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Recent discoveries and developments of Androgen Receptor based therapy for Prostate Cancer

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Abstract

The main focus of the review is to discuss the discoveries and developments of various therapies for prostate cancer. The AR has played an important role in the prostate cancer growth and functions. In this review, we discussed several groups of drugs that have sparingly good anti-cancer activities, also have a similar structure and behaviour. Recent new-generation AR antagonists, Enzalutamide (MDV3100) has approved for the treatment of advanced/metastatic prostate cancer. The nonsteroidal antiandrogens represent an important class of molecules acting as either antagonists or agonists. Recently, many therapeutic agents for prostate cancer have been approved that target the androgen receptor and reduces the prostate tumour growth. The strong response to this new use of Enzalutamide provides a viable, less toxic alternative to chemotherapy. The current status of prostate cancer drugs have been discussed here, but it is evident that much work for improvements in respect of efficacy, reduction of side effects and treatment strategies are to be addressed.

Keywords

Androgen Receptor

Prostate Cancer

Antiandrogen

SARM

CRPC

Introduction

Cancer is one of the major killer diseases worldwide. Breast cancer, blood cancer, lung cancer, oral cancer and prostate cancer, etc. are very common names now-a-day. The word cancer becomes the terror in the world and attacks people, irrespective of ages from child to old persons. Scientific community worldwide is fighting to combat this menace to save the precious life of people suffering from these diseases. Out of these, Prostate cancer (PCa) is one of the major causes of deaths in men worldwide.[1] National cancer institute has estimated that 2, 33,000 men will be diagnosed with and 29,480 men will die of prostate cancer in the United States in 2014.[2] Various types of treatment of PCa presently are available, such as surgery, cryosurgery, radiation therapy, chemotherapy, radical prostatectomy, endocrine therapy, hormone therapy, brachytherapy, vaccine treatment, bone directed treatment, etc. These therapies are provided alone or in combination that depends on the stage of the Prostate Cancer,[3,4] age of the patients, and so on. Radium-223 dichloride (radium-223) is a radioactive isotope that improves overall survival in men with advanced prostate cancer.[5] PCa tumor growths in the earlier stages are mainly dependent on androgen and androgen receptor (AR).

Androgen stimulates the development and maintenance of male characteristics in vertebrates by binding to AR, which is activated by either of androgenic hormones testosterone (T) or 5α-dihydrotestosterone (DHT)[6] in the cytoplasm then transferring into the nucleus. AR is a DNA-binding transcription factor, belonging to nuclear receptor subfamily, which regulates gene expression.[3,4,7,8] AR plays an important role in the development, growth, function and homeostasis of the prostate as well as effects on hair and skin (androgenic effects). In addition, other tissues, such as muscle and bone are also a target for androgens (anabolic effects). AR antagonists are used as a single agent (monotherapy) or in combination with castration.[9] Antiandrogens, such as abiraterone acetate (4b), cyproterone acetate (4c), flutamide (3e), nilutamide (3f) and bicalutamide (3c) have been used to block the androgen signal. AR antagonist therapy ultimately results in castration- resistant such as antiandrogen withdrawal syndrome. AR gene mutation, such as T877A and W741C/L is an important mechanism for castration-resistance.[10,11] The T877A mutant is activated by hydroxyflutamide, an active metabolite of flutamide. Bicalutamide is known to act as an agonist through the W741C/L mutation of the AR. The W741C mutant AR was detected in bicalutamide-resistant PC patient tissue.[12] It showed a superior pharmacokinetic profile along with minor side effects, it has been chosen as the routine clinical treatment.[13,14] Unfortunately, it is reported that bicalutamide loses its efficacy on long-term use; therefore some patients had to discontinue bicalutamide treatment. This behavior has been termed as “anti-

androgen withdrawal syndrome" and this drug then serves as an agonist under such circumstances.[10,11] In oncology, Mutation or variation in gene expression in cancer cells make resistant to hormonal blockage, leading to castration-resistant prostate cancer (CRPC). Despite its risk of severe adverse effects, docetaxel, a microtubule-stabilizing agent, is the only approved chemotherapeutic agent against CRPC. It is necessary to develop effective new-generation AR antagonists against CRPC.[15] Most prostate cancer patients receiving hormonal therapies progress to more aggressive CRPC. Recently, a full AR antagonist, Enzalutamide (MDV3100) has demonstrated efficacy against CRPC in preclinical models[16] and more importantly in patients.[17]

Androgen deprivation therapy (ADT) is currently recommended for the treatment of advanced/metastatic prostate cancer. Nonsteroidal antiandrogens are some of the most commonly prescribed ADT drugs and diminish androgenic effects by competitively inhibiting androgen.[18,19] Recent evidences from both preclinical and clinical studies are coherent with the importance of reactivation of AR signaling in a majority of castrate-resistant prostate tumors. It is also well established that the functional AR in castrate-resistant tumors are frequently mutated or amplified, and that over-expression can convert hormone responsive cell lines to hormone refractory. Recent new-generation AR antagonists, MDV3100 (3a) has progressed to late-stage clinical trials in patients with advanced prostate cancer.[17,20,21] Recently, it has been marketed as Xtandi. When a combination of AR antagonists and chemical castration is used, AR antagonists, such as bicalutamide show significant synergistic effects by blocking adrenal androgen signals as well as by suppressing the transient increase in testosterone levels induced by GnRH analogs.[22] The favorable safety profile and high therapeutic index of ARN-509 have the potential to allow for treatment across the entire spectrum of prostate cancer, as both monotherapy and in combination with other agents that target pathways critical to the malignant progression of the disease.[23,24] Preclinical development of ONC1-13B (3n) is currently completed and it is submitted for phase I clinical study in metastatic CPRC patients to determine the pharmacokinetics, safety, and pilot efficacy.[25] The combination of mitoxantrone and prednisone is approved as a second-line treatment for metastatic hormone-refractory prostate cancer. This combination of docetaxel and prednisone has been shown to improve survival and disease-free period.

Autologous cellular immunotherapy is medically considered as a treatment for individuals with metastatic CRPC or hormone refractory prostate cancer (HRPC). HRPC implies that the cancer no longer responds to hormone therapy, but the fact that prostate cancer responds to drugs like abiraterone and MDV 3100 shows that the tumor is

still “hormone sensitive”. As a result, some experts prefer the term CRPC. The goal of immunotherapy is to stimulate the body's natural defenses in a specific manner so that they attack and destroy, or at least prevent, the proliferation of cancer cells. Sipuleucel-T is only currently available vaccine for prostate cancer with metastatic, asymptomatic, HRPC.[26,27] Unlike traditional vaccines, which boost the body's immune system to prevent infectious diseases, this vaccine boosts the immune system to get it to attack prostate cancer cells in the body, but that is causing few or no symptoms. This vaccine is made especially for each man. Further, HRPC was still dependent on the AR ligand binding domain for growth. Therapeutic options for HRPC patients are limited, with lack of evidence for long-term survival. Cabazitaxel is a semi-synthetic derivative of a natural taxoid. It was approved for the treatment of CRPC and HRPC.[28] It is a microtubule inhibitor, and the fourth taxane to be approved as a cancer therapy. Indeed, there is an urgent need for novel compounds able to act as either antiandrogens in non-steroidal anabolic or HRPC conditions.[29] Various steroidal AR ligands have been developed, but their usage has been limited because of poor oral bio-availability and a lack of selectivity between anabolic and androgenic effects, leading to risk of serious side effects. Therefore, the concept of a non-steroidal, selective androgen receptor modulator (SARM) has also emerged as an attractive target to treat prostate cancer. This review will focus on androgen deprivation therapy, antiandrogens, SARMs and their indications.

Androgen deprivation therapy (ADT)

Hormone therapy is called androgen deprivation therapy (ADT) or androgen suppression therapy. The goal is to reduce the amount of androgens include testosterone and other male hormones, which response the growth of prostate cancer cells.[18] ADT is used along with radiation treatment, when there is a high risk of the cancer recurring and also after surgery or radiation if any cancer cells remain.[30] But it is used when prostate cancer has spread outside the prostate (metastatic disease). However, ADT does not eradicate the cancer, but it reduces its aggressiveness.[19]

It has two major types

1) Method based on surgery

(i) Orchiectomy (surgical castration method)

It consists to remove one or more testicles surgically, the organ where more than 90% of the body's androgens (testosterone and DHT) is made. This approach has been used successfully since 1940.Because it is permanent and irreversible, most of the men prefer this method instead of drug therapy. The main disadvantage is

that surgical castration is a permanent method. There is no way to reverse it once completed. Second, there is an obvious physical change after completing the surgery.[31]

(ii) Prostate brachytherapy (radiotherapy)

Prostate brachytherapy is a form of radiation therapy used to treat prostate cancer. The goal is to place the devices containing radiation in the prostate gland close to the cancer cells. So that it can be easily reached by brachytherapy needles. It can cause side effects such as urinary discomfort (incontinence, retention and irritation), small risk of bowel discomfort and risk of erectile dysfunction.

