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Review Article

17-Aza Steroids as 5α-Reductase Inhibitors: A Review

*Manav Malhotra, Richa Dhingra, Rajiv Sharma, T.R. Bhardwaj

Department of Pharmaceutical Chemistry, Indo-Soviet Friendship (ISF) College of Pharmacy, Ferozepur Road, Moga, India

ABSTRACT

17-aza steroids are the important class of compounds used as 5α-reductase inhibitors for the treatment of benign prostatic hyperplasia. As these agents blocks the conversion of Testosterone (T) into Dihydrotestosterone (DHT) which is the main reason for the development of benign prostatic hyperplasia. Benign prostatic hyperplasia (BPH) is the noncancerous proliferation of the prostate gland associated with benign prostatic obstruction and lower urinary tract symptoms (LUTS) such as frequency, hesitancy and urgency. Its prevalence increases with age affecting around 70% by the age of 70 years. Main attention given to the 17-aza steroids is due to the back binding or inverted action that was proposed by Mac Donald et al. In this review, different 17-aza steroids such as seco-steroids, alkyl chain derivates at 17-position, 3β-esters and many other derivatives were shown.

Keywords: 17-aza steroids, 5α-reductase inhibitors, Benign Prostatic Hyperplasia, Seco- steroids

INTRODUCTION

Steroids are the most important class of natural as well as synthetic drugs which performs the basic or fundamental biological function which not only leads to important discoveries in this field but also inspired biochemist and endocrinologist to develop new molecules in medicinal chemistry [1, 2]. Steroids are generally preferred due to their ability to cross membrane easily and perform several functions in biological system. Various functions of steroidal hormones, begins when they migrate from blood stream to cell across the membrane through diffusion. Inside the cell, there are binding proteins known as receptors which forms complex with steroids and leads to variations or modification in the molecule which acts in our body. In 1968, Jensen and Suzuki discovered the concept of steroid hormone and its mechanism. But later on Gorski demonstrate the new concept of hormone receptor which triggers the series of events that permit the expression of specific genes. When a steroid molecule enters the cell it gets modified to produce active molecule that acts on different receptors which shows its function. Medicinal chemist evaluated different changes in steroid molecule when there is introduction of different groups that leads to change in activity [3, 4]. Naturally occurring steroids modified at different positions to get active molecule which show less or few undesirable side-effect. Different analogues of steroids which are formed by the condensation of different groups or heterocyclic ring with cyclopentenophenanthrene in steroid nucleus which gets main attention for the new and intresting biological activities [5]. Replacement of one or more atoms in steroids with different groups also affects its chemical properties which lead to change in biological activity. In heterosteroids, Azasteroids acts as novel drugs used in the treatment of different diseases such as Benign Prostatic Hyperplasia (BPH), prostate cancer etc and their biological activity have been summarized in different review [6]. Most of azasteroids have synthetic origin due to presence of –NH group in the azasteroids which is isosteric to methylene group, that doesn't distort the shape of original steroid molecule [7] because of this reason that scientist focused on these azasteroids. SAR studies of azasteroids can be done by different empirical methods [8-10]. Rational drug design is increasing nowadays which is important for the selection of appropriate type of azasteroids as synthetic target for medicinal application. As literature on biological activity of azasteroids has been reported by alauddin and co-workers [11].

Synthetic Heterosteroids:

Number of synthetic nucleo-heterosteroids are known till now, which are reviewed by Burbiel and Ibrahim-Quail, Morand and Gogte which comprises total synthesis of heterosteroids and their analogues [12-16]. Introduction of heteroatom in the steroid nucleus through the sequence of different techniques such as Beckmann rearrangement, Schmidt reaction [17-21]. Different heterosteroids are known in which hetero atoms are the part of steroid nucleus or its side chain which was covered by Martin-Smith and its associates in their review [22]. Several synthetic heterosteroids are known till now which possess different functions such as antifungals, antilipemic, neuromuscular blocking agents, local anaesthetics, antimicrobials, antioxidants, 5α-Reductase inhibitors and anti cancer activity [23-26].

