butyric Acid (**5**): **5** (210 mg, 86.6%) was prepared from 3-indolebutyric acid (150 mg) and 4-chlorobenzyl chloride (127 mg), mp 113—115 °C. IR (KBr) cm^{-1}: 3060, 2910, 2840, 1705, 1465, 1320, 1220, 740. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (2H, quintet, J=8 Hz), 2.43 (2H, t, J=8 Hz), 2.84 (2H, t, J=8 Hz), 5.23 (2H, s), 6.90 (1H, s), 7.01 (2H, d, J=8 Hz), 7.08—7.18 (3H, m), 7.26 (2H, d, J=8 Hz), 7.62 (1H, d, J=8 Hz). ESI-MS *m/z*: 326 $(M-H)^-$.

3-(1-Benzylindol-3-yl)propionic Acid (**6**): **6** (210 mg, 79.2%) was prepared from 3-indolepropionic acid (150 mg) and benzyl bromide (135 mg), mp 125—127 °C. IR (KBr) cm^{-1}: 3010, 2920, 2840, 1710, 1470, 740. ^{1}H-NMR ($CDCl_3$) δ: 2.48 (2H, t, J=8 Hz), 2.89 (2H, t, J=8 Hz), 5.32 (2H, s), 6.98 (1H, t, J=8 Hz), 7.06 (1H, t, J=8 Hz), 7.15—7.30 (6H, m), 7.38 (1H, d, J=8 Hz), 7.53 (1H, d, J=8 Hz). ESI-MS *m/z*: 278 $(M-H)^-$.

3-[1-(4-Tolyl)indol-3-yl]propionic Acid (**7**): **7** (200 mg, 86.4%) was prepared from 3-indolepropionic acid (150 mg) and 4-tolyl chloride (111 mg), mp 158—160 °C. IR (KBr) cm^{-1}: 3040, 2910, 2840, 1700, 1470, 1290, 1220, 740. ^{1}H-NMR ($CDCl_3$) δ: 2.48 (2H, t, J=8 Hz), 2.89 (2H, t, J=8 Hz), 5.32 (2H, s), 6.98 (1H, t, J=8 Hz), 7.06 (1H, t, J=8 Hz), 7.15—7.30 (6H, m), 7.38 (1H, d, J=8 Hz), 7.53 (1H, d, J=8 Hz). ESI-MS *m/z*: 292 $(M-H)^-$.

3-[1-(4-Methoxybenzyl)indol-3-yl]propionic Acid (**8**): **8** (164 mg, 67.1%) was prepared from 3-indolepropionic acid (150 mg) and 4-methoxybenzyl chloride (124 mg), mp 137—138 °C. IR (KBr) cm^{-1}: 3040, 2910, 2860, 1700, 1620, 1520, 1250, 740. ^{1}H-NMR ($CDCl_3$) δ: 2.80 (2H, t, J=8 Hz), 3.12 (2H, t, J=8 Hz), 3.78 (3H, s), 5.22 (2H, s), 6.86 (2H, d, J=8 Hz), 6.96 (1H, s), 7.08 (2H, d, J=8 Hz), 7.13—7.32 (3H, m), 7.64 (1H, d, J=8 Hz). ESI-MS *m/z*: 309 $(M-H)^-$.

3-[1-(2-Chlorobenzyl)indol-3-yl]propionic Acid (**9**): **9** (174 mg, 70.2%) was prepared from 3-indolepropionic acid (150 mg) and 2-chlorobenzyl chloride (127 mg), mp 111—113 °C. IR (KBr) cm^{-1}: 3040, 2910, 1700, 1465, 1330, 1205, 1040, 740. ^{1}H-NMR (DMSO-d_6) δ: 2.58 (2H, t, J=8 Hz), 2.94 (2H, t, J=8 Hz), 5.45 (s, 2H), 6.64 (1H, d, J=8 Hz), 7.04 (1H, t, J=8 Hz), 7.10 (1H, t, J=8 Hz), 7.20 (1H, t, J=8 Hz), 7.23 (1H, s), 7.30 (1H, t, J=8 Hz), 7.33 (1H, d, J=8 Hz), 7.50 (1H, d, J=8 Hz), 7.58 (1H, d, J=8 Hz). ESI-MS *m/z*: 312 $(M-H)^-$.