There are two major methods of prostate brachytherapy:

(a) Permanent (low dose rate, or LDR) brachytherapy

(b) Temporary (high-dose rate, or HDR) brachytherapy

(a) Permanent (low dose rate, or LDR) brachytherapy

In this approach, pellets (seeds) of radioactive material (such as iodine-125 or palladium-103) are placed inside thin needles, which are inserted through the skin in the area between the scrotum and anus and into the prostate. The pellets are left in place as the needles are removed and give off low doses of radiation for weeks or months. Radiation from the seeds travels a very short distance, so the seeds can put out a very large amount of radiation to a very small area. This lowers the amount of damage done to the healthy tissues that are close to the prostate.[32,33]

(b) High-dose rate (HDR) temporary brachytherapy

This is a newer technique. Hollow needles are placed through the skin between the scrotum and anus and into the prostate. Soft nylon tubes (catheters) are placed in these needles. The needles are then removed, but the catheters stay in place. Radioactive iridium-192 or cesium-137 is then placed in the catheters, usually for 5 to 15 minutes. Generally, about 3 brief treatments are given, and the radioactive substance is removed each time. The treatments are usually given over 2 days. After the last treatment the catheters are removed.[34,35]

2) Methods based on drugs

Luteinizing hormone-releasing hormone (LH-RH) agonists and antagonists are drugs for hormone therapy that work by causing the pituitary gland to release luteinizing hormone, which travels to the testicles and adrenal glands to make testosterone. When the pituitary gland runs out of its hormones, testosterone level suddenly reduces that usually slows or stops the growth of prostate cancer for a period of time.[36,37]

(i) Castration resistant prostate cancer (CRPC)

Castrate-resistant prostate cancer is a type of cancer that has become resistant to medical or surgical treatments, which lowers testosterone and remains sensitive to further hormonal manipulation. Drug resistance in metastatic CRPC is multifactorial and complex. So, the development of new medical therapies remains challenging.[38,39] ARN-509 was safe and well tolerated, which displayed dose-proportional pharmacokinetics, demonstrated pharmacodynamic and antitumor activity across all dose levels tested. A maximum efficacious dose of 240 mg daily was selected for phase II exploration based on integration of preclinical and clinical data.[23,24] ODM-201 is a new generation AR inhibitor with superior preclinical efficacy compared to enzalutamide and bicalutamide, it does not enter the brain in preclinical studies, and it shows very promising activity and no significant toxicity in patients with CRPC.[40] The mechanisms for progression to CRPC are not still completely understood. Moreover, several AR-dependent molecular mechanisms in CRPC include:

(1) Gene amplification and increased expression of AR mRNA and protein,

(2) Selected mutations in AR that confers broader ligand specificity,

(3) Change in the ratio of expression levels of AR and its Co regulators,

(4) Increased expression of steroidogenic enzymes, and

(5) Up-regulation of crosstalk signal transduction pathways that activate AR in a ligand-independent manner has been proposed based on observations of experimental or clinical prostate cancer

There are two different medicines, Luteinizing hormone releasing hormone (LHRH) agonists and antagonists, which both lower the amount of testosterone made by the testicles.[41,42]

LHRH Agonists

Blocking the release of LHRH through the use of LHRH agonists or LHRH analogues are one of the most common hormone therapies used in men with prostate cancer.[43] Drugs in this class, including leuprorelin (1a) (Eligard, Lupron, and Viadur), goserelin (1b) (Zoladex), triptorelin (1c) (Trelstar), and histrelin (1d) (Vantas®) are used as LHRH agonists. These drugs allow the testicles to remain in place, but the testicles will shrink over time, and they may even become too small to feel. LHRH analogs are injected or placed as small implants under the skin. Depending on the drug used, they are given anywhere from once a month up to once a year. Buserelin (1e) and Deslorelin (1f) are the synthetic analogue of LHRH agonists, also used for the treatment of prostate cancer. When LHRH analogs are first given, testosterone levels go up briefly before falling to very low levels. This effect is

called *flare* and results from the complex way in which LHRH analogs work. The structure, chemical composition, properties and some details of LHRH agonists are given in table 1.

LHRH Antagonists

A newer class of medications can block LHRH (GnRH) from stimulating testosterone production without causing an initial testosterone surge. Cetrorelix (2a), Ganirelix (2b), Abarelix (2c), Degarelix (2d) and Relugolix (2e) are used as LHRH antagonists, are also used for the treatment of advanced prostate cancer. This class includes degarelix, which is given monthly to men as an alternative to orchiectomy or LHRH agonists.[37,44,45] Degarelix (Firmagon®) is an LHRH antagonist used to treat advanced prostate cancer. It is given as a monthly injection under the skin and quickly reduces testosterone levels.[46,47] LHRH antagonists reduce testosterone levels more quickly and do not cause tumor flare like the LHRH agonists do. The most common side effects are problems with hormonal side effects (hot flashes and weight gain), at the injection site (pain, erythema, and swelling) and increased levels of liver enzymes on lab tests. The details of LHRH antagonists are given in table 2.

(ii) Development of anti-androgens

Antiandrogen is one of a group of drugs that act as androgen receptor blockers. Antiandrogen prevents or inhibits the effects of a hormone by binding to that particular hormone receptor, at which point no response is elicited. Antiandrogens bind to the Androgen receptor to prevent the certain biological responses of the tissues in the body which usually slows prostate cancer growth. Anti-androgen or androgen antagonist was first discovered in the 1960's. Then Ferdinand Labrie (in Canada), using these drugs in combination with the LHRH agonist leuprolide acetate, first claimed a significant benefit for flutamide in the treatment of metastatic prostate cancer. Over the past 15 years, bicalutamide has become the dominant nonsteroidal antiandrogen due its fewer side effects than the other products and also it can be taken as a single tablet once a day in a variety of dosage strengths.[48,49] Antiandrogen medications can be used alone, known as antiandrogen monotherapy (AAM) or in combination with LHRH (luteinizing hormone releasing hormone) antagonists, which actually reduce the amount of testosterone produced in the body known as combined hormone blockade (CHB). Anti-androgen therapy is an effective treatment for prostate cancer but has some of the side effects that are unpleasant and even possibly dangerous.[50,51]

There are two types of antiandrogens.

a) Pure or Nonsteroidal antiandrogens

b) Steroidal antiandrogens

Pure or Nonsteroidal antiandrogens

However, flutamide (Eulexin), nilutamide (Anandron), and bicalutamide (Casodex), all seem to block the action of DHT, the primary masculinizing hormones in the human body in stimulating the synthesis of new protein in prostate and prostate cancer cells. In the prostate, the male hormone testosterone is converted into DHT, which is the "active" molecule in the prostate, acts on the prostate and prostate cancer cells to stimulate new growth.[49,52,53] In the treatment of metastatic prostate cancer, all major trials of the non-steroidal anti-androgens have occurred in combination with either an LHRH agonist or orchiectomy, so it is difficult to know exactly which side effects are exclusive to the use of the nonsteroidal androgens and are liable to occur when such agents are used on their own. A number of drugs were launched in the past two decades, such as flutamide, bicalutamide and nilutamide. Although RU58642 (3j) was more potent than bicalutamide, hydroxyflutamide, and nilutamide, which could be related to its high binding affinity to AR, no further development of this ligand has been reported since 1998. Recent new generation androgen receptor antagonist, BMS-641988 (3h) has the increased potency relative to bicalutamide in both in vitro and in vivo prostate cancer models. Also, PF-0998425 (3m) is a novel, nonsteroidal androgen receptor antagonist for sebum control and treatment of androgenetic alopecia. At present, the newly-developed non-steroidal androgen receptor antagonists such as RD162 (3g), BMS-779333 (3i), ONC1-13B (3n), MDV3100 (3a) and BMS-641988 (3h), showing more potent activity and are tested in clinical trials. Compound LG105 (3k) also binds to the AR with high affinity, and demonstrated strong antagonist activity in the prostate, which seemed to be more potent than LG120907 (3l). Both LG120907 and LG105 are orally available (as evidenced by animal studies), although detailed pharmacokinetic data is not available. MDV3100 is already approved. So, they could solve the problems to some extents. The structure, chemical composition, properties and some details of non-steroidal antiandrogens are given in table 3.

Steroidal antiandrogens

Steroidal antiandrogens are derived from the natural androgen testosterone to inhibit the binding of testosterone or DHT to AR.[54,55] Therefore, they block the negative feedback of androgens at the hypothalamic-pituitary level leading to increased luteinizing hormone (LH) serum levels that causes an increase in serum testosterone levels and ultimately diminishes the ability of a steroidal antiandrogen to compete for AR binding and to block androgenic stimulation. These are made the necessity in the development of steroidal antiandrogens with

fewer side effects, but the steroidal pharmacophores still have some limitations in recognition between anabolic and androgenic effects sufficiently. Also, potential risks for cardiovascular events and hepatotoxicity have been reported in several studies.[56,57] In addition, there are limitations with regard to the pharmacokinetic profiles and application routes (most steroidal androgens cannot be dosed orally), which impacts on the testosterone levels achieved in treating patients.[54,58] The direct antiandrogenic effect of cyproterone is blockage of the binding of dihydrotestosterone to the specific receptors in the prostatic carcinoma cell. In addition, cyproterone exerts a negative feedback on the hypothalamus-pituitary axis, by inhibiting the secretion of luteinizing hormone resulting in diminished production of testicular testosterone.[59,60]

Abiraterone (4a) is a drug used in combination with prednisone in metastatic castration-resistant prostate cancer. It is an inhibitor of CYP17 (17α-hydroxylase/C17,20-lyase). It is formulated as the prodrug, abiraterone acetate. Abiraterone acetate (4b) is the active ingredient of ZYTIGA which is the acetyl ester of abiraterone. It blocks the androgen production at three sources; the testes, the adrenal glands, as well as from the tumor itself. This medication is classified as an "adrenal inhibitor".[61-63] TAK 700 (3p) has a potent, orally bioavailable and highly selective androgen synthesis inhibitor of 17, 20-lyase (CYP17A1) with IC50 values of 19 nM and 48 nM for human and rat respectively. It was selected for evaluation in patients in phase III clinical trials for the potential treatment of prostate cancer.[64]

5α-reductase inhibitors (5-ARIs) are a class of drugs with antiandrogen effects, used primarily in the treatment of benign prostatic hyperplasia (BPH) and androgenic alopecia. Finasteride (4g) and Dutasteride (4h) are type II 5α-reductase inhibitors, which block the action of 5-alpha-reductase enzyme that convert testosterone into dihydrotestosterone, which has a greater affinity for androgen receptors. It is used for the treatment of prostate cancer, benign prostatic hyperplasia (BPH) and male pattern baldness (MPB). The details of steroidal antiandrogens are given in table 4.

