Therapeutic androgen receptor ligands

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In the past several years, the concept of tissue-selective nuclear receptor ligands has emerged. This concept has come to fruition with estrogens, with the successful marketing of drugs such as raloxifene. The discovery of raloxifene and other selective estrogen receptor modulators (SERMs) has raised the possibility of generating selective compounds for other pathways, including androgens (that is, selective androgen receptor modulators, or SARMs).

Received August 25th, 2003; Accepted September 17th, 2003; Published September 27th, 2003 | **Abbreviations:** **BPH:** benign prostatic hyperplasia; **CAB:** combined androgen blockade; **DHT:** dihydrotestosterone; **GnRH:** gonadotropin-releasing hormone; **SARM:** selective androgen receptor modulator; **SERM:** selective estrogen receptor modulator

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Pharmacology of Androgens

Androgens control sexual function in the male and are central to the anabolic processes that underlie the development of male sexual and physiological characteristics [Mooradian et al., 1987]. Serum androgen levels are low prior to puberty and climb exponentially during adolescence in the male, leading to the enhanced muscle growth and lean body mass typical of the gender. In the mature adult they range from 600 to 700 ng/dL. As men age, androgen levels decline during the so-called andropause, reaching 450 to 500 ng/dL in their seventies and eighties [Flynn and Hellstrom, 2001]. Concomitantly, lean body mass decreases and older men are frailer, with a greater tendency to falls and bone fractures.

Testosterone (T), acting via its more potent natural metabolite, dihydrotestosterone (DHT), stimulates maturation of the prostate during sexual development. DHT is produced from T by 5-α-reduction, and it binds to the androgen receptor with about five times greater affinity than T. The enzyme 5-α-reductase is expressed tissue-specifically, most prominently in prostate and in hair follicles. This has been taken advantage of pharmacologically, with the generation of specific inhibitors of the enzyme for the treatment of androgen-dependent disorders. For example, finasteride is a 5-α-reductase inhibitor that prevents local synthesis of DHT and is used to treat alopecia. T also has important physiological effects that are independent of DHT, including anabolic effects on muscle, maintenance of testicular function, and inhibition of pituitary gonadotropin secretion.

Prostate maturation results in the production of prostatic secretions that form a component of semen, and thus it is essential for normal fertility. DHT has proliferative effects on the epithelial compartment of the immature prostate. Removal of circulating androgens by testicular or medical castration in humans and rodents results in apoptosis of prostatic cells and shrinkage of the prostate. Administration of T to castrated or immature rodents stimulates prostate growth.

The stimulatory effect of androgens on the prostate throughout adulthood is often thought to be primarily responsible for the increased risk of prostate cancer after the age of 40, although there is no direct proof of this. Nevertheless, localized and early stage metastatic prostate cancers are readily treatable by surgery and combined androgen blockade (CAB). CAB typically consists of treatment with a gonadotropin-releasing hormone (GnRH) agonist (such as leuprolide), to shut down physiological sex steroid synthesis (surgical castration, or orchidectomy, has the same result); and an androgen antagonist (such as flutamide or bicalutamide), to shut down androgen-responsive pathways. Androgen antagonists have been approved in the US only for CAB of advanced prostate cancer. CAB is an expensive therapy and men experience hot flushes and bone loss due to the depletion of anabolic steroids. Recently, monotherapy with androgen antagonists has shown to be as effective as CAB in preventing disease recurrence [See et al., 2002], and some European regulatory authorities have approved the use of bicalutamide for this purpose. However, both currently used androgen antagonists, flutamide (Eulexin) and bicalutamide (Casodex), cause breast tenderness and gynecomastia, which limit their use for monotherapy. These side effects are due to the propensity of the compounds to raise serum estrogen levels, which in turn is due to antagonism of normal feedback inhibition by testicular androgens at the pituitary. With feedback inhibition blunted, T synthesis continues, serum T levels rise, and the excess is aromatized into estrogen [McLeod and Iversen, 2000].

Benign prostatic hyperplasia (BPH) is a common condition in middle-aged and older men. The stromal compartment of the prostate grows larger and obstructs urethral flow, resulting in difficulty in urination. The etiology of BPH is poorly understood, but the condition can be treated with inhibitors of DHT formation (finasteride) or with adrenergic antagonists. Androgen antagonists are also effective [Stone and Clejan, 1991], but they are not used due to their side effects on the male breast.

Testosterone and DHT are also active in the skin, where they appear to maintain normal secretory activity and hair growth. Excess androgens can cause acne and excessive hair growth on the body or face. Facial hair (hirsutism) is a common symptom of hyperandrogenism in women. In the scalp, where androgens have a different mechanism of action, excessive androgen levels cause male-pattern baldness (alopecia). As mentioned above, the 5-α-reductase inhibitor finasteride is used to treat hair loss.

