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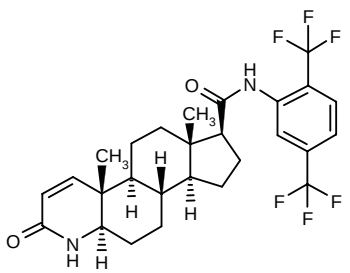
Dutasteride

Prop INN

Steroid 5α-Reductase Inhibitor
Treatment of BPH

GG745
GI-198745
GI-198745X

N-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide



$C_{27}H_{30}F_6N_2O_2$ Mol wt: 528.5430

CAS: 164656-23-9

EN: 222406

Synthesis

Dutasteride can be obtained by three different ways:

1) The reaction of 3-oxo-4-androstene-17β-carboxylic acid (I) with $SOCl_2$/pyridine in THF gives the acyl chloride (II), which is condensed with 2,5-bis(trifluoromethyl)aniline (III) by means of pyridine in refluxing THF, yielding amide (IV). The oxidation of (IV) with $KMnO_4$/$NaIO_4$/Na_2CO_3 in refluxing *tert*-butanol/water affords the *seco*-steroid (V), which is cyclized with NH_3 in ethyleneglycol at 180 °C to give the 5-unsaturated azasteroid (VI). The hydrogenation of (VI) with H_2 over PtO_2 in acetic acid yields the saturated azasteroid (VII), which is finally dehydrogenated by means of 2,3-dichloro-5,6-dicyanobenzoquinone (DCQ)/bis(trimethylsilyl)trifluoroacetamide in dioxane (1). Scheme 1.

2) The oxidation of 3-oxo-4-androstene-17β-carboxylic acid (I) with $KMnO_4$/$NaIO_4$/Na_2CO_3 in refluxing *tert*-butanol/water affords the *seco*-steroid (VIII), which is cyclized with NH_3 in ethyleneglycol at 180 °C, giving the 5-unsaturated steroid (IX). The hydrogenation of (IX) with H_2 over PtO_2 in acetic acid yields the saturated azasteroid (X), which is esterified with 2,2-dimethoxypropane/HCl in methanol to afford the corresponding methyl ester (XI). The dehydrogenation of (XI) with phenylseleninic anhydride in refluxing chlorobenzene gives the 1-unsaturated azasteroid (XII), which is hydrolyzed with KOH in refluxing methanol/water to yield the corresponding unsaturated free acid (XIII). The esterification of (XIII) with 2,2'-dipyridyl disulfide (XIV) by means of triphenylphosphine in toluene affords the 2-pyridyl thioester (XV) (2), which is finally amidated with 2,5-bis(trifluoromethyl)aniline (III) by means of silver trifluomethanesulfonate in dichloromethane (3). Scheme 2.

3) The already obtained unsaturated free acid (XIII) can also be treated with $SOCl_2$ in pyridine to give the corresponding acyl chloride (XVI), which is then condensed directly with 2,5-bis(trifluoromethyl)aniline (III) in pyridine (1). Scheme 2.

Description

White solid, m.p. 244-5 °C (1).

Introduction

Enlargement of the prostate gland, medically termed benign prostatic hyperplasia (BPH), is one of the most common medical conditions in older men. As many as 40% of men aged 70 years or older have been reported to suffer lower urinary tract symptoms consistent with BPH (4).

Current treatment options for BPH include certain medical devices, surgical therapy and phytotherapy, as well as the polyene mepartricine, seven marketed α_1-adrenoceptor antagonists and the type 2-selective

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Scheme 1: Synthesis of Dutasteride

