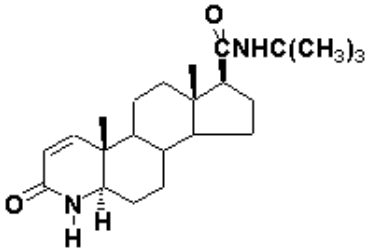
Finasteride (Propecia®)



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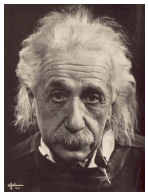
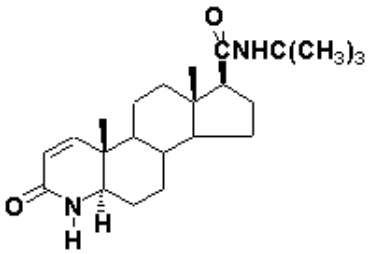
[Molecule of the Month - August 1998]

Would you like to go from this  to this  ?? (well, maybe).

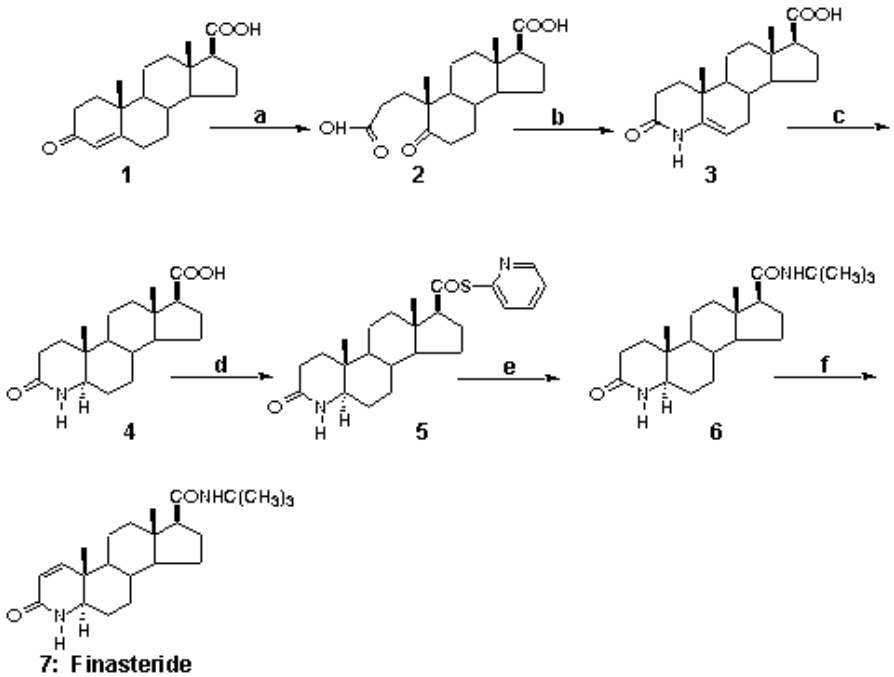
A drug for male pattern baldness has recently been approved for use by the FDA.[1] It is called finasteride and is being sold under the name Propecia for baldness in men. This article describes the synthesis of finasteride, how it works, SAR for this class of compounds, and application to another medical condition, benign prostatic hyperplasia.

FINASTERIDE: A MEDICINAL CHEMISTRY PERSPECTIVE

CHEMISTRY



Formerly known as MK-906, finasteride (**Figure 1**) ([5-α, 17-β -N-(1,1-dimethylethyl) -3-oxo-4-azaandrost- 1-ene-17-carboxamide) belongs to the 4-azasteroid structural class of compounds. (Click on the structure to the right to view a Chime rotatable structure.) Its synthesis, shown in **Scheme 1**, was published by Rasmusson et al. in 1986.[2] Briefly, beginning with a previously synthesized intermediate, the A-ring of the steroid skeleton was converted from its 3- keto precursor **(1)** to the required 4-aza system **(3)** through an open analog **(2)**. Saturation of the B-ring using catalytic hydrogenation gave intermediate **4**. Use of the 2-pyridyl thio ester **(5)** gave a reactive substrate to form the tertiary butyl carboxamide **(6)**. The final step in the synthesis, dehydration of the A-ring with benzeneselenic anhydride, gave the final product, finasteride **(7)**.



Scheme 1. Key intermediates in the synthesis of finasteride by Rasmusson et al. Reagents: a, KMnO4-NaIO4, t-BuOH, reflux; b, NH3, heat; c, H2, Pt, ArOH; d, 2,2'-dipyridyl disulfide, triphenylphosphine, toluene; e, t-butyl amine, THF; f, benzeneselenic anhydride, chlorobenzene.