AR splice variants and resistance mechanism

Prostate tumors develop resistance to androgen deprivation therapy (ADT) by multiple mechanisms, one of which is to express constitutively active androgen receptor (AR) splice variants lacking the ligand-binding domain. These AR-Vs enable the androgen receptor to be constitutively activated, theoretically rendering them immune to interruption of the steroid synthesis pathway (mechanism of abiraterone) and testosterone receptor antagonists (mechanism of enzalutamide). Currently, more than 20 identified AR-Vs are available. The majority of these AR-Vs

consist of the first 3 exons of the receptor, followed by a cryptic exon that encodes for a premature stop codon that creates a truncated androgen receptor. AR splice variant 7 (AR-V7) is the most abundantly expressed variant that drives prostate tumor progression under ADT conditions. However, the molecular mechanism by which AR-V7 is generated remains unclear. Detection of AR-V7 in circulating tumor cells from patients with CRPC may be associated with resistance to current androgen receptor drugs like enzalutamide, abiraterone.[65]

The field of AR splice variants is still in infancy and investigations encompassing the mechanistic characterization and clinical translation are still at a nascent stage. Successful clinical development of abiraterone and enzalutamide, both intended to target the AR LBD (which is missing in AR-Vs), is directly driven by laboratory mechanistic studies establishing intratumoral androgens and AR protein overexpression as the key molecular determinants of CRPC. So, there is an urgent need to dissect the various putative mechanisms of resistance to these new, more potent inhibitors of AR-FL signaling. Nevertheless, the discovery of AR splice variants has already stimulated efforts to develop novel agents that target all AR molecules to overcome resistance.[66,67] The schematic structure of human AR splice variants, structural domains of AR, AR gene structure with canonical and cryptic exon splice junctions, variant-specific mRNA and peptide sequences are shown in figure 1.

Structure and activity relationship

(i) Steroid based antiandrogens

Cyproterone acetate is a 6-chloro-1, 2-methylene derivative of 17 α-acetoxyprogesterone. It shows major antiandrogenic activity together with androgenic activities. Cyproterone acetate displays high affinity for AR in rats, which increases when the 1, 2-methylene group is removed from the compound. If the chlorine atom is replaced by a methyl group, the binding slightly decreases whereas further removal of the C6 double bond modifies the binding kinetics.[49] As abiraterone was poorly bioavailable and also susceptible to hydrolysis the 3-OH group by esterases, a prodrug, Abiraterone acetate was found to be resistant to esterases and was rapidly deacetylated to abiraterone in vivo, resulting in potent CYP17 inhibition.

(ii) Non-steroid based antiandrogens

Consider the non-steroidal antiandrogen such as bicalutamide, MDV-3100 and nilutamide series are shown re in the figures (Fig: 2, Fig: 3, Fig: 4, respectively). All of them have the anilide ring structure with two substitutions R_1 and R_2. The compounds which have either chloro or trifluoro group at R_1 and cyano or nitro at R_2 have a higher binding affinity than other combination. It is clearly shown that flutamide is an essential structure for

higher AR binding affinity. In bicalutamide series, AR binding affinity of bicalutamide B-ring or X-linkage was tested in *in vitro*.[68] In most of the cases, the sulfide shows at least 3-fold higher binding affinity than sulfone. Instead of H at R_3, fluorine shows better AR binding affinity. In nilutamide series, nilutamide has sparingly low binding affinity for AR than bicalutamide. But, the compounds which have H or CH_3 at R_3 and aryl group at R_4, have good binding affinity. In MDV-3100, R2 has cyano, R_3 has N-methyl carbamide groupand R4 has fluorine shows higher AR binding affinity. Instead of dimethyl group, a cyclopropane ring has presented in RD-162. So, both are having higher binding affinity than bicalutamide.[20,21,49]

Selective androgen receptor modulators (SARMs)

SARMs are a novel class of androgen receptor ligands that bind with androgen receptor and display tissue-selective activation of androgenic signaling, which improve physical function and bone health without adversely affecting the prostate and cardiovascular outcomes. These ligands should behave as antagonists in the prostate with either no activity or agonist activity in other target tissues, so as to have little or no effects in the anabolic tissues or central nervous system (CNS).[69a,69b] SARMs provide therapeutic opportunities in a variety of diseases, including muscle wasting associated with burns, cancer, or end-stage renal disease, osteoporosis, frailty, and hypogonadism.[70] The concept of nonsteroidal SARM emerged as an attractive target for the drug discovery and development.[71-74] BMS-564929 (5f) is currently in early human clinical trials, which is an orally active, potent and selective agonist for androgen receptors (Ki 2.1nM, 20x functional selectivity for muscle tissue over prostate). In studies on castrated rats, it was shown to counteract decrease in muscle mass over time, and at higher doses even increased muscle mass, without significantly affecting prostate tissue.[69a,69b] Ligand compounds LGD2226 (5j) and LGD 2941 that are bicycle 6-anilino quinolinone derivatives have shown anabolic activity on the Levator muscle as well as bone mass and strength, while having little effect on prostate size in a preclinical rodent model. At present, SARMs (such as S-23 (5g), S-40503 (5h), AC-262356 and ACP-105 (5c)) have shown potent bioavailability and good activity in earlier clinical trials. The details of some of SARMs and their properties and functions are given in table 5.

Natural antiandrogens

Natural antiandrogen is useful for human life if someone prevents androgen in the human body. Antiandrogenic chemicals also occur naturally in plants. For example, Mahanine is a natural antiandrogen isolated from *Murraya koenigii*, which is a small shrub, widely available in East Asia. Mahanine inhibits growth and induces apoptosis in both androgen-responsive, LNCaP and androgen-independent, PC3 cells.[75] Isoflavoneglucosides, 2'-

hydroxy genistein-7-O-gentibioside and 2'-hydroxy genistein-7-O-glucoside, are isolated from the groundnut of *Apios americana Medik*. That's proven to be androgen receptor antagonists due to their binding activities of androgen receptors (IC50 280 and 160 μM, resp.) and the inhibitory activity of androgen-induced expression of prostate-specific antigen (PSA) mRNA in LNCaP (prostate adenocarcinoma) cells (IC50 20 and 18 μM, respectively).[76] 3, 3'-Diindolylmethane (DIM) is an effective anti-androgen, present in the cruciferous vegetables such as broccoli, brussels' sprouts, cabbage and kale. Atraric acid and N-butylbenzenesulfonamide(NBBS) act as novel natural AR antagonists, have been purified from *Prunusafricana* (Red Stinkwood) root.[77-79] And also, some of the reports are shown that *Menthaspicata* (Spearmint tea),[80] *Scutellariabaicalensis*, *Korean Angelica gigasNakai* (AGN) and *Vitexagnus-castus* fruit have the role in the treatment of prostate cancer.[81-85]

Conclusions

The first report of a diagnosis of Prostate cancer dates back to 1853.[74] The occurrence of this male killer disease is increasing as the time passes by and now assuming an alarming stage all over the world. Many therapies and some case mode of action have been discussed here, but various drugs to treat the PCa's have been developed and reported by different groups of researchers all over the world, but their usages have been limited because of poor oral bio-availability, lack of selectivity, and have high risks of serious side effects. There are very limited options for accurate diagnostic tools or methodology of Prostate cancer, screening with PSA testing and a digital rectal examination are performed, but PSA test is not confirmed for the PCa. It is the need of the hour to work to develop for early perfect detection tools or methodologies.

Chemotherapy for advanced prostate cancer can palliate the disease and modestly improve survival. "Surgery is one of the treatment options, which gives relief to the PCa patients and reported 90-95% chances of cure, but there are 5-10 % chances of recurrences" is only true if the tumor has no metastases at the time of surgery. In such cases, drug treatment becomes inevitable. Bicalutamide is proved to be one of the best options of treatment, but it is reported that if used for longer periods, it becomes also resistant. Recently, a synthetic drug, Enzalutamide (MDV3100), which is the FDA approved drug, has been reported to be more effective than Bicalutamide, could solve the problems up to some extent.[10,11,17] This review may help to understand the possible therapies available right now and may useful to discover new active drugs for prostate cancer.