Figure 1. Non steroidal SARMs 1, Flutamide; 2, Nilutamide; 3, Bicalutamide

Testosterone and DHT act via the androgen receptor (AR), which is a member of the nuclear receptor superfamily. Binding of an agonist ligand to the receptor induces conformational changes that result in binding of the receptor-ligand complex to DNA elements adjacent to target genes in the genome, followed by changes in gene expression. These gene expression changes lead to cellular effects including increases in proliferation and metabolic activity. Androgen antagonists bind to the receptor, preventing binding of the natural steroid, but do not produce the correct receptor conformational change. Thus, the classic view of receptor-antagonist complexes is that they fail to elicit normal changes in gene expression, disrupting androgen-signaling pathways. The androgen receptor ligand-binding domain has been crystallized [Matias et al., 2000; Sack et al., 2001], and it has the typical helical sandwich structure found in other nuclear receptors.

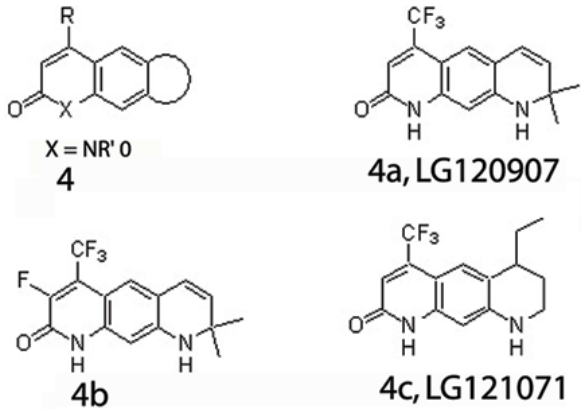


Figure 2. 2 quinolone and coumarins See text for more details.

In the past several years, the concept of tissue-selective nuclear receptor ligands has emerged. This concept has come to fruition with estrogens, with the successful marketing of drugs such as raloxifene. Raloxifene is an estrogen antagonist in some estrogen-responsive tissues (breast and uterus), and an agonist in others (bone). While the molecular mechanism of action of these selective estrogen receptor modulators (SERMs) is not understood, a commonly accepted hypothesis is that tissue-specific coregulators interact with the steroid receptor-ligand complexes to modulate their activities in different ways [Heinlein and Chang, 2002]. The discovery of SERMs has raised the possibility of generating selective compounds for other pathways, including androgens (that is, selective androgen receptor modulators, or SARMs) [Zhi and Martinborough, 2001]. For example, a compound that is an antagonist at the prostate, but an agonist or weak antagonist at the pituitary, would have an improved side effect profile over currently marketed androgen antagonists. Similarly, a compound that is a strong agonist on muscle, but an antagonist or weak agonist on prostate could be used to treat muscle-wasting conditions and age-related frailty, with a reduced concern for the potential to stimulate nascent or undetected prostate cancer.

There are four marketed androgen antagonists. Three are non-steroidal and the fourth (cyproterone) is a steroid with mixed progestational and androgen antagonist activities. Of the non-steroids, bicalutamide is currently the biggest seller, probably due to its long half-life relative to flutamide, which facilitates once-per-day dosing. However, flutamide has recently come on the market as a generic in the United States, which is likely to significantly impact the future sales of bicalutamide here. Bicalutamide itself will come off patent in 2008. Nilutamide's patent has also expired, but it was always a poor third to its competitors in terms of side effects and clinical use, and has not been developed as a generic compound.

There is a large body of literature supporting their efficacy in animal models of alopecia [Pan et al., 1998; Sintov et al., 2000] and in clinical trials treating alopecia [Diamanti-Kandarakis, 1999], hirsutism [Muderris et al., 2002; Venturoli et al., 1999; Venturoli et al., 2001] and acne [Carmina and Lobo, 2002]. A new androgen antagonist, RU 58841, is in phase II clinical trials in Europe for the topical treatment of acne and alopecia. As mentioned above, androgen antagonists also have clinical efficacy in BPH [Stone and Clejan, 1991].

To our knowledge, there are no non-steroidal androgens other than RU 58841 in clinical development. A number of companies, including Bristol Myers Squibb, Ligand Pharmaceuticals, GTx Technologies and Karo Bio have internal SARM research programs. The next section will review new classes of non-steroidal androgen receptor ligands that are in the public domain.