Benign Prostatic Hyperplasia (BPH): BPH is the noncancerous growth prostate gland due to over proliferation of stromal and basal cells of prostate, as it occur mostly in men over the age of 70 yrs. As we know, androgens play important role in the growth and development at normal levels but their level gets

*Author for correspondence: E.mail: manavmalhotra99@yahoo.com

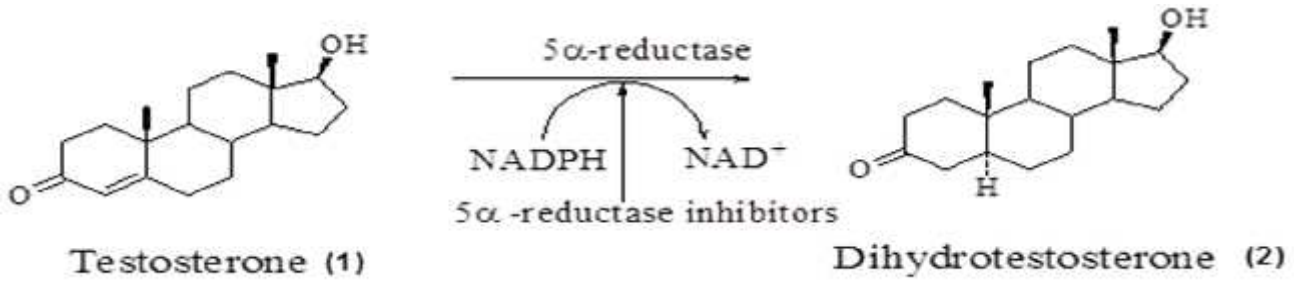


Figure 1 showing conversion of testosterone into dihydrotestosterone

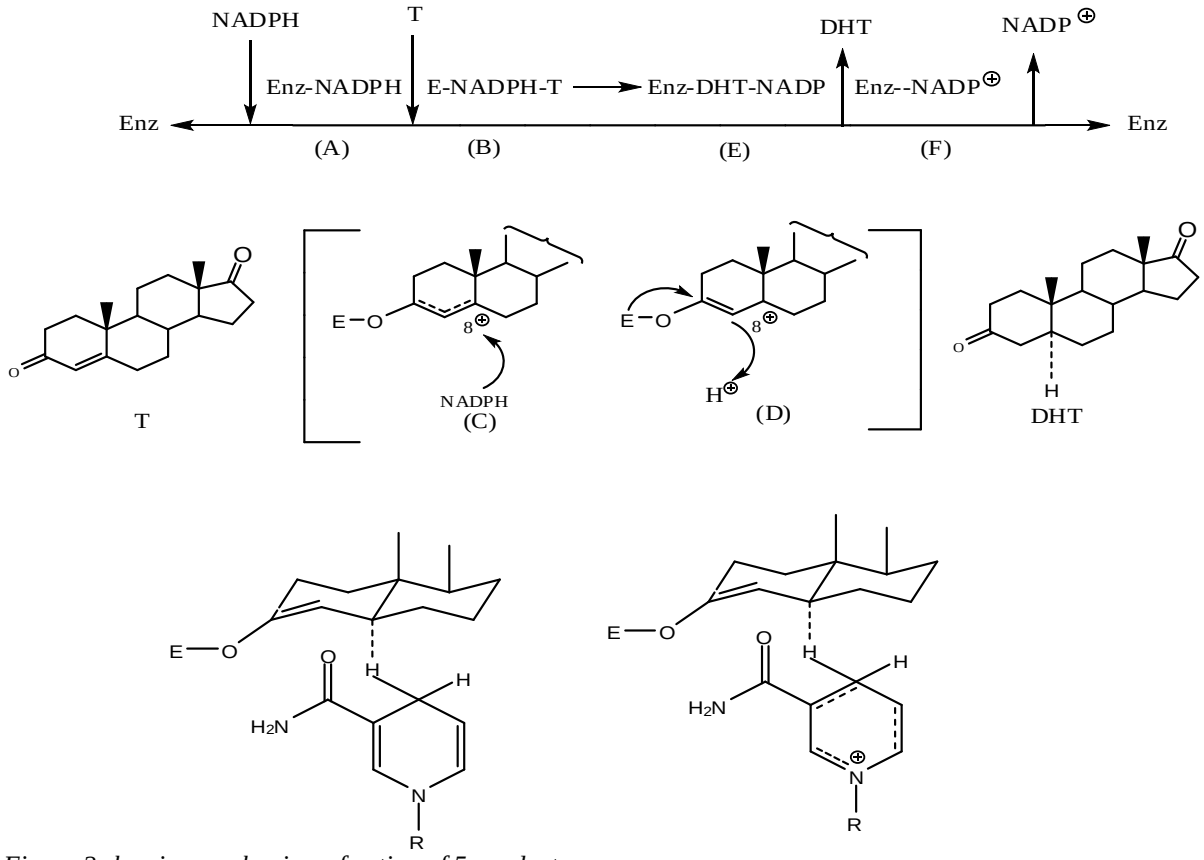


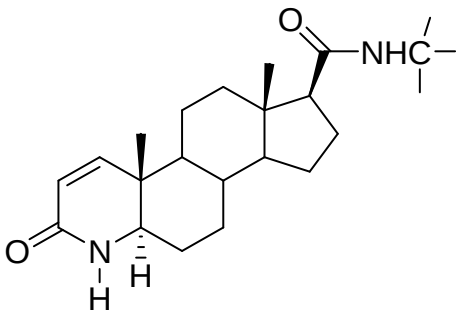
Figure 2 showing mechanism of action of 5α-reductase enzyme

abnormally increase it leads to the development of different diseases such as prostate cancer, BPH, acne etc. Testosterone in the presence of 5α-Reductase enzyme and NADPH is gets

converted into dihydrotestosterone. Augmented level of androgen dihydrotestosterone [27, 28, 29] in body is the main cause of BPH.

In BPH, increase number of basal and stromal cell in the periurethal transition zone of prostate that result into constriction of prostatic urethra which displace normal prostatic tissue which leads to urethral compression [30]. Along with this sympathetic nerve stimulation contraction of prostate and urethral smooth muscle obstructs the outflow. BPH is the chronic, progressive and highly prevalent disease that manifests lower urinary tract