3-[1-(3-Chlorobenzyl)indol-3-yl]propionic Acid (**10**): **10** (160 mg, 64.5%) was prepared from 3-indolepropionic acid (150 mg) and 3-chlorobenzyl chloride (127 mg), mp 133—135 °C. IR (KBr) cm^{-1}: 3080, 1920, 2880, 1700, 1470, 1295, 1210, 740. ^{1}H-NMR (DMSO-d_6) δ: 2.58 (2H, t, J=8 Hz), 2.93 (2H, t, J=8 Hz), 5.38 (2H, s), 7.02 (1H, t, J=8 Hz), 7.06—7.13 (2H, m), 7.25 (1H, s), 7.27—7.35 (3H, m), 7.40 (1H, d, J=8 Hz), 7.54 (1H, d, J=8 Hz). ESI-MS *m/z*: 312 $(M-H)^-$.

3-[1-(3,4-Dichlorobenzyl)indol-3-yl]propionic Acid (**11**): **11** (150 mg, 54.5%) was prepared from 3-indolepropionic acid (150 mg) and 3,4-dichlorobenzyl chloride (155 mg), mp 125—126 °C. IR (KBr) cm^{-1}: 3020, 2900, 2880, 1700, 1480, 1300, 1210, 750, 745. ^{1}H-NMR ($CDCl_3$) δ: 2.78 (2H, t, J=8 Hz), 3.12 (2H, t, J=8 Hz), 5.20 (2H, s), 6.85 (1H, dd, J=2, 8 Hz), 6.94 (1H, s), 7.10—7.26 (4H, m), 7.35 (1H, d, J=8 Hz), 7.62 (1H, d, J=8 Hz). ESI-MS *m/z*: 346 $(M-H)^-$.

3-[1-[4-(Trifluoromethyl)benzyl]indol-3-yl]propionic Acid (**12**): **12** (65 mg, 60.2%) was prepared from 3-indolepropionic acid (150 mg) and 4-(trifluoromethyl)benzyl bromide (190 mg), mp 118—119 °C. IR (KBr) cm^{-1}: 3220, 3040, 2920, 1720, 1670, 1460, 1320, 1110, 750. ^{1}H-NMR ($CDCl_3$) δ: 2.78 (2H, t, J=8 Hz), 3.13 (2H, t, J=8 Hz), 5.32 (2H, s), 6.95 (1H, s), 6.98—7.14 (2H, m), 7.11—7.26 (5H, m), 7.53 (2H, d, J=10 Hz), 7.62 (1H, d, J=10 Hz). ESI-MS *m/z*: 346 $(M-H)^-$.

3-[1-(4-Fluorobenzyl)indol-3-yl]propionic Acid (**13**): **13** (110 mg, 46.8%) was prepared from 3-indolepropionic acid (150 mg) and 4-fluorobenzyl bromide (150 mg), mp 101—102 °C. IR (KBr) cm^{-1}: 3080, 3920, 2860, 1700, 1520, 1470, 1220, 740. ^{1}H-NMR ($CDCl_3$) δ: 2.60 (2H, t, J=8 Hz), 2.93 (2H, t, J=8 Hz), 5.33 (2H, s), 6.98 (1H, d, J=8 Hz), 7.04—7.28 (6H, m), 7.40

(1H, d, J=8 Hz), 7.55 (1H, d, J=8 Hz). ESI-MS m/z: 296 $(M-H)^-$.

3-[1-(4-Biphenylmethyl)indol-3-yl]propionic Acid (**14**): **14** (210 mg, 74.8%) was prepared from 3-indolepropionic acid (150 mg) and 4-(chloromethyl)biphenyl (160 mg), mp 156—157 °C. IR (KBr) cm^{-1}: 3040, 2920, 1730, 1710, 1470, 1340, 760, 750. ^{1}H-NMR (DMSO-d_6) δ: 2.11 (2H, t, J=8 Hz), 2.95 (2H, t, J=8 Hz), 5.40 (2H, s), 7.00 (1H, t, J=8 Hz), 7.10 (1H, t, J=8 Hz), 7.27 (1H, d, J=8 Hz), 7.32 (1H, s), 7.34 (1H, d, J=8 Hz), 7.40—7.46 (3H, m), 7.54—7.62 (5H, m). ESI-MS m/z: 354 $(M-H)^-$.