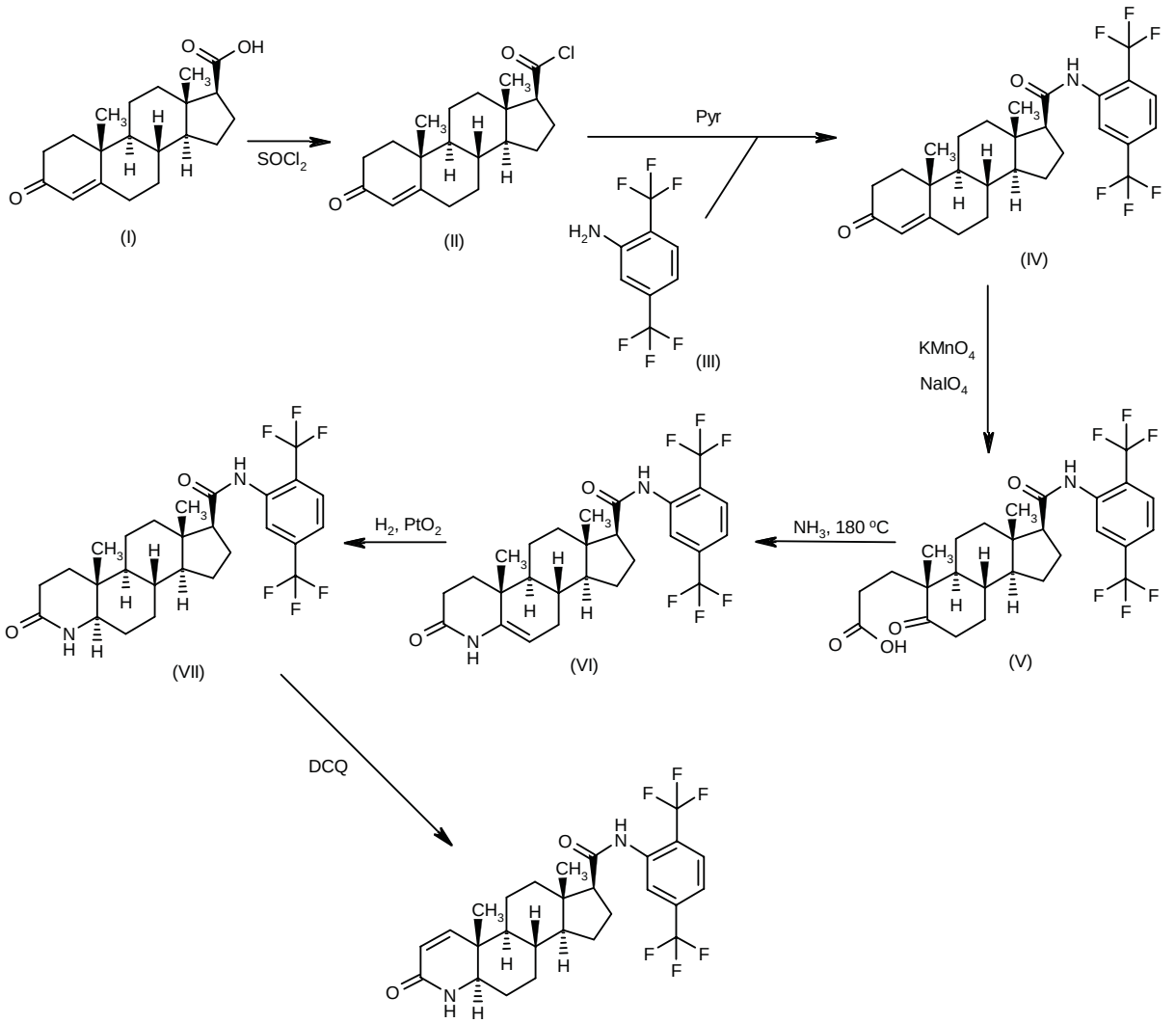