MECHANISM OF ACTION

Finasteride exerts its influence by inhibiting the enzyme 5-α-reductase (5α-R). This enzyme is responsible for the conversion of testosterone (T) to dihydrotestosterone (DHT) with the cofactor NADPH, **Figure 2**. Inhibition of 5α-R results in decreased level of DHT. Two isoforms of the enzyme, types I and II, are known to exist. The two forms have only 50% amino acid homology and are found in differing regions in the body. Type I is found in skin tissues, including the scalp. Type II is found mainly in genitalia tissues, including the prostate and skin of the genitalia. Finasteride has higher affinity for 5α-R type II (IC50 = 9.4 nM) versus type I (IC50 = 410 nM).[3] The lactam in the A-ring of finasteride was initially thought to mimic the enol intermediate proposed in the catalyzed conversion of T to DHT (see **Figure 2**). It would be, then, a transition state inhibitor of the enzyme. Kinetic studies performed by Merck[4] and Glaxo[5] since the mid-1980s, however, have revealed that finasteride may act as a slow offset, essentially irreversible, inhibitor of 5-α-reductase.

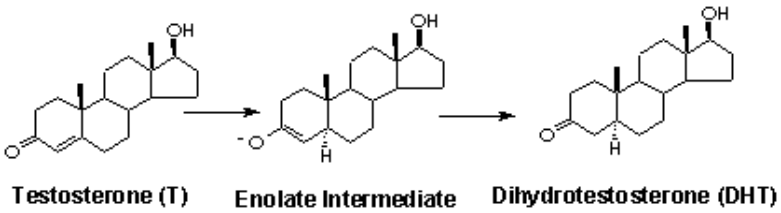


Figure 2. Conversion of testosterone to dihydrotestosterone.

Due to the potential importance of 5-α-reductase inhibition in a variety of disease states, pharmaceutical companies have published many studies concerning its structure-activity relationships (SARs). **Figure 3** shows the basic SAR for 4-azasteroids at 5-α-reductase (published in a review by Kenny et al.[3]). In general, a ketone in the 3-position is preferred. Lipophilic substituents in the 17-position are thought to bind in a lipophilic pocket of the receptor. Small lipophilic groups are tolerated around the ring as well as expanding the A-ring from six to seven-membered. The size and shape of the amide substituents at C-17 may influence both selectivity between types I and II and potency at both isoforms. Other structural classes of molecules are known to bind to 5α-R including 10 and 6-azasteroids, benzoquinolinones, benzoylaminophenoxybutanoic acid derivatives, and polyunsaturated fatty acids.[6-9] Detailed SAR for these and other structural types are available and can be found in the literature.

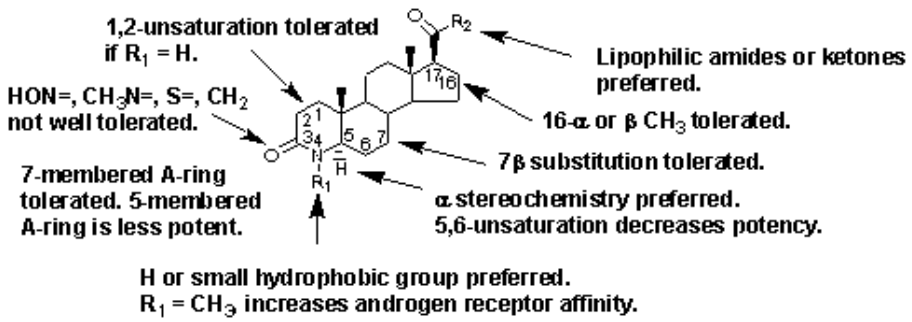


Figure 3: SAR of Finasteride.

MEDICINAL EFFECTS

Hormones have been implicated in a variety of disorders. Specifically, male hormones (androgens, among them: testosterone (T) and dihydrotestosterone (DHT)) have been linked to disorders of the prostate (e.g., cancer and benign prostatic hyperplasia), hair growth, pubertal changes in boys, and acne. Medicinal control over hormone systems could, then, be advantageous in treating these disorders.

BENIGN PROSTATIC HYPERPLASIA (BPH)

BPH is a common disorder that affects many males over the age of 65. Symptoms include reduced urinary stream, increased urine retention, urgency and frequency. These symptoms are the result of increased glandular/fibromuscular tissue growth. Hyperplasia (overgrowth of cells) of prostate tissue results in the obstruction of the bladder outlet and, thus, obstructed urine passage. Two components may be involved in producing the symptoms of BPH:

- Prostatic smooth muscle tone, and
- Prostate size (its growth obstructing urination)

The former has been targeted through the use of α-1 adrenergic antagonists and will not be discussed here. The latter is the objective of 5a-R inhibition.

Published information pertaining to the cause of BPH and related disorders has been available for some time.[3] In 1895, males, who had BPH, were castrated and showed a decrease in prostate size and improved BPH symptoms. In 1944, it was noted that males (<40 years of age) without testicular function had a reduced tendency to develop bph and prostate cancer. these observations pointed to testosterone as influencing bph and possibly prostate cancer. in the prostate, however, testosterone is rapidly converted to dihydrotestosterone (dht) by the action of 5-α-reductase. DHT has a 4-5 fold higher affinity for androgen receptors than testosterone and comprises ~90% of the total androgen content. Plus, it was noted that male pseudohermaphrodites (individuals deficient in 5-α-reductase) did not develop BPH. These two pieces of evidence implicated DHT as playing a role in the development of BPH. Decreased levels of DHT might decrease prostate size which would, in turn, improve the symptoms of BPH. . . thus, the development of finasteride, a 5-α-reductase inhibitor.