[1-(4-Biphenylmethyl)indol-3-yl]acetic Acid (**15**): **15** (233 mg, 79.0%) was prepared from 3-indoleacetic acid (150 mg) and 4-(chloromethyl)-biphenyl (175 mg), mp 156—158 °C. IR (KBr) cm^{-1}: 3060, 2920, 1710, 1470, 1230, 740. ^{1}H-NMR (DMSO-d_6) δ: 3.67 (2H, s), 5.42 (2H, s), 7.02 (1H, t, J=8 Hz), 7.12 (1H, t, J=8 Hz), 7.28 (1H, d, J=8 Hz), 7.34 (1H, s), 7.39—7.47 (4H, m), 7.52 (1H, d, J=8 Hz), 7.56—7.62 (4H, m). ESI-MS m/z: 340 $(M-H)^-$.

4-[1-(4-Biphenylmethyl)indol-3-yl]butyric Acid (**16**): **16** (220 mg, 80.6%) was prepared from 3-indolebutyric acid (150 mg) and 4-(chloromethyl)-biphenyl (150 mg), mp 169—170 °C. IR (KBr) cm^{-1}: 3040, 2920, 1710, 1460, 1330, 740. ^{1}H-NMR (DMSO-d_6) δ: 1.88 (2H, quintet, J=8 Hz), 2.28 (2H, t, J=8 Hz), 2.72 (2H, t, J=8 Hz), 5.40 (2H, s), 6.99 (1H, t, J=8 Hz), 7.09 (1H, t, J=8 Hz), 7.26 (1H, d, J=8 Hz), 7.32 (1H, s), 7.34 (1H, d, J=8 Hz), 7.40—7.46 (3H, m), 7.53 (1H, d, J=8 Hz), 7.57 (2H, d, J=8 Hz), 760 (2H, d, J=8 Hz). ESI-MS m/z: 368 $(M-H)^-$.

5-[1-(4-Biphenylmethyl)indol-3-yl]valeric Acid (**17**): **17** (46 mg, 26.1%) was prepared from 3-indolevaleric acid (100 mg) and 4-(chloromethyl)-biphenyl (93 mg). ^{1}H-NMR ($CDCl_3$) δ: 1.71—1.90 (4H, m), 2.42 (2H, t, J=8 Hz), 2.84 (2H, t, J=8 Hz), 5.33 (2H, s), 6.96 (1H, s), 7.10 (1H, dd, J=2, 8 Hz), 7.19 (2H, d, J=8 Hz), 7.22—7.64 (11H, m). ESI-MS m/z: 382 $(M-H)^-$.

6-[1-(4-Biphenylmethyl)indol-3-yl]hexanoic Acid (**18**): **18** (14 mg, 10.2%) was prepared from 3-indolehexanoic acid (80 mg) and 4-(chloromethyl)biphenyl (70 mg). ^{1}H-NMR (DMSO-d_6) δ: 1.33—1.46 (2H, m), 1.50—1.72 (4H, m), 2.22 (2H, t, J=8 Hz), 2.70 (2H, t, J=8 Hz), 5.38 (2H, s), 6.98 (1H, dd, J=2, 8 Hz), 7.04 (1H, dd, J=2, 8 Hz), 7.10 (1H, dd, J=2, 8 Hz), 7.24 (1H, s), 7.30 (2H, d, J=8 Hz), 7.32—7.62 (8H, m). ESI-MS m/z: 396 $(M-H)^-$.

4-[1-(4-Styrylbenzyl)indol-3-yl]butyric Acid (**19**): **19** (482 mg, 82.5%) was prepared from 3-indolebutyric acid (300 mg) and 4-styrylbenzyl chloride (338 mg). ^{1}H-NMR (DMSO-d_6) δ: 1.88 (2H, quintet, J=7 Hz), 2.30 (2H, t, J=7 Hz), 2.72 (2H, t, J=7 Hz), 5.36 (2H, s), 7.00 (1H, t, J=8 Hz), 7.09 (1H, t, J=8 Hz), 7.14—7.42 (12H, m), 7.56 (2H, t, J=8 Hz). ESI-MS m/z: 394 $(M-H)^-$.