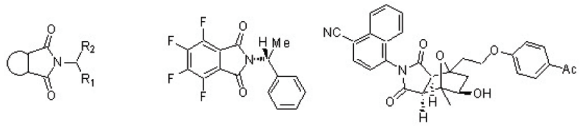
New Non-Steroidal Androgen Receptor Ligands

Some progress has been made in identifying new structural classes of non-steroidal SARMs since the launch of flutamide (Figure 1, Structure 1), nilutamide (Figure 1, Structure 2) and bicalutamide (Figure 1, Structure 3). Among many structures explored, the following three series have received the most attention: 2-quinolone and coumarins (Figure 2, Series 4),

phthalimide analogs (Figure 3, Series 5) and bicalutamide derivatives (Figure 4, Series 6).

2-quinolones

The structures of compounds 4a to 4c represent the 2-quinolones (Figure 2). Compounds 4a and 4b are potent AR antagonists while 4c is an agonist. As frequently seen in modulators of other steroid receptors such as the progesterone receptor, small structural changes can lead to the reversal of agonistic and antagonistic activity. Both 4a and 4b bind to AR in the nanomolar range, with Kis of 26 nM and 21 nM, respectively. Compound 4a seems more potent and more efficacious in a CV-1 cell functional assay (4a: 74% efficacy, 27 nM antagonist potency; 4b: 39% efficacy, 34 nM antagonist potency). In addition, 4b showed some agonist activity in the same cells (39% efficacy, 125 nM potency). However, in castrated immature male rats, 4b demonstrated better efficacy as an antagonist. It inhibited testosterone-induced increases in prostate weight and seminal vesicle weight (4a: ED50 [prostate] = 18 mg/kg, ED50 [seminal vesicle] = 19 mg/kg; 4b: ED50 [prostate] = 3.1 mg/kg, ED50 [seminal vesicle] = 7.5 mg/kg), and was orally active [Edwards et al., 2000]. Compound 4c binds to AR with similar affinity (Ki = 17 nM), but showed very good efficacy as an agonist in CV-1 cell functional assays (EC50 = 4 nM). In intact mature male rats, compound 4a did not raise serum levels of luteinizing hormone or testosterone, at 20 mg/kg or 40 mg/kg by the oral route. This was in contrast to flutamide and bicalutamide, which raised the levels of these hormones two- to eight-fold at these doses [Hamann et al., 1999]. Thus, compound 4a may have an advantage over current androgen antagonists because of its reduced potential for side effects in prostate cancer patients.



5 5a 5b

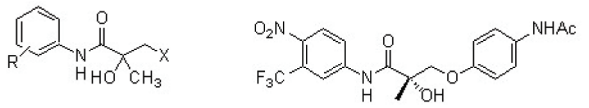
Figure 3. Phthalimide analogs See text for more details

Phthalamides

Phthalamides (Figure 3) such as 5a were identified as androgens antagonists with more potency than flutamide [Miyachi et al., 1997]. Recently, several series of compounds containing an imide moiety were reported as SARMs. For example, compound 5b was as potent as bicalutamide in a CWR22 human prostate cancer xenograft model [Salvati et al., 2002].

Bicalutamides

Bicalutamide derivatives (Figure 4) continue to receive attention as SARMs. One of the compounds from this series, GTx-007, showed an agonist effect in increasing the weight of the levator ani muscles of castrated male rats. It had a reduced stimulatory effect on prostate and seminal vesicles. In addition, the compound did not suppress luteinizing hormone and follicle stimulating hormone levels [Dalton et al., 2002].



6 6a, S-GTx-007

Figure 4. Bicalutamide derivatives See text for more details

Conclusion

Androgen receptor antagonists have found therapeutic use in the treatment of androgen-responsive prostate cancer for over two decades. This use will continue for the foreseeable future, but therapeutic regimens may change. In particular, androgen antagonist monotherapy, rather than CAB or antagonists in combination with orchidectomy, will likely see increased use, due to its relatively fewer negative effects on quality of life. Androgen antagonists will be approved for new clinical uses, including the treatment of hirsutism in women, alopecia in men and acne in both sexes. New SARM antagonists with improved tissue specificity, such as with reduced effects on the hypogonadal axis, will emerge for prostate cancer monotherapy, as well as for skin indications. It is possible that SARM antagonists will find use in BPH, provided that they have sufficient efficacy. New laboratory tools, such as the availability of crystal structures of the receptor for rational drug design, will facilitate the discovery of new SARMs.

A promising area of research is on the development of SARM agonists for increasing lean body mass and muscle strength in hypogonadal men and in cancer and immunodeficient patients. Ultimately, SARM agonists may be used to counteract the frailty associated with aging. As well as being extremely safe overall, such drugs will have to stimulate muscle strength without increasing the risk of prostate cancer. Their abuse potential will also be a factor impacting approval and marketing. Nevertheless, it is possible to see a day when tissue-specific androgens of many flavors will be of great medical benefit.

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