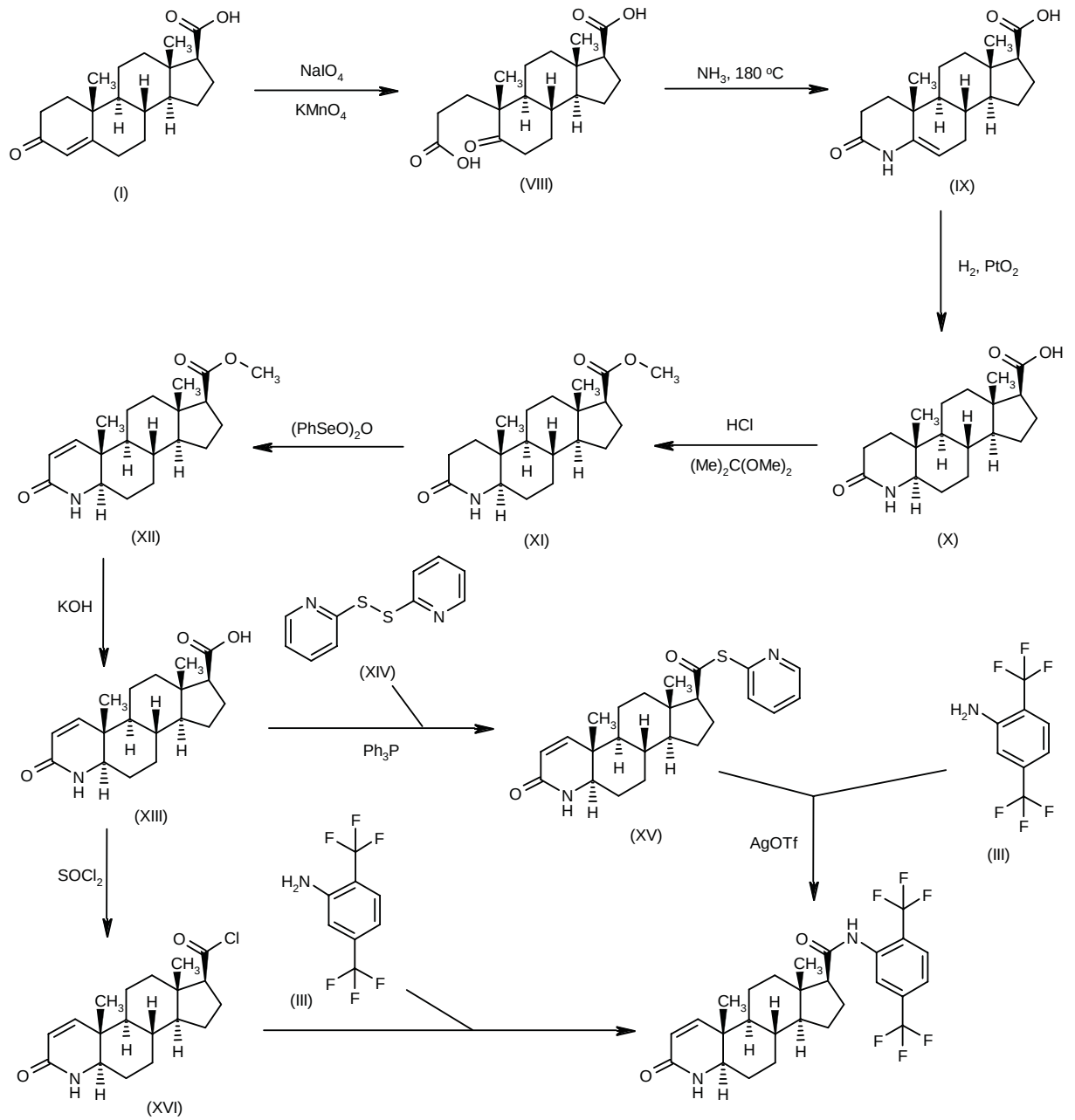