symptoms (LUTS). Prostate cancer currently the most common malignancy and age related cause of death in elderly men. As BPH is associated with LUTS, it involves hesitancy, urgency, nocturia, incomplete voiding [31]. Earlier choice of treatment was for BPH was transurethral resection of prostate (TURP) or prostactomy like therapies that involves suppression of androgen stimulation of prostate growth [32]. But after sometime, the androgen level again stimulated which leads to reoccurrence of this disease. So 5α-reductase inhibitors emerged as target for the treatment of BPH. As enzyme involves in the formation of DHT in tissues, which acts as logical treatment for this disease [33]. Medicinal chemist took 5α-reductase enzyme and synthetically synthesizing no. of agents that block this enzyme. Several analogues that were synthesized may also act as androgen receptor blockers without undesirable side effects such as castrate testosterone level on muscle and bone mass, energy level and libido that is of particular concern.

Enzyme 5α-Reductase: Androgen and prostate are relate with each other as testicular androgen constituents important *in vivo* mitogenic factor for prostate. Androgens



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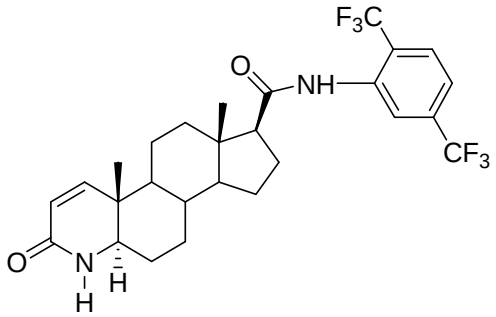

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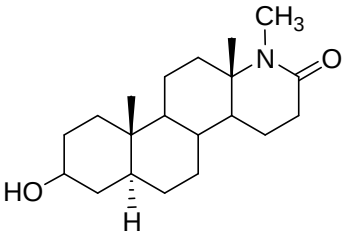