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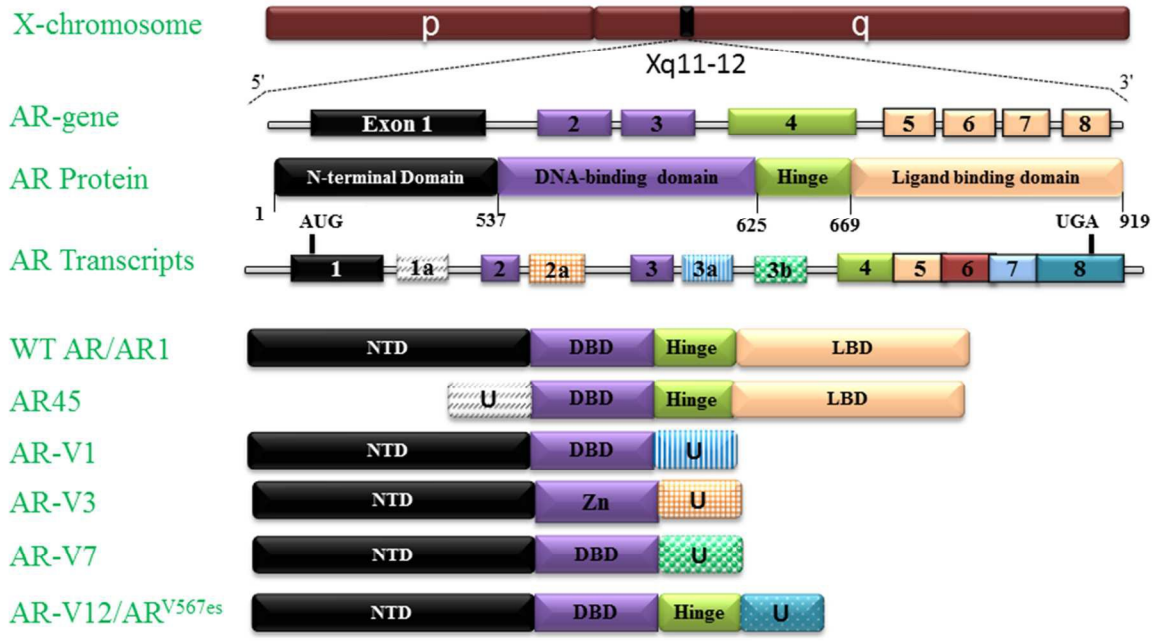
Figures

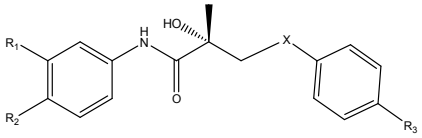
1)



AR Variants	Proteins
AR-FL	MTLGDNLPEQAAFWRHLHIFWDHVVKK stop
AR-V1	MTLGAVVVSERILRVFGVSEWLP stop
AR-V2	MTLGAVVVSERILRVFGVSEWLP stop
AR-V3	RAAEGFFRMNKLKESSDTNPKPYCMAAPMGLTENNRNRKKSYRETNLKAVSWPLNHT stop
AR-V4	MTLGGFFRMNKLKESSDTNPKPYCMAAPMGLTENNRNRKKSYRETNLKAVSWPLNHT stop
AR-V5	MTLGD stop
AR-V6	MTLGAGSRVS stop
AR-V7	MTLGEKFRVGNCKHLKMTRP stop
AR-V12	KALPDCERAASVHF stop

Fig: 1. Schematic structure of human AR splice variants, Structural domains of AR and its more important isoforms, AR gene structure with canonical and cryptic exon splice junctions, variant-specific mRNA and peptide sequences are shown. U: unique, NTD: N-terminal domain, DBD: DNA binding domain, LBD: ligand binding domain

2)



R_1 – CN, NO_2, OCH3

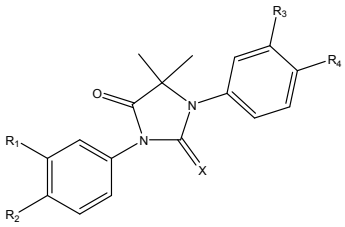
R_2 _ Cl or CF_3

X – Carbonyl or sulfonyl group

R_3 – F or H

Fig: 2. Bicalutamide Series

3)



R_1 – CN, NO_2, OCH3

R_2 – Cl or CF_3

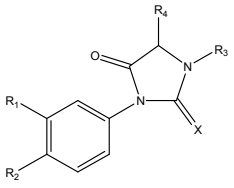
X – O or S

R_3 – F or H

R_4 – NH2, $NHCOCH_3$

Fig: 3. MDV-3100 Series

4)



R_1 – CN, NO_2, OCH3

R_2 – Cl or CF_3

X – O or S

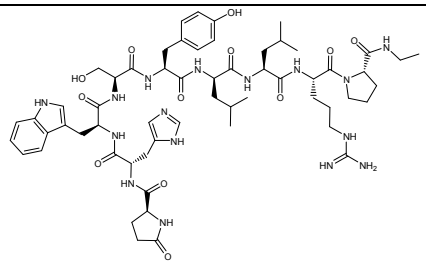
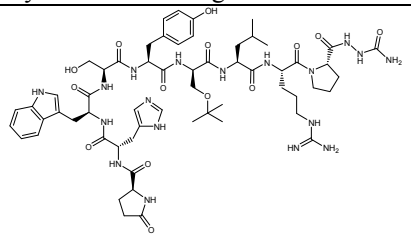
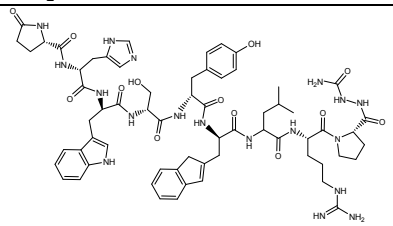
R_3 – H, alkyl or aryl group

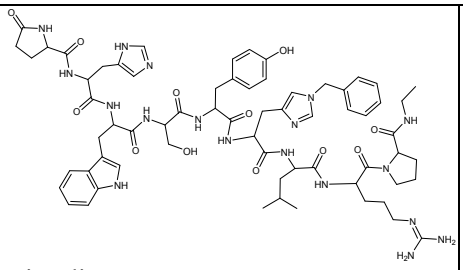
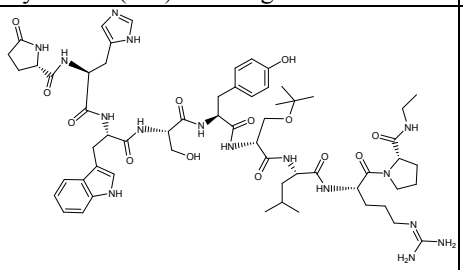
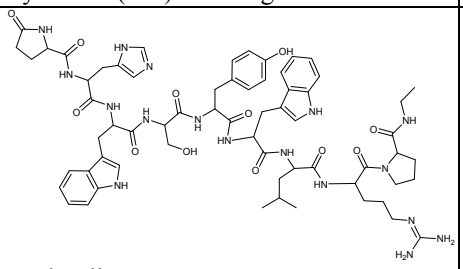
R_4 – Alkyl or aryl group

Fig: 4. Nilutamide Series

Tables

Table: 1. Comparative studies of LHRH (GHRH) agonists

S.No	STRUCTURE, NAME AND COMPOSITION OF COMPOUND*	PROPERTIES#	COMPANY /STAGE OF DEVELOPMENT / IDENTIFIERS	OTHER INFORMATION
1a	 Leuprorelin (INN) or leuprolide acetate Formula: $C_{59}H_{84}N_{16}O_{12}$ Mass:1209.4 Proper Sequence: pGlu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NHEt	logP: -2.40 No. of HBA:28 No. of HBD:17 Molar Refractivity: 327.242 cm^3 Molar Volume: 834.6±7.0 cm^3 Polarizability:123.91 X 10^{-24} cm^3	Wyeth/Drug Bank: DB00007 Pub Chem Compound: CID 441410 ChemSpider ID: 571356	It is a gonadotrophin-releasing hormone (GnRH) agonist used to treat a wide range of sex hormone-related disorders including advanced prostate cancer, endometriosis and precocious puberty. It is a type of hormone therapy drug called a luteinizing hormone (LH) blocker.[86,87]
1b	 Goserelin Formula: $C_{59}H_{84}N_{18}O_{14}$ Mass:1269.41046 Proper Sequence: pGlu-His-Trp-Ser-Tyr-D-Ser(tBu)-Leu-Arg-Pro-azaGly-NH_2	logP: 1.95 No. of HBA: 32 No. of HBD: 20 Molar Refractivity: 362.378 cm^3 Molar Volume: 844.7±7.0 cm^3 Polarizability: 126.65 X 10^{-24} cm^3	AstraZeneca/ Drug /Drug Bank: DB00014 Pub Chem Compound: CID 25077993 ChemSpider ID: 10482012	Goserelin is a synthetic decapeptide analogue of LHRH agonist. It is used to suppress production of the sex hormones (testosterone and estrogen), particularly in the treatment of breast and prostate cancer. It is used to treat hormone-sensitive cancers of the prostate in men and uterine fibroids in women.[88]
1c	 Triptorelin Formula:$C_{64}H_{82}N_{18}O_{13}$ Mass: 1311.44868 Proper Sequence: pGlu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2	logP: -3.59 No. of HBA: 31 No. of HBD: 20 Molar Refractivity: 352.432 cm^3 Molar Volume: 858.4±7.0 cm^3 Polarizability: 134.37 X 10^{-24} cm^3	Jpsen & Ferring/ Pub Chem Compound: CID 16133851 ChemSpider ID: 17290424	It is a GnRH agonist used as the acetate or pamoate salts. It works by decreasing the production of certain hormones, which reduces testosterone levels in the body. It can slow or stop the growth of cells (including prostate cancer cells) that depend on testosterone. If the medicine is stopped, hormone levels return to normal.[89]