Table I: Current treatment options for BPH (from Prous Science Ensemble database).

Product	Company	Mechanism of Action
Alfuzosin HCl (*Xatral*)	Synthélabo	α_1-Adrenoceptor antagonist
Alfuzosin HCL (*Xatral SR*)	Lorex	α_1-Adrenoceptor antagonist
Doxazosin mesylate (*Cardura*)	Pfizer	α_1-Adrenoceptor antagonist
Doxazosin-GITS	Pfizer	α_1-Adrenoceptor antagonist
Finasteride (*Proscar*)	Merck & Co.	5α-Reductase inhibitor
Indoramin (*Doralese*)	SmithKline Beecham	α_1-Adrenoceptor antagonist
Mepartricin (*Ipertrofan*)	SPA	Polyene compound
Prazosin (*Hypovase*)	Pfizer	α_1-Adrenoceptor antagonist
Tamsulosin HCl (*Flomax MR*)	Yamanouchi	α_{1A}-Adrenoceptor antagonist
Terazosin HC (*Hytrin BPH*)	Abbott	α_1-Adrenoceptor antagonist

5α-reductase inhibitor finasteride (Table I). Phytotherapy, first described in Egypt in the 15th century B.C., is currently common in Europe and the U.S. In 1993, nearly half of all medications dispensed for the treatment of BPH in Italy were phytotherapeutic medications, compared to just 5% for α_1-adrenoceptor antagonists and 5%

Scheme 2: Synthesis of Dutasteride

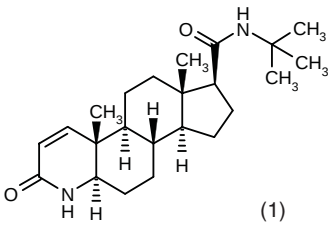


for finasteride (5). Approximately 30 phytotherapeutic compounds are currently used in the treatment of BPH (6). The most widely used is the extract of the dried ripe fruit of the American dwarf saw palmetto plant *Serenoa repens* (*Sobal serrulata*). The therapeutic efficacy of this plant extract has recently been reviewed (7).

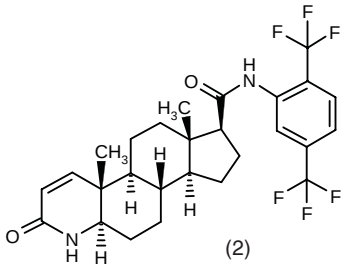
The symptomatic treatment of BPH, particularly in patients unfit for or awaiting surgery, includes the use of α_1-adrenoceptor antagonists. Use of the latter is based on the concept of a dynamic component of prostatic obstruction that depends upon the sympathetically controlled tone of smooth muscle in the prostate and its capsule. Blockade of α_1-adrenoceptors minimizes this tone and, hence, the degree of obstruction and also relieves irritating symptoms.

Table II: Structures of 5α-reductase inhibitors launched and under development (from Prous Science Ensemble database).

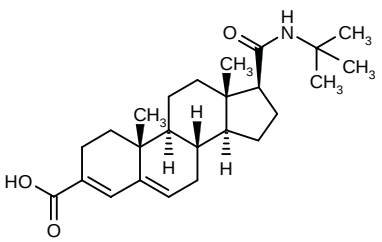
1. Finasteride
   Merck & Co.
   Launched 1992
2. Dutasteride
   Glaxo Wellcome
   Phase III
3. Epristeride
   SmithKline Beecham
   Phase III
4. FK-143
   Fujisawa
   Phase II
5. CS-891[1]*
   Sankyo
   Phase II
6. Z-350[1]
   Zeria
   Preclinical
7. FR-119680
   Fujisawa
   Preclinical
8. PNU-157706
   Pharmacia & Upjohn
   Preclinical
9. SNA-4606-1[2]
   Snow Brand Milk
   Research



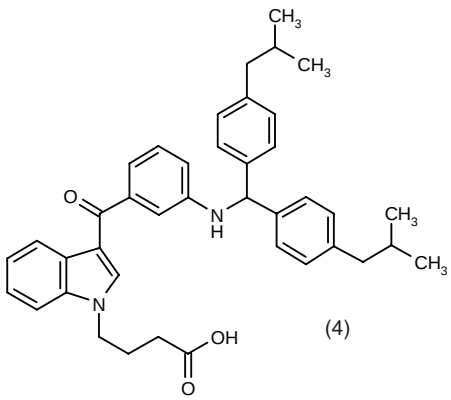
(1)