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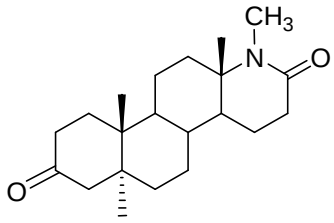

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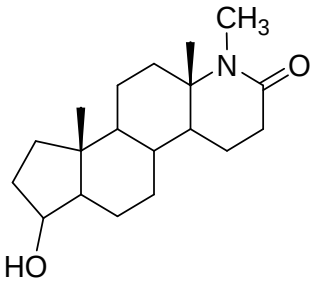

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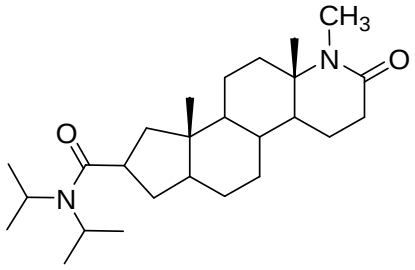

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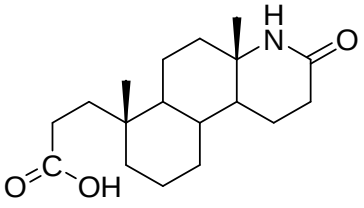

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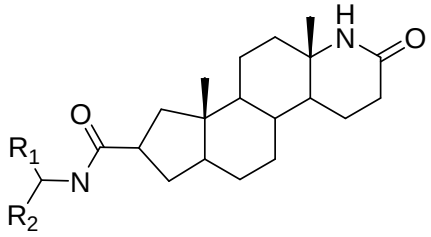

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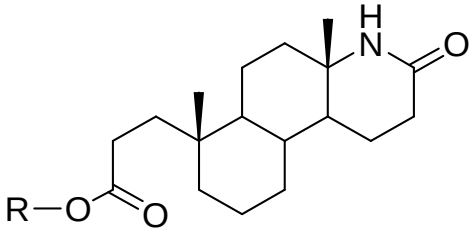

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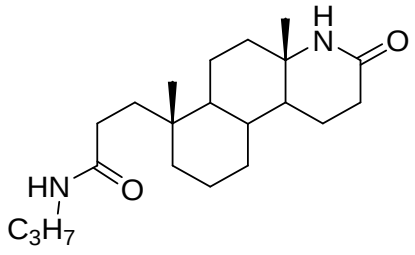

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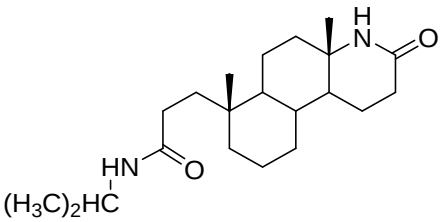

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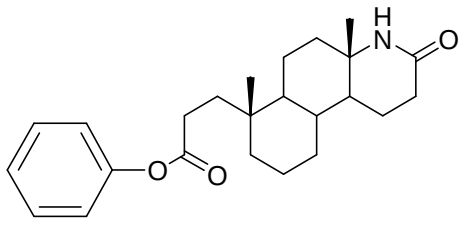
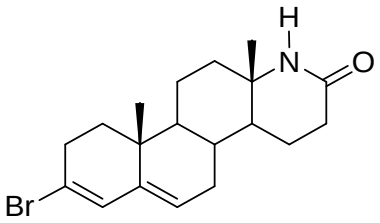


(11a)

are required for normal functioning of prostate [34] as well as they enhances the production of growth factor in prostate tissue by forming cell complex which form interaction with basal and stromal cells [35]. Signalling cascade of androgens involves synthesis of testosterone (**1**)



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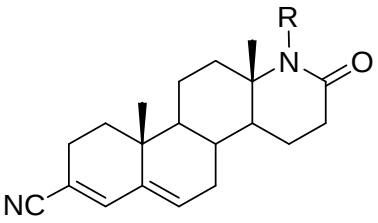

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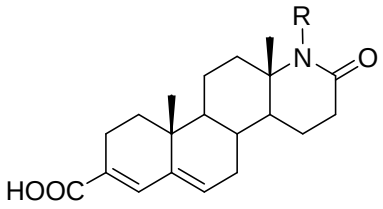

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Different substitutions of compound (**12**), (**13**) and (**14**) were synthesised and having different IC_{50} values and % inhibition.