4-[1-[3-(Phenoxymethyl)benzyl]indol-3-yl]butyric Acid (**20**): **20** (730 mg, 76.7%) was prepared from 3-indolebutyric acid (484 mg) and 3-(phenoxymethyl)benzyl chloride (660 mg), mp 90—92 °C. IR (KBr) cm^{-1}: 3020, 2960, 2880, 1710, 1600, 1460, 1250, 740. ^{1}H-NMR (DMSO-d_6) δ: 1.87 (2H, quintet, J=8 Hz), 2.28 (2H, t, J=8 Hz), 2.70 (2H, t, J=8 Hz), 5.02 (2H, s), 5.36 (2H, s), 6.90—7.10 (6H, m), 7.22—7.32 (6H, m), 7.40 (1H, d, J=8 Hz), 7.52 (1H, d, J=8 Hz). ESI-MS m/z: 398 $(M-H)^-$.

4-[1-(4-Phenoxybenzyl)indol-3-yl]butyric Acid (**21**): **21** (2.50 g, 87.9%) was prepared from 3-indolebutyric acid (1.50 g) and 4-phenoxylbenzyl chloride (1.61 g). ^{1}H-NMR (DMSO-d_6) δ: 1.86 (2H, quintet, J=8 Hz), 2.28 (2H, t, J=8 Hz), 2.70 (2H, t, J=8 Hz), 5.35 (2H, s), 6.92—7.21 (8H, m), 7.22 (1H, s), 7.28 (2H, t, J=8 Hz), 7.38 (1H, d, J=8 Hz), 7.45 (2H, d, J=8 Hz), 7.55 (2H, d, J=8 Hz). ESI-MS m/z: 384 $(M-H)^-$.

4-[1-[4-(Phenoxycarbonyl)benzyl]indol-3-yl]butyric Acid (**22**): **22** (70 mg, 11.4%) was prepared from 3-indolebutyric acid (300 mg) and phenyl 4-(bromomethyl)benzoate (431 mg), mp 114—116 °C. IR (KBr) cm^{-1}: 3000, 2960, 1700, 1680, 1460, 1250, 760. ^{1}H-NMR (DMSO-d_6) δ: 1.85 (2H, quintet, J=8 Hz), 2.28 (2H, t, J=8 Hz), 2.68 (2H, t, J=8 Hz), 5.24 (2H, s), 6.98 (1H, t, J=8 Hz), 7.06 (1H, d, J=8 Hz), 7.19 (1H, s), 7.30—7.42 (4H, m), 7.66 (2H, d, J=8 Hz), 7.68 (1H, s), 7.80 (2H, d, J=8 Hz), 8.26 (1H, d, J=8 Hz). ESI-MS m/z: 412 $(M-H)^-$.

4-[1-[3-(Phenoxylcarbonyl)benzyl]indol-3-yl]butyric Acid (**23**): **23** (65 mg, 10.6%) was prepared from 3-indolebutyric acid (300 mg) and phenyl 3-(bromomethyl)benzoate (430 mg). ^{1}H-NMR (DMSO-d_6) δ: 1.78 (2H, quintet, J=8 Hz), 2.17 (2H, t, J=8 Hz), 2.42 (2H, t, J=8 Hz), 5.00 (2H, s), 6.99 (1H, t, J=8 Hz), 7.09 (1H, t, J=8 Hz), 6.80—8.10 (14H, m). ESI-MS m/z: 412 $(M-H)^-$.

4-[1-(Dibenzopyranon-8-yl)methylindol-3-yl]butyric Acid (**24**): To a mixture of ethyl cyclohexanone-2-carboxylate (20 g, 118 mmol) and *p*-cresol (17.2 ml, 163 mmol) was added dropwise conc. H_2SO_4 (40 ml) with ice-cooling. The resulting solution was stirred overnight at 20 °C and poured onto ice and extracted with EtOAc. The extract was washed with water, 10% $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The crystalline residue was washed with hexane and recrystallized (EtOH) to give 2-methyl-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-6-one (**29**) (14.7 g, 58.6%). ^{1}H-NMR ($CDCl_3$) δ: 1.78—1.92 (4H, m), 2.40 (3H, s), 2.60 (2H, t, J=8 Hz), 2.78 (2H, t, J=8 Hz), 7.20 (1H, d, J=8 Hz), 7.26 (1H, dd, J=1, 8 Hz), 7.57 (1H, d, J=1 Hz).