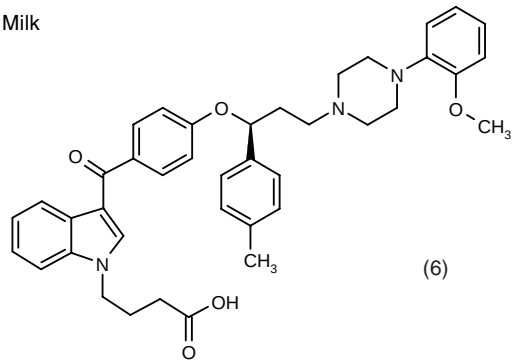
(2)



(3)

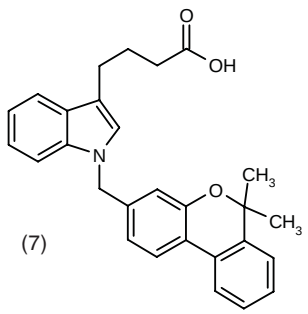


(4)

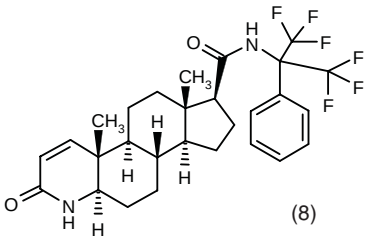


.HCl

(6)



(7)



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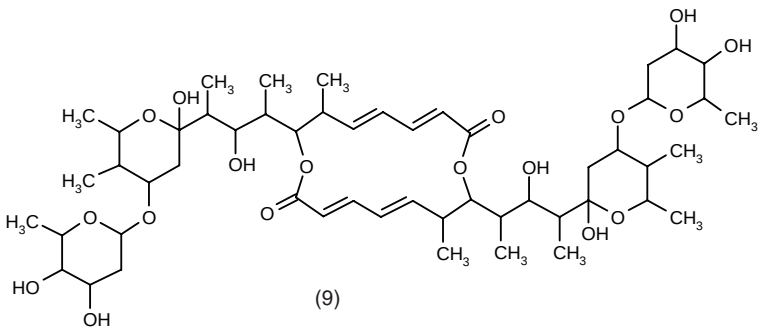

(9)

*Structure not yet detected.[1]Dual steroid 5α-reductase inhibitor and α_1-adrenoceptor antagonist. [2]Elaiophyllin compound isolated from the culture broth of *Streptomyces* sp.

Steroid 5α-reductase [EC 1.3.1.30] is an NADPH-dependent enzyme that is abundant within the prostate and that converts testosterone to the more potent androgen dihydrotestosterone (DHT). DHT is critical for the development of the prostate gland and has been implicated in the pathogenesis of BPH. Inhibition of the enzyme 5α-reductase represents an important target for the discovery of new drugs to treat BPH.

Experimental data support the existence of at least two genes for 5α-reductase and two distinct isozymes of 5α-reductase, with type-2 being the most abundant in prostate tissue; 5α-reductase type-1 is believed to be

Table III: Pharmacological actvity of selected 5α-reductase inhibitors (from Prous Science MFLine database).

Compound	Steroid 5α-reductase	Parameter	Value (nM)	Ref.
Dutasteride	Human type-1	K_i	6.0	9
	Human type-2	K_i	7.0	9
Epristeride	Rat	K_i	23[a]	20,21
	Rat	IC_{50}	11.3	22
	Human type-1	K_i	10	23
	Human type-2	K_i	2.0	23
Finasteride	Rat	K_i	5.8	24
	Rat	IC_{50}	32[a]	25,26
	Human type-1	K_i	183[a]	9,23
	Human type-1	IC_{50}	313	26
	Human type-2	K_i	36.5[a]	9,23
	Human type-2	IC_{50}	11.3	26
FK-143	Rat	IC_{50}	4.7[a]	27,28
	Human type-1	IC_{50}	22	28
FR-119680	Rat	IC_{50}	5.0	25
PNU-157706	Rat	IC_{50}	34	26
	Human type-1	IC_{50}	3.9	26
	Human type-2	IC_{50}	1.8	26
SNA-4606-1	Rat	IC_{50}	6600	27
Z-350	Rat	IC_{50}	3.83	30

[a]Mean value from different studies using comparable experimental methods.

more abundant in scalp tissue. In the treatment of BPH and other hyperandrogenic disease conditions, a drug that is capable of inhibiting both isozymes would be most desirable, as it could block the production of dihydrotestosterone (DHT) more effectively.