Table 1 showing IC_{50} values of compounds (5-8)

Compound	IC_{50} (µM)
5	4
6	15
7	12
8	40

Table 2 showing different substitutions at 17-position of 3-cyano-17a-aza-D-homo-3, 5-androstadien-17-one and IC_{50} (µM) values.

Compound	Different Substituents	IC_{50} (µM)
12	R= H	236.06
13(a)	R= H	N.I
(b)	R=CH_3	N.I
(c)	R= C_2H_5	75
(d)	R=$CH_2CH=CH_2$	48
(e)	R= $CH_2C_6H_5$	N.I
(f)	R= CH_2CH_2CN	N.I
(g)	R= $COCH_3$	255.34
(h)	R= COC_6H_5	N.I

Table 3 showing different percentage inhibition at 10 µM for type-I 5α-reductase and Type-II 5α-Reductase for compound (12) and (13).

Compound	Type-I 5α-reductase percentage inhibition at 10 µM	Type-II 5α-Reductase percentage inhibition at 10 µM
12	34.5 ± 1.7	45.6 ± 5.2
13 (a)	27.6 ± 9.3	9.9 ± 5.9
(b)	93.0 ± 3.1	13.5 ± 7.1
(c)	56.1 ± 3.7	48.9 ± 2.7
(d)	20.8 ± 3.9	3.3 ± 5.7
(e)	0.0 ± 0.0	34.7 ± 8.6
(f)	0.0 ± 0.0	9.9 ± 10.8
(g)	2.2 ± 3.0	23.2 ± 9.8
(h)	0.0 ± 0.0	11.4 ± 3.9
Finasteride	453.0 nM (IC_{50})	30.3 nM (IC_{50})

in testes presence of 5α-reductase enzyme (3-oxo-steroid-4-ene dehydrogenase) and NADPH. Both testosterone and DHT (**2**) activates androgen receptor (AR) but DHT shows higher affinity toward AR due to different kinetic processes. Thus 5α reductase enzyme is responsible for the conversion of testosterone to DHT, shown in figure 1 which shows that cellular availability of DHT to prostatic cell which modulate growth [36-38]. Proposed mechanism of formation of DHT by 5α-reductase enzyme, shown in figure 2. As they are based on region and stereo chemistry of reduction that includes formation of binary complex between enzyme and NADPH, further that forms complex with testosterone (substrate).

After formation of ternary complex, there is delocalisation of carbocation due to activation of enone system due to the presence of electrophilic residue present in the enzyme. Enolate of DHT is formed by direct hydride transfer from

Table 4 showing different substituents at 17-position of 17-oxo-17a-aza-D-homo-3, 5-androstadien-3-oic acid and their IC_{50} (µM).

Compound	Different Substituents	IC_{50} (µM)
14(a)	R= H	N.I
(b)	R=CH_3	-
(c)	R= C_2H_5	N.I
(d)	R= $CH_2CH=CH_2$	N.I
(e)	R= $CH_2C_6H_5$	-
(f)	R= $CH_2CH_2COOC_2H_5$	N.I

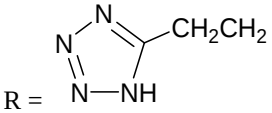
N.I- not significant inhibition.

Table 5 showing % age inhibition at 10 µM for type I and type II 5 α-reductase in comparison to finasteride

Compound	Type-I 5α-reductase percentage inhibition at 10 µM	Type-II 5 α-reductase percentage inhibition at 10 µM
14 (a)	0.0 ± 0.0	62.9 ± 2.2
(b)	18.9 ± 1.1	100.0 ± 0.0
(c)	32.3 ± 1.5	100.0 ± 0.0
(d)	0.4 ± 0.5	100.0 ± 0.0
(e)	n.d.	n.d.
(f)	8.5 ± 3.0	100.0 ± 0.0
3 (Finasteride)	453.0 nM (IC50)	-

n.d: not defined

Table 6 showing different substituents at 17-position of 3-tetrazolo-17a-aza-D-homo-3, 5-androstadien-17-one and IC_{50} (µM) values