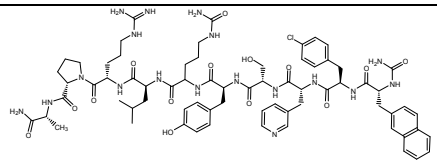
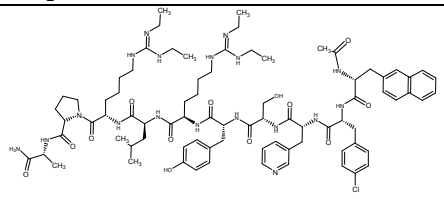
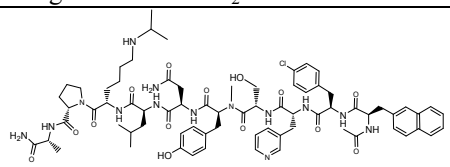
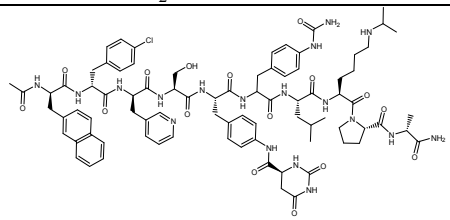
1d	 Histrelin Formula:$C_{66}H_{86}N_{18}O_{12}$ Mass: 1323.50244 Proper Sequence: pGlu-His-Trp-Ser-Tyr-D-His(Bzl)-Leu-Arg-Pro-NHEt	logP: -2.14 No. of HBA:30 No. of HBD:17 Molar Refractivity: 360.073 cm3 Molar Volume: 906.4±7.0 cm^3 Polarizability: 136.13 X 10^{-24} cm^3	Valera & Endo Pharmaceuticals /Pub Chem Compound: CID 25077993 ChemSpider ID: 10482012	Histrelin acetate is a synthetic nonapeptide analogue of the naturally occurring LHRH agonist. It is used to treat hormone-sensitive cancers of the prostate in men and uterine fibroids in women.[90,91]
1e	 Buserelin Formula:$C_{60}H_{86}N_{16}O_{13}$ Mass:1239.42424 Proper Sequence: pGlu-His-Trp-Ser-Tyr-D-Ser(tBu)-Leu-Arg-Pro-NHEt	logP: No. of HBA: 29 No. of HBD: 17 Molar Refractivity: 338.930 cm3 Molar Volume: 861.4±7.0 cm^3 Polarizability: 126.09 X 10^{-24} cm^3	Sanofi-Aventis /Drug Bank: DB06719 Pub Chem Compound: CID 50225 ChemSpider ID: 45545	It is a synthetic peptide analog of GnRH agonist, which stimulates the pituitary glands gonadotrophin-releasing hormone receptor (GnRHR). It is used in prostate cancer treatment. It is normally delivered via a nasal spray, but is also available as an injection.[92,93]
1f	 Deslorelin Formula:$C_{64}H_{83}N_{17}O_{12}$ Mass: 1282.45052 Proper Sequence: pGlu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-NHEt	logP: -2.60 No. of HBA:29 No. of HBD:18 Molar Refractivity: 345.624 cm3 Molar Volume: 863.7±7.0 cm^3 Polarizability: 132.18 X 10^{-24} cm^3	Peptech/Pub Chem Compound: CID 25077495 ChemSpider ID: 16736553	It is a synthetic analogue of a naturally occurring LHRH agonist. It stops the production of sex hormones (testosterone and estrogen).[94]

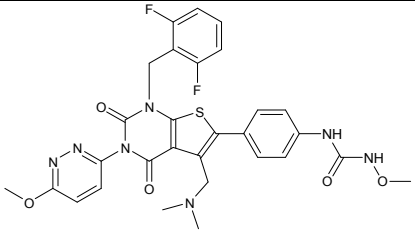
*Data generated by using Chem draw software

#Data generated from Chem Axon, chemspider and NCBI website

(In proper sequence, pGlu: pyroglutamyl, His: histidyl, Trp: tryptophyl, Ser: seryl, Tyr: tyrosyl, Leu: leucyl, Arg: arginyl, Pro: prolyl, Gly: glycyl, Et: ethyl, tBu: tert-butyl, Bzl: benzyl)

Table: 2. Comparative studies of LHRH (GHRH) antagonists

S.No	STRUCTURE, NAME AND COMPOSITION OF COMPOUND*	PROPERTIES#	COMPANY /STAGE OF DEVELOPMENT/ IDENTIFIERS	OTHER INFORMATION
2a	 Cetrorelix Formula: $C_{70}H_{92}ClN_{17}O_{14}$ Mass: 1432.02604 Proper Sequence: Ac-D-Nal-D-Cpa-D-Pal-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2	logP: 5.89 No. of HBA:31 No. of HBD:20 Molar Refractivity: 410.727 cm3 Molar Volume: 1003.4±7.0 cm^3 Polarizability: 145.63 X 10^{-24} cm^3	Merck/Drug Bank: DB00050 Pub Chem Compound: CID 25078429 ChemSpider ID: 10482082	It is a synthetic decapeptide with GnRH antagonistic activity. It is used for treatment of infertility and of hormone-sensitive cancers of the prostate and breast.[95,96]
2b	 Ganirelix Formula: $C_{80}H_{113}ClN_{18}O_{13}$ Mass: 1570.31902 Proper Sequence: Ac-D-Nal- D-Cpa-D-Pal-Ser-Tyr-D-$(Et)_2$-hArg-Leu-$(Et)_2$-hArg-Pro-D-Ala-NH_2	logP: 6.74 No. of HBA: 31 No. of HBD: 17 Molar Refractivity: 439.094 cm3 Molar Volume: 1190.838 cm^3 Polarizability: 164.65 X 10^{-24} cm^3	Organon Pharmaceuticals/ Pub Chem Compound: CID 16186319 ChemSpider ID: 16736620	It is a man-made form of a protein that reduces the amount of certain hormones in the body, including estrogen. It is used along with other medications to regulate hormones during treatment for infertility in women.[97]
2c	 Abarelix Formula: $C_{72}H_{95}ClN_{14}O_{14}$ Mass: 1416.0631 Proper Sequence: Ac-D-Nal-D-Cpa-D-Pal-Ser-(N-Me)Tyr-D-Asn-Leu-iPrLys-Pro-DAla-NH_2	logP: -0.47 No. of HBA: 28 No. of HBD: 15 Molar Refractivity: 373.910 cm3 Molar Volume: 1100.4±3.0 cm^3 Polarizability: 147.10 X 10^{-24} cm^3	Praecis Pharmaceuticals/ Drug Bank: DB00106 Pub Chem Compound: CID 16131215 ChemSpider ID: 10482301	It is primarily used in oncology to reduce the amount of testosterone made in patients with advanced symptomatic prostate cancer for which no other treatment options are available.[96,98]
2d	 Degarelix Formula: $C_{82}H_{103}ClN_{18}O_{16}$ Mass: 1632.25922 Proper Sequence: Ac-D-Nal-D-Cpa-D-Pal-Ser-4-aminoPhe(L-hydroorotyl)-D-4-aminoPhe(carbamoyl)-Leu-iPrLys-	logP: 0.06 No. of HBA:34 No. of HBD:19 Molar Refractivity: 431.128 cm3 Molar Volume: 1231.3±3.0 cm^3 Polarizability: 167.52 X 10^{-24} cm^3	Ferring Pharmaceuticals/ Drug Bank: DB06699 Pub Chem Compound: CID 16186010 ChemSpider ID: 17292756	It is used for the treatment of advanced prostate cancer. It is a synthetic peptide derivative drug which binds to GnRH receptors in the pituitary gland and blocks interaction with GnRH. This antagonism reduces luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which ultimately causes testosterone suppression. Reduction in testosterone is important in treating men with

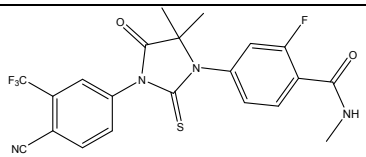
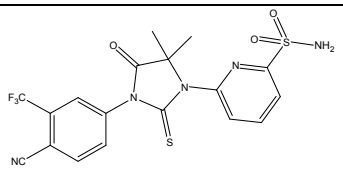
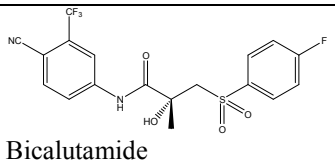
	Pro-D-Ala-NH_2			advanced prostate cancer.[96,99]
2e	 Relugolix (TAK-385) Formula: C29H27F2N7O5S Mass: 623.6303864	logP: 3.87 No. of HBA:12 No. of HBD:2 Molar Refractivity: 160.924 cm3 Molar Volume: 432.3±3.0 cm^3 Polarizability: 60.27 X 10^{-24} cm^3	Takeda/ ChemSpider ID: 8524431	It is also known as TAK-385, is a LHRH receptor antagonist administered orally. TAK-385 possesses higher affinity and more potent antagonistic activity for human and monkey. It may provide useful therapeutic interventions in hormone-dependent diseases including endometriosis, uterine fibroids and prostate cancer.[100]