The first 5α-reductase inhibitor, finasteride (Proscar®); Merck & Co.), was launched in 1992 for the treatment of BPH. Last year, finasteride was launched for the new indication of alopecia (as Propecia®). At present, four 5α-reductase inhibitors are under clinical development, as shown in Table II: dutasteride (Glaxo Wellcome) and epristeride (SmithKline Beecham), both in phase III clinical trials, and FK-143 (Fujisawa) and CS-891 (Sankyo), both in phase II. Other 5α-reductase inhibitors are in preclinical studies: Z-350 (Zeria), FR-119680 (Fujisawa) and PNU-157706 (Pharmacia & Upjohn). Table III presents the pharmacological activity of selected type-1 and type-2 5α-reductase inhibitors.

The discovery and development of GG-745 (dutasteride), a new potent dual 5α-reductase inhibitor, was described by scientists at Glaxo Wellcome (8).

Pharmacological Actions

Dutasteride is a potent, selective and irreversible 5α-reductase inhibitor that is active against both isoforms of the enzyme, acting by an identical two-step mechanism to inhibit both type-1 and type-2 5α-reductases in a time-dependent fashion (9, 10). Its inhibition of the type-2 isoform is similar to that of finasteride, whereas its activity against type-1 5α-reductase is fully 60 times more potent than that of the reference drug. It is also approximately 5 times more rapid than finasteride in inactivating the enzyme. The resulting inhibition by dutasteride of circulating DHT levels is also significantly more potent than by finasteride (10, 11).

In a preclinical study, male Sprague-Dawley rats were administered equimolar doses of dutasteride (1, 10 or 100 mg/kg/day) or finasteride (0.7, 7 or 70 mg/kg/day) by oral gavage for 14 days, and the compounds' effects on total body weight and weights of various organs (prostate, seminal vesicles, adrenals, liver and testis) were assessed. Prostate volume was reduced significantly in rats treated with all three doses of dutasteride as compared to untreated controls, with no significant difference between doses. Finasteride, in contrast, showed dose-dependent effects on prostate volume, with the greatest activity at the highest dose; as such, much lower doses of dutasteride are expected to be required to produce efficacy comparable to finasteride. Both 5α-reductase inhibitors reduced seminal vesicle weight to a similar extent (~50%); effects of the two compounds on other organ weights were also comparable. The activity of dutasteride in this rat model was calculated to be approximately 72 times more potent (on a mg:mg basis) than that of finasteride, while blood samples taken from animals administered comparable doses of the two compounds indicated that the activity of the title compound was approximately 56 times more potent (on a concentration:concentration basis) (10, 11).

Pharmacokinetics and Pharmacodynamics

Based on the favorable activity observed with dutasteride in preclinical models, extensive pharmacokinetic

studies were conducted in rats and dogs. Administered to rats at a dose of 1 mg/kg i.v. or p.o., dutasteride gave $t_{1/2}$, Cl, V_{ss} and oral bioavailability (F) values of 13.7 h, 4.1 ml/min/kg, 4 l/kg and 100%, respectively. These values in dogs (5 mg/kg i.v. or p.o.) were 65 h, 0.5 ml/min/kg, 3 l/kg and 43%, respectively. Drug concentrations in blood peaked 2.5 h after oral dosing in dogs and 7 h after oral dosing in rats. Drug concentrations in blood following i.v. administration were 3430 ng/ml in dogs 10 min postdosing and 200 ng/ml in rats 15 min postdosing. The terminal half-life of the title compound was longer than that of finasteride in both species (65 h *vs.* 4 h in dogs and 14 h *vs.* 1 h in rats) (10, 11).

In another pharmacokinetic study in rats, dutasteride was administered as single or multiple (daily x 30) doses of 2 or 500 mg/kg by oral gavage. Pharmacokinetic parameters of the compound following a single dose were dose-dependent, with t_{max}, half-life and MRT increasing in relation to dose. This is consistent with slow drug absorption following oral dosing. Flip-flop kinetics were suggested. Following multiple dosing, half-life and C_{max} increased and tmax decreased as compared to single-dose administration; this was attributed to changes in the elimination mechanism or in the volume of distribution when the compound is administered as multiple doses (12).