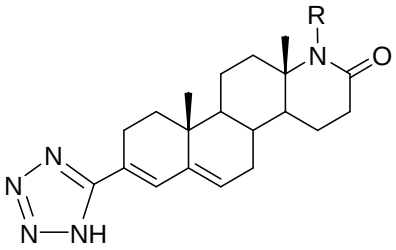
Compound	Different Substituents	IC_{50} (µM)
15(a)	R= H	N.I
(b)	R= CH_3	N.I
(c)	R= C_2H_5	-
(d)	R= $CH_2CH=CH_2$	N.I
(e)	R= $CH_2C_6H_5$	-
(f)		-

N.I- not significant inhibition

the NADPH to the α face of delocalized carbocation which shows selective reduction at C-5. Intermediate that presumably co-ordinated with $NADP^+$ on α face, is attacked by proton on β-face of C-4 forming tertiary complex of E-$NADP^+$-DHT. After detachment of DHT occurs that forms binary complex of E-$NADP^+$ that releases $NADP^+$ leaves the enzyme for further reduction [39, 40].

Types of 5α-Reductase Enzyme: Two types of 5α-reductase enzyme have been recognized till now. As, in modern method molecular biology assist for two different type of enzymes from human and rat prostatic complementary deoxyribonucleic acid libraries [41,42]. Type 1 is mainly present in skin, liver and hair follicles and acts at pH basic to neutral where as type 2 is mainly present in stromal and basal cells of prostate gland of seminal vesicle that acts at acidic pH of 5-5.5. These two isoenzymes differ in the constitution of amino acid as well as molecular weight and location of gene structure, type 1 is located at 5p15 while type 2 is located at 2p22 although they have same gene structure [43, 44]. Type 1 is constituently expressed in brain and in adulthood, it reaches in myelin membranes which shows catabolic action in brain whereas type 2 expressed in prenatal period in males, its expression is controlled by hypothalamus after stress, hence type 2 is mainly responsible for perinatal differentiation of brain towards male pattern [45].

More recently with the advancement in gene expression profile analysis, type 3 5α-reductase enzyme has also been identified which shows similar conversion mechanism as that of type 1 and it acts at pH 6.9 [46]. It has been recognised as a ubiquitous enzyme in mammals. Northern blot and real time analyses shows that this enzyme is present in androgen and non-androgen target hormone in different tissues such as brain, pancreases, prostate cancer cell, skin [47].



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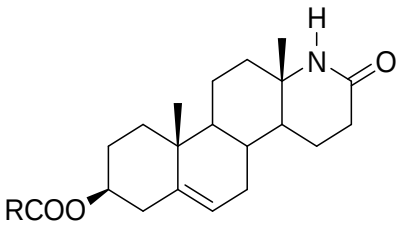

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Table 7 showing 3β-yl-Esters substitutions of 17-oxo-17-a-aza steroids with IC_{50} values.

Compound	Different Substituents	IC_{50} (µm)
16 (a)	R= chloroacetate	N.I
(b)	R= benzoate	9.5
(c)	R= 4-nitrobenzoate	5.2
(d)	R= 4-aminobenzoate	7.1
(e)	R= 4-hydroxybenzoate	5.7
(f)	R= 4-methoxybenzoate	15.1
(g)	R= 4-chlorobenzoate	8.3
(h)	R= 4-methylbenzoate	7.5
(i)	R= phenylacetate	7.1
(j)	R= phenoxyacetate	N.I