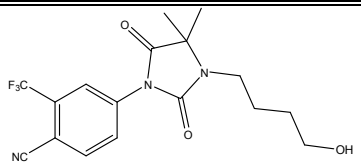
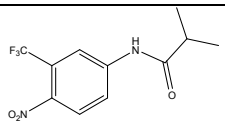
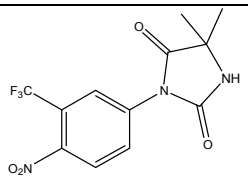
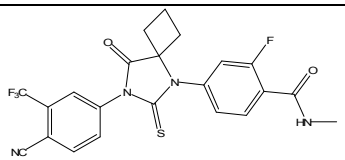
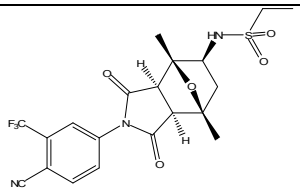
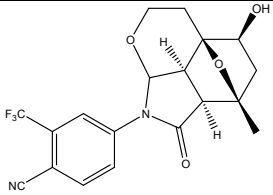
*Data generated by using Chem draw software

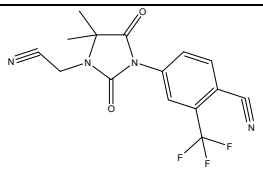
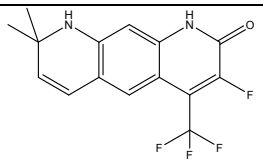
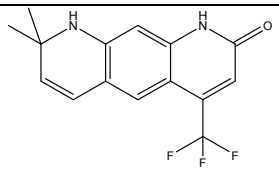
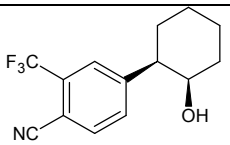
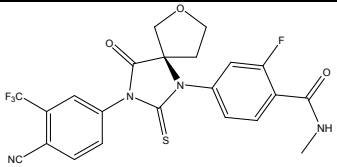
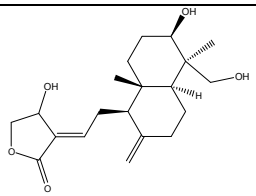
#Data generated from Chem Axon, chemspider and NCBI website

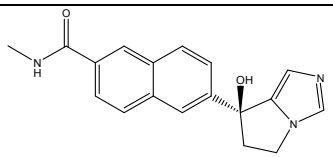
(In proper sequence, Ac: acetyl, Nal: 2-naphthylalanyl, Cpa: 4-chlorophenylalanyl, Pal: 3-pyridylalanyl, Ala: alanyl, Ser: seryl, Tyr: tyrosyl, Cit: citrullyl, Leu: leucyl, Arg: arginyl, Pro: prolyl, Gly: glycyl, $(Et)_2$: N^9,N^{10}-diethyl, hArg: homoarginyl, Asn: asparagyl, iPr: isopropyl, Phe: phenylalanyl)

Table: 3. Comparative studies of Nonsteroidal Antiandrogens

S.No	STRUCTURE, NAME AND COMPOSITION OF COMPOUND*	PROPERTIES#	COMPANY /STAGE OF DEVELOPMENT/ IDENTIFIERS	OTHER INFORMATION
3a	 Enzalutamide (MDV3100) Formula: $C_{21}H_{16}F_4N_4O_2S$ Mass: 464.436	logP: 4.16 No. of HBA: 4 No. of HBD: 1 Molar Refractivity: 111.523 cm^3 Molar Volume: 310.0 ± 5.0 cm^3 Polarizability: 40.83 X 10^{-24} cm^3	Medivation/ Pub Chem Compound: CID 15951529 ChemSpider ID: 13093347	Compared to bicalutamide, It has fivefold higher binding affinity for AR. It induces tumor cell apoptosis, has no agonist activity and also clinically active in metastatic castration-resistant prostate cancer.[17,20,21]
3b	 CH5137291 Formula: $C_{18}H_{14}F_3N_5O_3S_2$ Mass: 469.461	logP: 3.52 No. of HBA: 6 No. of HBD: 2 Molar Refractivity: 111.523 cm^3 Molar Volume: 284.4 ± 5.0 cm^3 Polarizability: 40.83 X 10^{-24} cm^3	Chugai Pharmaceutical Co. Ltd/ Preclinical/ ChemSpider ID: 26368379	It completely inhibits in vivo tumor growth and PSA production in the LNCaP-BC2 xenograft model, which is bicalutamide-resistant.[15,101]
3c	 Bicalutamide Formula: $C_{18}H_{14}F_4N_2O_4S$ Mass: 430.373	logP: 2.71 No. of HBA: 6 No. of HBD: 2 Molar Refractivity: 111.523 cm^3 Molar Volume: 284.4 ± 5.0 cm^3 Polarizability: 40.83 X 10^{-24} cm^3	AstraZeneca pharmaceutical company/Drug/ Drug Bank: DB 01128 Pub Chem Compound: CID 2375 ChemSpider ID: 2284	It is an oral non-steroidal anti-androgen acts by binding to the androgen receptor (AR) and preventing the activation of the AR and subsequent up regulation of androgen responsive genes by androgenic hormones. It is used to treat advanced prostate cancer.[20,102,103]

3d	 RU-58841 Formula: $C_{17}H_{18}F_3N_3O_3$ Mass: 369.3383	logP: 2.28 No. of HBA: 6 No. of HBD: 2 Molar Refractivity: 111.523 cm^3 Molar Volume: 284.4 ± 5.0 cm^3 Polarizability: 40.83 X 10^{-24} cm^3	Roussel-Uclaf SA/ / Pub Chem Compound: CID 132981 ChemSpider ID: 117358	It is used for the topical treatment of androgen-dependent skin disorders such as acne, androgenetic alopecia and hirsutism, is analogous to nilutamide.[20,104]
3e	 Flutamide Formula: $C_{11}H_{11}F_3N_2O_3$ Mass: 276.2118	logP: 3.27 No. of HBA: 3 No. of HBD: 1 MolLogP: 2.90 Number of stereo centers: 0	Schering-Plough /Drug/ Drug Bank: DB 00499 Pub Chem Compound: CID 3397 ChemSpider ID: 3280	It is a non-steroidal antiandrogen drug, is used to treat prostate cancer. It has different side effects such as hot flashes, impotence, diarrhea.[20,105]
3f	 Nilutamide Formula: $C_{12}H_{10}F_3N_3O_4$ Mass: 317.2207	logP: 2.25 No. of HBA: 6 No. of HBD: 2 Molar Refractivity: 111.523 cm^3 Molar Volume: 284.4 ± 5.0 cm^3 Polarizability: 40.83 X 10^{-24} cm^3	Sanofi Winthrop Industries/Drug/ Drug Bank: DB 00665 Pub Chem Compound: CID 4493 ChemSpider ID: 433	It is an antiandrogen medication used in the treatment of advanced-stage prostate cancer. Specific use of nilutamide, Night blindness has observed as side effects.[20,106-108]
3g	 RD162 Formula: $C_{22}H_{16}F_4N_4O_2S$ Mass: 476.45	logP: 3.85 No. of HBA: 6 No. of HBD: 2 Molar Refractivity: 111.523 cm^3 Molar Volume: 284.4 ± 5.0 cm^3 Polarizability: 40.83 X 10^{-24} cm^3	Medivation/ Preclinical/ Pub Chem Compound: CID 11957756 ChemSpider ID: 10132004	It is a non-steroidal androgen receptor antagonist, shows more potent activity and is tested in clinical trials and also shows high binding affinity to AR.[21,22]
3h	 BMS-641988 Formula: $C_{20}H_{20}F_3N_3O_5S$ Mass: 471.45	logP: 0.96 No. of HBA: 6 No. of HBD: 1 Molar Refractivity: 104.89 cm^3 Molar Volume: 116.57 cm^3 Polarizability: 40.73 X 10^{-24} cm^3	Bristol-Myers Squibb/Phase I clinical trial/ Pub Chem Compound: CID 24768935	Compared to bicalutamide, It has tenfold higher binding affinity for AR. But, Phase I trial was discontinued because of anepileptic seizure in a patient.[20,109,110]
3i	 BMS-779333 Formula: $C_{19}H_{17}F_3N_2O_4$ Mass: 394.3445	logP: 2.298 No. of HBA: 6 No. of HBD: 2 Molar Refractivity: 82.79 cm^3 Molar Volume: 284.4 ± 5.0 cm^3 Polarizability: 34.02 X 10^{-24} cm^3	Bristol-Myers Squibb	It is selected for further preclinical evaluation. Because it did not exhibit agonist activity for AR mutant isoforms. Tumors that failed bicalutamide treatment were shown to retain their sensitivity to respond to it. Transcriptomic changes in LuCaP-35 tumors treated with BMS-779333 were closer to castration than with