Pharmacokinetic simulations were performed, based on the data obtained in animal studies, to determine that the dose of 3 mg would provide peak drug concentrations of approximately 15 ng/ml in humans, leading to significant suppression of DHT levels. However, in anticipation of its prolonged terminal half-life, a conservative starting dose some 2 orders of magnitude lower (0.01 mg) was selected for human studies. This was significantly lower than the doses evaluated in toxicology studies, during which no toxicological effects were observed (10).

In an early human study designed to evaluate the pharmacokinetic parameters of dutasteride in humans, title compound and finasteride were administered to 48 healthy male volunteers in a randomized, blinded, placebo-controlled sequential cohort dose-escalation study. Subjects were given single doses of dutasteride (0.01, 0.1, 1.0, 2.5, 5.0, 10.0, 20.0 or 40.0 mg), finasteride (5 mg) or placebo, with dose escalation in sequential cohorts following a safety evaluation. Plasma drug concentrations and circulating DHT levels were measured for up to 8 weeks postdosing. Pharmacokinetics were described using a standard noncompartmental model, with Cl, V_{ss} and terminal half-life calculated to be 1.3 l/h, 385 l and 247 h, respectively. DHT levels decreased in a dose-dependent fashion following administration of dutasteride, ranging from a 34 ± 18% reduction at the dose of 0.01 mg to a 95 ± 5% reduction at the 40-mg dose. Finasteride, at the dose used in this study, reduced DHT levels by 80 ± 5.6%; inhibition by dutasteride was significantly more potent at doses above 10 mg. Pharmacodynamics were well described using a model that accounted for rates of DHT formation and elimination, 5α-reductase turnover, relative capacity of the two isozymes and the rate of irreversible inhibition of one or both isozymes. Based on this model, type-2 5α-reductase was shown to contribute 80% of all circulating plasma DHT. The inhibitory activity of dutasteride against the type-2 isozyme was approximately 3 times more potent than that of finasteride, with full blockade of both type-1 and type-2 5α-reductases obtained at doses of 10 mg or higher (10, 13, 14).

In another single-dose pharmacokinetic study in 32 healthy male volunteers, dutasteride was shown to have both linear and nonlinear elimination. Data were best described using a two-compartment model, with first-order absorption and parallel linear and nonlinear elimination pathways. The absorption of dutasteride (0.01-40 mg p.o.) was rapid, followed by a short distribution phase. The high volume of distribution, combined with its low linear clearance (511 l and 0.58 l/h, respectively), resulted in a prolonged half-life of up to 5 weeks at the highest concentrations. At lower concentrations more approximate to the K_m (0.96 ng/ml), maximum clearance decreased and the proportion of drug eliminated by the more rapid saturable elimination pathway increased, resulting in a short half-life of about 3 days. Simulations performed with the model described indicated that the steady-state concentrations of dutasteride, and the rate at which they are attained, are primarily nonlinear at doses of 0.1 mg/day, whereas they are almost entirely linear at doses above 1 mg/day (15).

Clinical Studies

Fifty-three patients with benign prostatic hyperplasia were admnistered daily oral doses of dutasteride (0.1-5.0 mg/day or a loading dose of 40 mg plus 2.5 mg/day), finasteride (5 mg) or placebo in a randomized, blinded, parallel-group study. Significantly greater inhibition of serum DHT was obtained with the dual inhibitor dutasteride as compared to finasteride; the title compound, at doses of 2.5 mg/day or higher, reduced serum DHT levels by 95% or more, compared to a reduction of 76% with finasteride (16) (Box 1).