Steroidal 5α-reductase Inhibitors: 5α-Reductase inhibitors suppresses the DHT concentration by blocking the enzyme and thus reduces the size of prostate which provides relief from the symptoms related to the obstruction caused by BPH. Further, the rationale use of 5α-reductase inhibitors is that these are more specific to DHT androgens action without affecting / lowering testosterone level, thus capable of decreasing long term side effect of castration due to loss of testosterone without compromising the efficacy of hormonal therapy [48, 49]. During last two decades, continuous search for potent and selective 5α-reductase inhibitors have resulted into the development of several compounds, but steroidal derivatives attracted more attention, as these are highly active and small changes in the steroid nucleus may result into significant alteration in biological activity. Finasteride **(3)** and Dutasteride **(4)** are two clinically used steroidal drugs having lactam in ring A of the steroidal nucleus [50, 51]. Their 5α-reductase inhibitory activity is considered to be attributed by the lactam that mimics intermediate transition state. Therefore, it was considered of interest to synthesize analogues related to Finasteride **(3)** and Dutasteride **(4)** having a lactam in ring D of the steroid nucleus instead of ring A and N alkyl carbamoyl moiety at the position 3 instead of position 17. In addition, the related analogues will have steroidal ring A open, having various conformations on account of free rotation between positions 1 and 10 and other between positions 1 and 3, thus more flexibility and freedom for interaction at the receptor site. Such compounds are expected to have 5α-reductase inhibitory activity [52].

17 and 17-a-aza-D- Homosteroid: Regan and Hayes synthesised different 17 and 17-a-aza-D-Homosteroids from different 17-ketosteroidal oximes [53]. These synthesised compounds have been found to possess different biological activities such as 5α-reductase inhibitors and many others [54-61]. Synthesised compounds were evaluated for their anti cancer activity against different cell lines of prostate cancer.

Main attention given to the 17-aza steroids is due to the back binding or inverted action that was proposed by Mac Donald *et al* [62]. As steroids have different orientations which help them to bind in the active site of the various metabolizing enzymes.

Synthesised compounds were evaluated *in vitro* for their 5α-reductase inhibitory activity given in table 1

A substitution at 17 position is responsible for increased potency by binding to the lipophilic pocket of the enzyme. But here substitutions were done at the 3 β-position. By ring contraction and substitutions on them shows different inhibitory activity. As presence of alkyl chain at 3β amide shows maximum IC_{50} values.

17-a-aza-D- Homo-seco-steroids: Aggarwal and his co-workers synthesised different 17-a-aza-D- Homo-seco-steroids (9, 10 and 11) which were active against 5α-reductase enzyme.

17-oxo-17-a-aza-D-Homo 3, 5-seco-4-nor androstan-3-oic acid (9), substituted 17-oxo-17-a-aza-D-Homo 3, 5-seco-4-nor androstan-3, 7 dione (10) and substituted 17-oxo-17-a-aza-D-Homo 3, 5-seco-3-oates (11) were synthesised with different substitutions [63].

Derivative of 17-oxo-17-a-aza-D-Homo 3, 5-seco-4-nor androstan-3, 7 dione

Derivatives of 17-oxo-17-a-aza-D-Homo 3, 5-seco-3-oates Saurabh *et al* in 2011 synthesised series of 17-aza steroids which contains different groups at 17-position on N-R with different A ring substitutions that may be –CN, COOH [64] etc.

Neelima and his co-workers synthesised series of 3β-yl-Esters of 17-oxo-17-a-aza steroids which were evaluated for their in vitro study of 5α-reductase activity by calculating their IC_{50} values for different substituted esters [65].

SUMMARY AND CONCLUSION

5α-reductase inhibitors are the one of the best choice for the treatment of benign prostatic hyperplasia. Benign prostatic hyperplasia is the noncancerous growth of prostate due to increased level of dihydrotestosterone. Previously, this disease was treated with surgery but because of some complication nowadays it is not preferred. In place of that 5α-reductase inhibitors are used different which includes azasteroids. In this review, we described different 17a-aza steroids that include different compounds that are having lactam at 17^{th} position and substitutions at different positions which are having different inhibitory concentrations. This includes different seco compounds, such as compounds having seco in ring A which are having different substitutions in ring A as carboxylic acid (**9**), substituted amides (**10**) and esters (**11**). Compounds having CN, COOH and Br at 3β position with different substitutions at R-N 17^{th} position [12, 13 (a-h), 14 (a-f)]. Different substituted esters at 3β position have mentioned. Similarly, different substituents at 3β position of homo steroids have been mentioned (5-8).

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