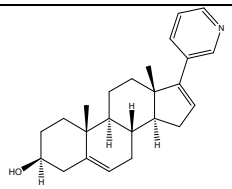
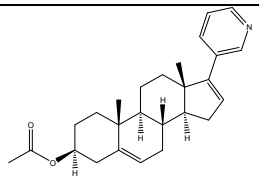
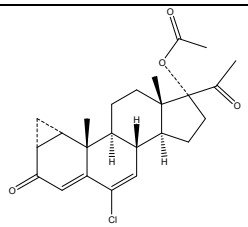
				other drug treatments.[20,111]
3j	 RU-58642 Formula: $C_{15}H_{11}F_3N_4O_2$ Mass: 336.2686	logP: 1.93 No. of HBA: 6 No. of HBD: 2 Molar Refractivity: 76.584 cm^3 Polarizability: 27.90 X 10^{-24} cm^3	Roussel-Uclaf SA/ Preclinical – no further developments since 1998/ Pub Chem Compound: CID 9840708 ChemSpider ID: 8016425	It is an orally active and more potent non-steroidal antiandrogen drug with high affinity and selectivity.[112]
3k	 LG105 Formula: $C_{15}H_{12}F_4N_2O$ Mass: 312.2622	logP: 2.99 No. of HBA: 1 No. of HBD: 2 Molar Refractivity : 78.821 cm^3 Polarizability: 26.53 X 10^{-24} cm^3	Ligand Pharmaceuticals/ Preclinical/ Pub Chem Compound: CID 59211420	It is an orally available, strong antagonistic activity in the prostate without raising plasma levels of LH and testosterone. It seems to be more potent than LG120907.[113,114]
3l	 LG120907 Formula: $C_{15}H_{13}F_3N_2O$ Mass: 294.2717	logP: 2.79 No. of HBA: 2 No. of HBD: 1 Molar Refractivity: 70.741cm^3 Molar Volume: 227.718 cm^3 Polarizability: 28.044 X 10^{-24} cm^3	Ligand Pharmaceuticals/ Preclinical/ PubChem: CID 10851308 ChemSpider ID: 9026602	It is orally active, strong antagonistic activity in the prostate without raising plasma levels of LH and testosterone.[115,116]
3m	 PF-998425 Formula: $C_{14}H_{14}F_3NO$ Mass: 269.2623	logP: 3.51 No. of HBA: 5 No. of HBD: 1 Molar Refractivity: 65.537cm^3 Molar Volume: 44.02 cm^3 Polarizability: 24.12 X 10^{-24} cm^3	PubChem: CID 25093231 ChemSpider ID: 24606067	It is a selective non-steroidal androgen receptor (AR) antagonist (IC_{50} values are 26 nM and 90 nM in AR binding assays and cellular assays respectively). It displays low affinity for progesterone receptor (IC_{50}> 10 μM).[117]
3n	 ONC1-13B Formula: C22H16F4N4O3S Mass: 492.446	logP: 3.28 No. of HBA: 4 No. of HBD: 1 Molar Refractivity: 117.922cm^3 Polarizability: 43.41 X 10^{-24} cm^3	Chemical Diversity Research Institute, Russia/ Preclinical	ONC1-13B inhibits DHT-induced PSA expression (Ki 20nM) around 10-fold more efficiently than bicalutamide (Ki 190 nM, data not shown) and slightly more efficiently than two other clinical stage antiandrogens, MDV3100 (Ki 30.8 nM) and ARN-509 (Ki 38.4 nM).[25]
3o	 Andrographolide Formula: $C_{20}H_{30}O_5$	logP: 1.66 Molar Refractivity: 94.930cm^3 Molar Volume: 86.99 cm^3 Polarizability: 37.54 X 10^{-24} cm^3	ChemSpider ID: 16735664	It is an inhibitor of NF-κB signaling; also attenuates concanavaline-induced IFNγ production in murine T cells (IC_{50} = 1.7 μM). Blocks androgen receptor (AR) expression in AR-expressing C4-2 cells. It activates Nrf2 in

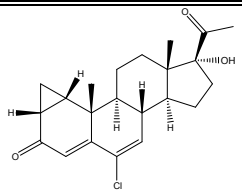
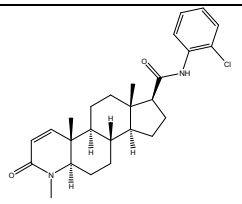
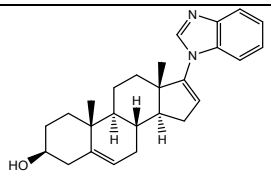
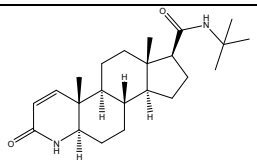
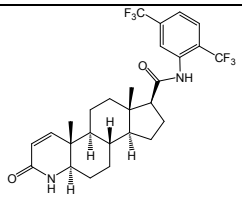
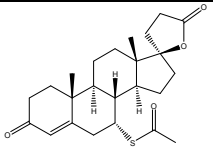
	Mass: 350.4492			BEAS-2B cells in response to cigarette smoke extract.[118,119]
3p	 Orteronel (TAK 700) Formula: C18H17N3O2 Mass: 307.3465	logP: 3.64 Molar Refractivity: 88.298 cm^3 Polarizability: 34.24 X 10^{-24} cm^3	Takeda Pharmaceutical Company/ PubChem Compound: CID 9883029 ChemSpider ID: 8058704	It completed two phase III clinical trials for metastatic, hormone-refractory prostate cancer but failed to extend overall survival rates, and development was voluntarily terminated as a result. It selectively inhibits the enzyme CYP17A1.[25]

*Data generated by using Chem draw software

#Data generated from Chem Axon, chemspider and NCBI website

Table: 4. Comparative studies of Steroidal Antiandrogens

S.No	STRUCTURE, NAME AND COMPOSITION OF COMPOUND*	PROPERTIES#	COMPANY /STAGE OF DEVELOPMENT/ IDENTIFIERS	OTHER INFORMATION
4a	 Abiraterone Molecular Formula: $C_{24}H_{31}NO$ Mass: 349.509	logP: 3.64 Molar Refractivity: 111.809 cm^3 Polarizability: 43.97 X 10^{-24} cm^3	Cadila Pharmaceuticals / drug/ ChemSpider ID: 117349	It inhibits 17 α-hydroxylase/ C17,20 lyase (CYP17A1), an enzyme which is expressed in testicular, adrenal, and prostatic tumor tissues.[61-63]
4b	 Abiraterone acetate Formula: C26H33NO2 Mass: 391.5457	logP: 4.41 Molar Refractivity: 116.454 Polarizability:45.56 X 10^{-24} cm^3	Cadila Pharmaceuticals/ ChemSpider ID: 117348	Abiraterone acetate is a prescription medicine that is used along with prednisone, is used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has spread to other parts of the body.[61-63]
4c	 Cyproterone acetate Formula: $C_{24}H_{29}ClO_4$ Mass: 416.938	logP: 3.64 Molar Refractivity: 111.809 cm^3 Molar Volume: 60.44 cm^3 Polarizability: 43.97X $10^{-24}cm^3$	Drug Bank: DB04839 Pub Chem Compound: CID 9880 ChemSpider ID : 9496	Its primary action is to suppress the activity of the androgen hormones in the body, effects which it mediates via competitive antagonism of the androgen receptor and inhibition of enzymes in the androgen biosynthesis pathway.[120,121]

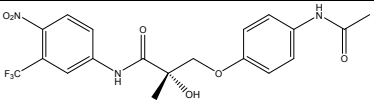
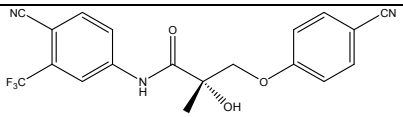
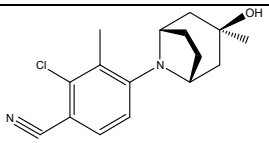
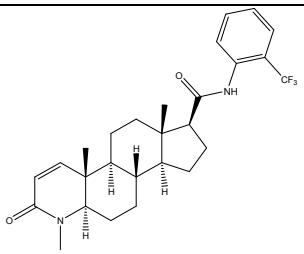
4d	 Cyproterone Formula: $C_{22}H_{27}ClO_3$ Mass: 374.901	logP: 3.20 Molar Refractivity: 102.658 cm^3 Molar Volume: 54.37 cm^3 Polarizability: 39.73X $10^{-24}cm^3$	Pub Chem Compound: CID 5284537 ChemSpider ID: 4447594	It is a steroidal antiandrogen which did not marketed but its acetylated derivative is widely used in clinical trials.[59,60]
4e	 Cl-4AS-1 Formula: $C_{26}H_{33}ClN_2O_2$ Mass: 441.005	logP: 4.86 Molar Refractivity: 125.650cm^3 Molar Volume: 49.41 cm^3 Polarizability: 48.28 X $10^{-24}cm^3$	ChemSpider ID: 26232143	It is a potent steroidal androgen receptor agonist (IC_{50} = 12 nM). It mimics the action of DHT and transactivates the mouse mammary tumor virus (MMTV) promoter. It represses MMP1 promoter activity.[122]
4f	 Galeterone (TOK-001 or VN/124-1) Formula: $C_{26}H_{32}N_2O$ Mass: 388.54508	logP: 4.47 Molar Refractivity: 118.578 cm^3 Molar Volume: 301.6±7.0 cm^3 Polarizability: 47.00 X $10^{-24}cm^3$	Tokai Pharmaceuticals/ Pub Chem Compound: CID 11188409 ChemSpider ID: 9363493	It is a novel antiandrogen for the treatment of prostate cancer. It possesses a unique dual mechanism of action, acting as both an androgen receptor antagonist and an inhibitor of CYP17A1, an enzyme required for the biosynthesis of the androgens. Recently, It is in phase III clinical trials for castration-resistant prostate cancer.[123]
4g	 Finasteride Formula: $C_{23}H_{36}N_2O_2$ Mass: 372.5441	logP: 3.07 Molar Refractivity: 108.196 cm^3 Molar Volume: 58.20 cm^3 Polarizability: 42.35 X $10^{-24}cm^3$	Merck/ Drug Bank: DB01216 Pub Chem Compound: CID 57363 ChemSpider ID: 51714	It is an orally active antiandrogen, which inhibits type II 5α reductase (IC_{50} = 65 nM) and suppresses the conversion of testosterone to dihydrotestosterone. It reduces prostatic dihydrotestosterone levels and prostate size *in vivo*.[73, 124]
4h	 Dutasteride Formula: $C_{27}H_{30}F_6N_2O_2$ Mass: 528.5297192	logP: 5.79 Molar Refractivity: 127.896 cm^3 Molar Volume: 405.6±3.0 cm^3 Polarizability: 46.83 X 10^{-24} cm^3	GlaxoSmithKline/ Drug Bank: DB01126 Pub Chem Compound: CID 6918296 ChemSpider ID: 5293502	It is a dual 5-α reductase inhibitor that inhibits conversion of testosterone to dihydrotestosterone (DHT). It is used to treat benign prostatic hyperplasia.[125]
4i	 Spironolactone Formula: $C_{24}H_{32}O_4S$	logP: 3.64 Molar Refractivity: 113.504 cm^3 Molar Volume: 60.44 cm^3 Polarizability:	Drug Bank: DB00421 Pub Chem Compound: CID 5833 ChemSpider ID:	Competitive mineralocorticoid (aldosterone) receptor antagonist that exhibits antihypertensive activity *in vivo*. Also displays antiandrogen activity and inhibits steroid hormone