So far, results have shown that men with the most severe BPH symptoms respond best to finasteride treatment (5mg/day). The New England Journal of Medicine reported that, under this regimen, prostate volume decreased by 19% and urinary flow increased by 22-23%.[10] The treatment is reported to have no effect on sperm count, motility, or morphology. Loss of libido and/or impotence was reported by a small percentage of the patients. The alternative therapy for BPH being surgery, finasteride could prove useful and invaluable for a number of BPH- symptomatic men.

MALE PATTERN BALDNESS (ANDROGENETIC ALOPECIA)

Referring again to observations made throughout history:

- Individuals deficient in 5a-reductase do not develop male pattern baldness. They have scant body hair, but full scalp hair.
- Hypogonadal men do not become bald on their own, but can be made so when given testosterone.
- It has been noted that men receiving 5-α-reductase inhibitors for the treatment of BPH experience an increase in hair growth on the scalp.

These observations point to the influence of male androgens on scalp hair growth and the importance of DHT.[13,14] As mentioned above, finasteride has recently been approved for use in the treatment of male pattern baldness and will be available soon.[11,12]

Finasteride has the potential for application in a variety of medical disorders. Its action on the male hormonal system gives it selectivity without unnecessary side effects. Benign prostatic hyperplasia (BPH) and male pattern baldness have been approved for use. Acne, female hirsutism, and prostate cancer could be potential applications of finasteride. While the drug has been found to be safe, it is not without fault. It should be noted that finasteride decreases the level of prostate specific antigen (PSA), an indicator of prostate cancer. Masking PSA levels could decrease our ability to monitor this type of cancer. Also, due to the possibility of harming male fetuses, women of reproductive age are cautioned against the drug.[15] Future publications will examine applications and safety issues associated with this versatile drug and its place in current medicinal chemistry.

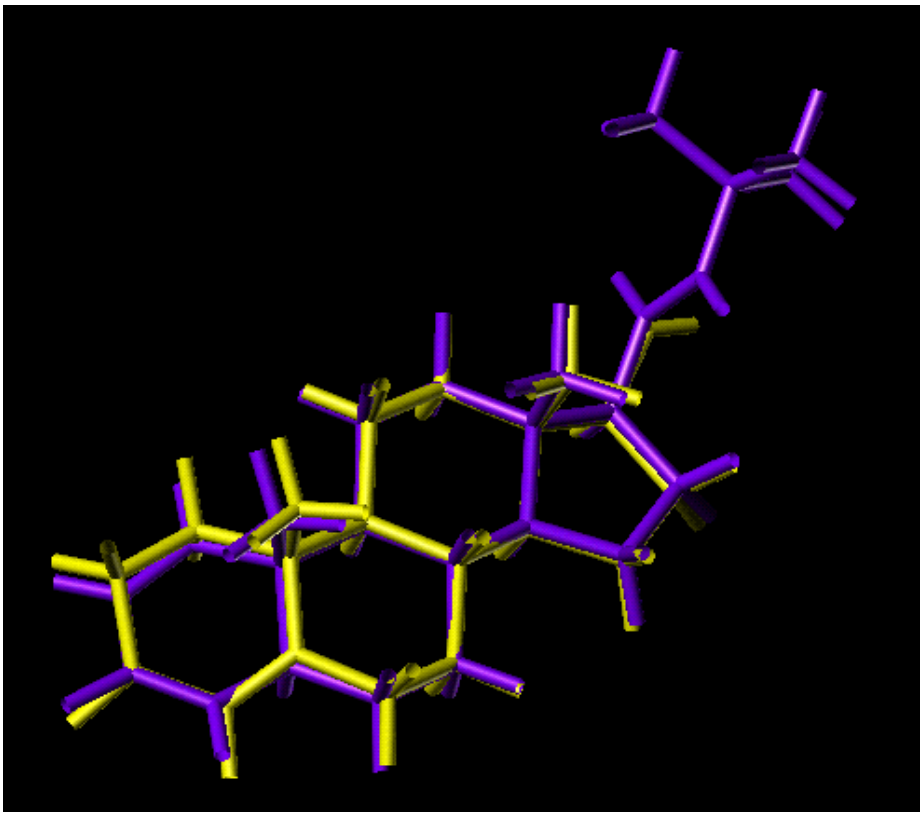


Figure 4. An overlay of molecular models of finasteride (purple) and testosterone (yellow).

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Back to Molecule of the Month page. [DOI:10.6084/m9.figshare.5469451]