A mixture of **29** (11.7 g, 55.0 mmol) and DDQ (30 g, 130 mmol) in toluene (240 ml) was heated under reflux for 4 h. After cooling to 20 °C, the reaction mixture was concentrated and the residue purified by silica gel column chromatography (hexane : CH_2Cl_2=1 : 1) and recrystallization (EtOH) to give 2-methyl-6*H*-dibenzo[*b*,*d*]pyran-6-one (**30**) (2.6 g, 22.5%). ^{1}H-NMR ($CDCl_3$) δ: 2.46 (3H, s), 7.28 (2H, s), 7.56 (1H, dt, J=1, 8 Hz), 7.75—7.84 (2H, m), 8.01 (1H, d, J=8 Hz), 8.38 (1H, dd, J=1, 8 Hz).

A mixture of **30** (1.5 g, 7.13 mmol), NBS (1.27 g, 7.13 mmol) and 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (30 mg, 0.097 mmol) in CCl_4 (30 ml) was heated to reflux for 1.5 h. After cooling to 20 °C, the reaction mixture was concentrated and the residue chromatographed on silica gel (hexane : CH_2Cl_2=2 : 3) to give 2-(bromomethyl)-6*H*-dibenzo[*b*,*d*]pyran-6-one (**31**) (1.34 g, 65.0%). ^{1}H-NMR ($CDCl_3$) δ: 4.60 (2H, s), 7.36 (1H, d, J=8 Hz), 7.52 (1H, dd, J=2, 8 Hz), 7.64 (1H, dt, J=1, 8 Hz), 7.86 (1H, dt, J=1, 8 Hz), 8.09 (1H, d, J=1 Hz), 8.14 (1H, dd, J=1, 8 Hz), 8.42 (1H, dd, J=1, 8 Hz).

Following method A, **24** (70 mg, 4.9%) was prepared from 3-indolebutyric acid (703 mg) and **31** (1.0 g), mp 187—192 °C (dec). IR (KBr) cm^{-1}: 3040, 2960, 2920, 2880, 1730, 1700, 1260, 1140, 750. ^{1}H-NMR (DMSO-d_6) δ: 2.08 (2H, quintet, J=8 Hz), 2.40 (2H, t, J=8 Hz), 2.86 (2H, t, J=8 Hz), 5.38 (2H, s), 6.98 (1H, s), 7.10—7.34 (5H, m), 7.58 (1H, t, J=8 Hz), 7.65 (1H, d, J=8 Hz), 7.80 (1H, t, J=8 Hz), 7.81 (1H, s), 7.98 (1H, d, J=8 Hz), 8.38 (1H, d, J=8 Hz). ESI-MS m/z: 410 $(M-H)^-$.

4-[1-(Dibenzopyranon-5-yl)methylindol-3-yl]butyric Acid (**25**): Following the procedure described above for **29**, 9-methyl-3-hydroxy-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-6-one (**33**) (29.2 g, 69.1%) was prepared from methyl 4-methyl-2-cyclohexanonecarboxylate (25 g) and resorcinol (19.2 g), mp 202—203 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, d, J=7 Hz), 1.22—1.34 (1H, m), 1.74—1.34 (2H, m), 2.20—2.38 (2H, m), 2.50—2.58 (1H, m), 2.88—2.96 (1H, m), 6.68 (1H, d, J=2 Hz), 6.77 (1H, dd, J=2, 10 Hz), 7.48 (1H, d, J=10 Hz).

To a mixture of **33** (15.0 g, 65.2 mmol) and Et_3N (10.04 ml, 72 mmol) in CH_2Cl_2 (150 ml) was added trifluoromethanesulfonic anhydride (21.2 g, 75 mmol) at 0 °C. After stirring at 0 °C for 2 h, the reaction mixture was partitioned betweeen EtOAc and water. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on silica gel (hexane : $CHCl_3$=1 : 1 to $CHCl_3$) to give 9-methyl-7,8,9,10-tetrahydro-3-trifluoromethanesulfonyloxy-6*H*-dibenzo[*b*,*d*]pyran-6-one (**34**) (17.42 g, 74.2%), mp 101—102 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, d, J=7 Hz), 1.32—1.45 (1H, m), 1.88—2.04 (2H, m), 2.26—2.38 (1H, m), 2.46—2.60 (1H, m), 2.76—2.84 (1H, m), 2.90—2.98 (1H, m), 7.22 (1H, dd, J=2, 8 Hz), 7.27 (1H, d, J=2 Hz), 7.66 (1H, d, J=8 Hz).