The hormonal effects of dutasteride were evaluated in a double-blind, placebo- and active drug (finasteride)-controlled parallel-group trial in 313 men with BPH. Subjects were randomized to daily treatment with dutasteride (0.01, 0.05, 0.5, 2.5 and 5.0 mg), finasteride (5 mg) or placebo for 24 weeks. In patients treated with dutasteride, serum DHT levels decreased dose-dependently, ranging from –5.3 ± 27% at the dose of 0.01 mg/day to –98.1 ± 1% with the 5.0 mg/day dose. Finasteride, in contrast, caused a 66.9 ± 18% reduction in DHT, compared to an increase of 5.3 ± 23% with placebo. Serum testosterone levels tended to increase in subjects treated with both active drugs (with the exception of the lowest dose of dutasteride), but remained within normal ranges in all but 3 subjects. Again, dual inhibition of both type-1 and type-2 5α-reductases with dutasteride was demonstrated to be more effective in reducing serum DHT levels than simple type-1 enzyme inhibition with finasteride. Based

Box 1: Dutasteride in the treatment of BPH (16) [from Prous Science CSLine database].

Design	Randomized, double-blind, placebo-controlled clinical study
Population	Men with benign prostate hyperplasia (n = 53)
Treatments	Dutasteride (D), 0.1 mg/d x 28 d (n = 8) D0.5 mg/d x 28 d (n = 8) D2.5 mg/d x 28 d (n = 8) D5.0 mg/d x 28 d (n = 9) D40 mg loading dose + 2.5 mg/d x 28 d (n = 8) Finasteride (F), 5 mg/d x 28 d (n = 6) Placebo (P) (n = 6)
Results	DHT reduction (%): P (3) < F (76) ≥ D0.1 (72) < D0.5 (90) ≤ D2.5 (95) ≤ D40 (96) ≤ D5 (97) [F and all D *vs.* P, p <0.05; all D except 0.1 *vs.* F, p <0.05] AUA7 change from baseline: P (–2.5) ≤ F (–4.2) ≥ D0.1 (–6.3) ≤ D0.5 (–2.6) ≥ D2.5 (–6.5) ≤ D40 (–5.0) < D5 (–8.4) [D5 *vs.* P, p <0.05]
Conclusions	Dual inhibition of 5-α reductase by dutasteride significantly decreased serum DHT

Box 2: Hormonal effects of dutasteride (17) [from Prous Science CSLine database].

Design	Double-blind, parallel, multicenter clinical study
Population	Men with benign prostatic hyperplasia (n = 313)
Treatments	Dutasteride (D), 0.01 mg/d x 24 wk (n = 47) D0.05 mg/d x 24 wk (n = 47) D0.5 mg/d x 24 wk (n = 48) D2.5 mg/d x 24 wk (n = 39) D5 mg/d x 24 wk (n = 44) Finasteride (F), 5 mg/d x 24 wk (n = 45) Placebo (P) (n = 43)
Results	DHT reduction (%): P (+5.3) < D0.01 (–5.3) < D0.05 (–47.9) < D0.5 (–93.6) ≥ D2.5 (–97.2) ≥ D5 (–98.1) > F (–66.9) [all D except 0.01 *vs.* P, p <0.05; D0.5, D2.5, D5 *vs.* F, p < 0.05] Testosterone change (%): P (9.7) ≤ D0.01 (12.1) ≥ D0.05 (8.8) < D0.5 (24.6) < D2.5 (27.3) > D5 (21.6) > F (18.2) [D0.5, D5 *vs.* P, p <0.05] Serum testosterone stayed within the normal range except for 3 patients
Conclusions	Dutasteride may be clinically effective in a variety of DHT-related conditions, with 0.5 mg being the minimally effective dose

on the findings obtained in this study, the dose of 0.5 mg was recommended for future clinical trials (17).

Dutasteride is currently being evaluated in phase III trials for the treatment of BPH. The compound is also in phase II testing for the treatment of androgenic alopecia. Based on its increased ability to inhibit serum DHT levels, dutasteride is potentially more potent than finasteride in promoting the growth of hair on the scalp in men. It is also suggested to have excellent potential in the treatment of acne, and clinical trials for that indication are also planned (18, 19).

Manufacurer

Glaxo Wellcome plc (GB).

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