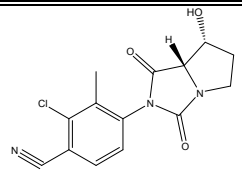
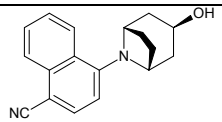
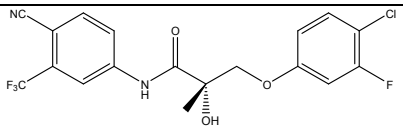
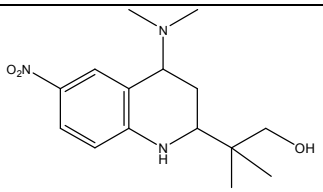
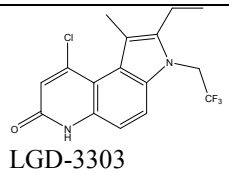
	Mass: 416.573	45.07 X 10^{-24} cm^3	5628	biosynthesis.[126,127]

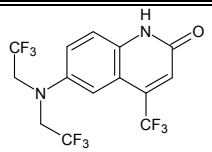
*Data generated by using Chem draw software

#Data generated from Chem Axon, chemspider and NCBI website

Table: 5. Comparative studies of SARMS

S.No	STRUCTURE, NAME AND COMPOSITION OF THE COMPOUNDS*	PROPERTIES#	COMPANY /STAGE OF DEVELOPMENT/ IDENTIFIERS	OTHER INFORMATION
5a	 Andarine Formula: $C_{19}H_{18}F_3N_3O_6$ Mass: 441.3579	logP: 2.74 No. of HBA: 6 No. of HBD: 2 Molar Refractivity : 111.523 cm^3 Molar Volume : 284.4 ± 5.0 cm^3 Polarizability : 40.83 X 10^{-24} cm^3	GTx, Inc/ PubChem Compound:CID 9824562 ChemSpider: 8000309	It is an orally active partial agonist, has less potent in both anabolic and androgenic effects than other SARMs.[73,128]
5b	 Ostarine (Enobosarm) Formula: $C_{19}H_{14}F_3N_3O_3$ Mass: 389.328	logP: 3.27 No. of HBA: 6 No. of HBD: 2 Molar Refractivity : 111.523 cm^3 Molar Volume : 284.4 ± 5.0 cm^3 Polarizability : 40.83 X 10^{-24} cm^3	GTX, Inc , formerly under development by Merck & Company/ PubChem Compound:CID 10181786	It is an investigational selective androgen receptor modulator (SARM).[129,130]
5c	 ACP-105 Formula: $C_{16}H_{19}ClN_2O$ Mass: 290.788	logP: 3.18 No. of HBA: 3 No. of HBD: 1 Molar Refractivity: 79.108 cm^3 Molar Volume: 225.971 cm^3 Polarizability: 31.361 X 10^{-24} cm^3	Acadia Pharmaceuticals/ ChemSpider ID: 24633808	It is a novel and potent nonsteroidal selective androgen receptor modulator (SARM) with partial agonist activity relative to the natural androgen testosterone.[131]
5d	 TFM-4AS-1 Formula: C27H33F3N2O2 Mass: 474.5583	logP: 5.14 No. of HBA: 3 No. of HBD: 1 Molar Refractivity: 123.904 cm^3 Molar Volume: 387.081cm^3 Polarizability: 47.40 X 10^{-24} cm^3	Merck Research Laboratories/ ChemSpider ID: 8452600	It is a potent selective androgen receptor modulator (SARM) (IC50 = 30 nM). It is a Steroidal compound which promotes the buildup of bone and muscle mass while having reduced effects on reproductive organs and sebaceous glands.[122]

5e	 BMS-564929 Formula: $C_{14}H_{12}ClN_3O_3$ Mass: 305.716	logP: 2.79 Number of HBA: 6 Number of HBD: 1 Molar Refractivity: 73.953 cm^3 Molar Volume: 193.366 cm^3 Polarizability: 29.317 X 10^{-24} cm^3	Bristol-Myers Squibb/drug/ Drug Bank: DB07286 Pub Chem Compound: CID 9882972 ChemSpider ID: 8058647	It is used for the treatment of the symptoms of age-related decline in androgen levels in men ("andropause"). [69a,69b]
5f	 AC-262,356 Formula: $C_{18}H_{18}N_2O$ Mass: 278.3483	logP: 2.14 Number of HBA: 3 Number of HBD: 1 Molar Refractivity: 82.554 cm^3 Polarizability: 32.727 X 10^{-24} cm^3	Acadia Pharmaceuticals/ Pub Chem Compound: CID 11673547	It is a partial agonist of the androgen receptor with a Ki of 5nM, and it has no significant affinity for any other receptors tested.[132]
5g	 S-23 Formula: $C_{18}H_{13}ClF_4N_2O_3$ Mass: 416.754	logP: 4.16 Number of HBA: 3 Number of HBD: 1 Molar Refractivity : 94.351 cm^3 Polarizability: 34.57 X 10^{-24} cm^3	GTX, Inc/ Pub Chem Compound: CID 24892822 ChemSpider ID: 24715019	It is a potential male hormonal contraceptive, which binds to the androgen receptor strongly than older drugs such as andarine with a Ki of 1.7nM, and in animal studies it shows a good ratio of anabolic to androgenic effects, and dose-dependent suppression of spermatogenesis with spontaneous recovery after cessation of treatment.[129,133]
5h	 S-40503 Formula: $C_{15}H_{23}N_3O_3$ Mass: 293.3614	logP: 1.68 Number of HBA: 3 Number of HBD: 1 Molar Refractivity: 84.273 cm^3 Polarizability: 31.32 X 10^{-24} cm^3	Kaken Pharmaceuticals/ PubChem Compound: CID 9879175 ChemSpider: 8054852	It is developed for the treatment of osteoporosis. It is a new class of drugs shows good functional selectivity for bone tissue, and has relatively little effect on muscle mass and no observable effect on the prostate gland. It may also be used by athletes to increase physical stamina and fitness. For this reason, SARMs have already been banned by the World Anti-Doping Agency since January 2008.[134]
5i	 LGD-3303 Formula: $C_{16}H_{14}ClF_3N_2O$ Mass: 342.743	logP: 4.26 Number of HBA: 3 Number of HBD: 1 Molar Refractivity: 86.144 cm^3 Polarizability: 31.39 X 10^{-24} cm^3	Ligand Pharmaceuticals/ PubChem Compound:CID 25195253	It acts as a selective androgen receptor modulator, with good oral bioavailability and selective agonist for AR. It has been investigated as a possible treatment for osteoporosis, and was shown in animal studies to enhance the effectiveness of a bisphosphonate drug.[135]

5j	 LGD-2226 Formula: C14H9F9N2O Mass: 392.2197	logP: 4.28 Number of HBA: 3 Number of HBD: 1 Molar Refractivity: 75.822 cm^3 Polarizability: 25.41 X 10^{-24} cm^3	Ligand Pharmaceuticals Inc/ PubChem Compound: CID 11560224	It is an orally active, potent and selective agonist for androgen receptors, which was shown to have anabolic effects in both muscle and bone tissue, but with considerably less effect on prostate weight and lutenizing hormone levels than testosterone.[20,136]

*Data generated by using Chem draw software

#Data generated from Chem Axon, chemspider and NCBI website