Formic acid (0.53 ml, 13.9 mmol) was added to a mixture of **34** (2.52 g, 6.96 mmol), Et_3N (2.91 ml, 20.9 mmol), $Pd(OAc)_2$ (32 mg, 0.14 mmol) and DPPF (156 mg, 0.28 mmol) in DMF (14 ml). The mixture was heated at 60 °C for 3 h and partitioned between EtOAc and water. The organic layer was washed with 1 N HCl, water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on silica gel (hexane : CH_2Cl_2=1 : 1 to CH_2Cl_2) to give 9-methyl-7,8,9,10-tetrahydro-6*H*-dibenzo-[*b*,*d*]pyran-6-one (**35**) (1.31 g, 88.6%) as colorless crystals, mp 123—125 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, d, J=8 Hz), 1.36—1.50 (1H, m), 1.85 (1H, m), 1.95—2.16 (2H, m), 2.70—3.00 (3H, m), 7.28 (1H, t, J=8 Hz), 7.32 (1H, d, J=8 Hz), 7.46 (1H, t, J=8 Hz), 7.57 (1H, d, J=8 Hz).

Following the procedure described above for **30**, 9-methyl-6*H*-dibenzo[*b*,*d*]pyran-6-one (1.23 g, 23.8%) was prepared from **35** (5.14 g) and DDQ (13.6 g), mp 100—101 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.57 (3H, s), 7.33 (1H, t, J=8 Hz), 7.35 (1H, d, J=8 Hz), 7.40 (1H, d, J=8 Hz), 7.48 (1H, t, J=8 Hz), 7.92 (1H, d, J=1 Hz), 8.06 (1H, dd, J=1, 8 Hz), 8.30 (1H, d, J=8 Hz).

Following the procedure described above for **31**, 9-(bromomethyl)-6*H*-dibenzo[*b*,*d*]pyran-6-one (**36**) (420 mg, 50.8%) was prepared from 9-methyl-6*H*-dibenzo[*b*,*d*]pyran-6-one (600 mg) and NBS (508 mg), mp 168—170 °C. ^{1}H-NMR ($CDCl_3$) δ: 4.63 (2H, s), 7.37 (1H, t, J=8 Hz), 7.39 (1H, d, J=8 Hz), 7.52 (1H, t, J=8 Hz), 7.60 (1H, d, J=8 Hz), 8.08 (1H, dd, J=1, 8 Hz), 8.14 (1H, d, J=1 Hz), 8.38 (1H, d, J=8 Hz).

Following method A, **25** (160 mg, 32.1%) was prepared from 3-indolebutyric acid (230 mg) and **36** (350 mg). ^{1}H-NMR (DMSO-d_6) δ: 1.93 (2H,

quintet, J=8 Hz), 2.30 (2H, t, J=8 Hz), 2.76 (2H, t, J=8 Hz), 5.60 (2H, s), 7.02 (1H, t, J=8 Hz), 7.10 (1H, t, J=8 Hz), 7.32—7.62 (7H, m), 8.17 (1H, d, J=8 Hz), 8.25 (1H, dd, J=1, 8 Hz), 8.37 (1H, d, J=1 Hz). ESI-MS *m/z*: 410 $(M-H)^-$.

4-[1-(Dibenzopyranon-9-yl)methylindol-3-yl]butyric Acid (**26**): Following the procedure described above for **29**, 3-methyl-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-6-one (**37**) (19.1 g, 60.6%) was prepared from ethyl cyclohexanone-2-carboxylate (25 g) and *m*-cresol (21.5 ml). ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s), 2.60 (2H, m), 2.75 (2H, m), 7.07 (1H, d, J=8 Hz), 7.11 (1H, s), 7.43 (1H, d, J=8 Hz).

Following the procedure described above for **30,** 3-methyl-6*H*-dibenzo-[*b*,*d*]pyran-6-one (6.0 g, 61.1%) was prepared from **37** (10 g) and DDQ (21.2 g). ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s), 7.12 (1H, d, J=10 Hz), 7.14 (1H, s), 7.52 (1H, dt, J=1, 8 Hz), 7.78 (1H, dt, J=1, 8 Hz), 7.87 (1H, d, J=10 Hz), 8.03 (1H, d, J=8 Hz), 8.33 (1H, dt, J=1, 8 Hz).

Following the procedure described above for **31**, 3-(bromomethyl)-6*H*-dibenzo[*b*,*d*]pyran-6-one (**38**) (5.1 g, 61.8%) was prepared from 3-methyl-6*H*-dibenzo[*b*,*d*]pyran-6-one (6.0 g) and NBS (5.09 g). ^{1}H-NMR ($CDCl_3$) δ: 4.53 (2H, s), 7.35 (1H, d, J=10 Hz), 7.38 (1H, s), 7.58 (1H, dt, J=1, 8 Hz), 7.82 (1H, dt, J=1, 8 Hz), 8.03 (1H, d, J=3 Hz), 8.10 (1H, d, J=10 Hz), 8.39 (1H, dt, J=1, 8 Hz).

Following method A, **26** (730 mg, 30%) was prepared from 3-indolebutyric acid (1.0 g) and **38** (5.1 g) as colorless crystals, mp 152—153 °C. IR (KBr) cm^{-1}: 3040, 2940, 1740, 1705, 1620, 1460, 1320, 1270, 750. ^{1}H-NMR ($CDCl_3$) δ: 2.08 (2H, quintet, J=8 Hz), 2.46 (2H, t, J=8 Hz), 2.85 (2H, t, J=8 Hz), 5.36 (2H, s), 6.97 (1H, s), 7.03 (1H, d, J=8 Hz), 7.08 (1H, s), 7.10—7.23 (3H, m), 7.57 (1H, t, J=8 Hz), 7.63 (1H, d, J=8 Hz), 7.79 (1H, t, J=8 Hz), 7.96 (1H, d, J=8 Hz), 8.05 (1H, d, J=8 Hz), 8.38 (1H, d, J=8 Hz). ESI-MS *m/z*: 410 $(M-H)^-$.

4-[1-(6,6-Dimethyl-6*H*-dibenzo[*b*,*d*]pyran-3-yl)methyl-indol-3-yl]butyric Acid (**27**, FR119680): To a solution of **37** (9.0 g, 42.0 mmol) in anisole (280 ml) was added a 3 M ether solution of MeMgBr (28 ml, 84.0 mmol) at 20 °C. The reaction mixture was heated under reflux for 8 h, and cooled to 0 °C. The reaction was quenched with 1 N HCl, and the organic layer was separated, washed with water, 10% $NaHCO_3$ and brine, and dried over $MgSO_4$. After evaporation of solvent, the residue was chromatographed on silica gel (hexane) to give 3,6,6-trimethyl-7,8,9,10-tetrahydro-6*H*-dibenzo-[*b*,*d*]pyran (**39**) (5.00 g, 52.1%). ^{1}H-NMR ($CDCl_3$) δ: 1.34 (6H, s), 1.65—1.80 (4H, m), 2.00—2.10 (2H, m), 2.26 (3H, s), 2.30—2.40 (2H, m), 6.62 (1H, s), 6.67 (1H, d, J=10 Hz), 6.96 (1H, d, J=10 Hz).

Following the procedure described above for **29**, 3,6,6-trimethyl-6*H*-dibenzo[*b*,*d*]pyran (**40**) (4.63 g, 94.1%) was prepared from **39** (5.0 g) and DDQ (9.94 g). ^{1}H-NMR ($CDCl_3$) δ: 1.63 (6H, s), 2.33 (3H, s), 6.75 (1H, s), 6.82 (1H, d, J=10 Hz), 7.20—7.40 (3H, m), 7.61 (1H, d, J=10 Hz), 7.68 (1H, dd, J=1, 10 Hz).

Following the procedure described above for **31**, 3-(bromomethyl)-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran (**41**) (3.05 g, 48.8%) was prepared from **40** (4.63 g) and NBS (3.67 g). ^{1}H-NMR ($CDCl_3$) δ: 4.53 (2H, s), 7.35 (1H, d, J=8 Hz), 7.38 (1H, s), 7.58 (1H, dt, J=1, 8 Hz), 7.82 (1H, dt, J=1, 8 Hz), 8.03 (1H, d, J=8 Hz), 8.10 (1H, d, J=10 Hz), 8.39 (1H, dt, J=1, 8 Hz).

Following method A, FR119680 (**27**) (1.30 g, 62.1%) was prepared from **41** (1.49 g) and 3-indolebutyric acid (1.0 g), mp 144—145 °C. IR (KBr) cm^{-1}: 3040, 2980, 2880, 1720, 1420, 1270, 740. ^{1}H-NMR ($CDCl_3$) δ: 1.60 (6H, s), 2.08 (2H, quintet, J=8 Hz), 2.43 (2H, t, J=8 Hz), 2.84 (2H, t, J=8 Hz), 5.24 (2H, s), 6.72 (1H, s), 6.75 (1H, d, J=10 Hz), 6.95 (1H, s), 7.07—7.34 (6H, m), 7.60—7.68 (3H, m). ESI-MS *m/z*: 424 $(M-H)^-$. *Anal.* Calcd for $C_{28}H_{27}NO_3$: C, 79.03; H, 6.40; N, 3.29. Found: C, 78.39; H, 6.37; N, 3.25.

Biological Data Preparation of Prostatic Enzyme: Rat ventral prostates, removed from 10—20 weeks old male Wistar rats, dissected free of their capsules, were washed with saline, and stored at −80 °C. Prostatic enzyme fractions were prepared as previously discribed in the literature.[11] Frozen tissues were thawed on ice and minced with scissors. Unless specified, all of the following procedures were carried out at 4 °C. The tissues were homogenized with a Polytron homogenizer in 3—4 tissue volumes of medium A (0.32 M sucrose, 0.1 mM dithiothreitol (DTT), and 20 mM sodium phosphate buffer pH 6.5). The homogenates were centrifuged at 1.5×10^3 ***g*** for 20 min, and the nuclear membrane fractions were precipitated. The pellets were then resuspended in medium A and filtered with gauze. The suspension (3—10 mg/ml) was stored at −80 °C until use.

5α-Reductase Assay: 5α-Reductase activites were assayed as previously described in the literature.[12] The reaction mixture contained in a final volume of 200 μl: 1 mM DTT, 40 mM of sodium phosphate buffer, 0.1 mM NADPH, 2 nM [1,2,6,7-^{3}H]testosterone, and the rat prostatic enzyme fraction. The amount of the prostatic enzyme fractions were adjusted to set the rate of conversion of testosterone into DHT at around 30% at pH 6.5. The reaction, in duplicate, was started by adding the enzyme fraction, followed by incubation at 37 °C for 60 min, and stopped by mixing with 200—300 μl of ethyl acetate containing cold 500 μg/ml testosterone and 300 μg/ml of DHT as UV markers (245 nm for testosterone, 305 nm for DHT). 50 μl of ethyl acetate was spotted on Kieselgel 60 F_{254} plates and testosterone and DHT were chromatographed using ethyl acetate/cyclohexane (1 : 1) as the developing solvent. The plate was air dried, sprayed with primuline solution (10 mg/400 ml in acetone/water (4 : 1)), and the testosterone and DHT located under UV light. Androgen containing areas were cut and the strips soaked in 5 ml of aquasol-2 and radioactivities were counted in a scintillation counter.

Effects in Castrated Young Rats: Four-week-old prepubertal male Wistar rats were anesthetized by pentobarbital and castrated. From the incised abdomen vas deferens, testicular artery and vein were fastened and testes were cut out.[13] After 3 d, subcutaneous administration of 2 ml/kg of drug solution was started once daily for 5 consecutive days. Drugs were dissolved in sesame oil. 300 μg/kg of TP in sesame oil was subcutaneously injected to the rats at the same time as drug administration. Rats were sacrificed with CO_2 gas about 6 h after the last dosing, and ventral prostates and seminal vesicles were removed and weighed.

References and Notes

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