Selective Androgen Receptor Modulators in Drug Discovery: Medicinal Chemistry and Therapeutic Potential

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Abstract: Modulation of the androgen receptor has the potential to be an effective treatment for hypogonadism, andropause, and associated conditions such as sarcopenia, osteoporosis, benign prostatic hyperplasia, and sexual dysfunction. Side effects associated with classical anabolic steroid treatments have driven the quest for drugs that demonstrate improved therapeutic profiles. Novel, non-steroidal compounds that show tissue selective activity and improved pharmacokinetic properties have been developed. This review provides an overview of current advances in the development of selective androgen receptor modulators (SARMs).

Keywords: SARMs, AR, modulation, tissue selectivity, testosterone, dihydrotestosterone, estradiol, hypogonadism.

INTRODUCTION

The androgen receptor (AR) represents a tractable target that has enjoyed limited success based on the application of steroids as ligands [1]. The medicinal chemistry community is beginning to see the emergence of carefully designed non-steroidal ligands for the AR. Non-steroidal AR ligands offer numerous advantages over traditional steroid-based therapies. Recent peer-reviewed and patent publications have disclosed SARMs with improved pharmacokinetic properties and tissue selective activity. A handful of excellent reviews on non-steroidal AR ligands have been published [2-9]. This review will provide a comprehensive overview of the SARM literature up to August 2005 and will put particular emphasis on the therapeutic potential of this exciting class of molecules.

ANDROGEN RECEPTOR PHARMACOLOGY

Nuclear receptors (NRs) are a class of structurally related proteins that modulate gene expression by acting as ligand-dependent transcription factors [10]. The steroid receptors, namely the androgen receptor (AR), the estrogen receptor (ER), the glucocorticoid receptor (GR), the mineralo-corticoid receptor (MR), and the progesterone receptor (PR) represent a subclass of the nuclear receptor superfamily. NR ligands in this subclass exert their effects by binding to an intracellular steroid hormone receptor. In the presence of an agonist ligand the AR binds as a homodimer to the androgen response element (ARE), a consensus sequence for steroid receptors (GGTACAnnnTGTTCT) [11-13]. Selective DNA binding is conferred by the receptor's second zinc finger along with the C-terminal extension. Response elements are recognized as a direct repeat rather than the classical inverted repeat [14]. The AR has been shown to be localized in the cytoplasm in the absence of ligand [15]. Ligand binding causes dissociation of heat shock proteins and translocation to the cell's nucleus. The rate of nuclear transport has also been shown to be ligand dependent.

AR has numerous interaction partners allowing it to regulate transcription in many ways [12, 16]. As with many NRs, two major activation domains, the N-terminus AF-1 and the C-terminus AF-2 play key roles in binding interactions with coactivator and corepressor proteins. A major difference between AR and other NRs is the much stronger function of the AF-1 over the AF-2 domain. Interestingly, AF-1 domain function has been shown to be regulated by interaction with the AF-2 ligand binding domain (LBD) [13, 17]. Intra- or intermolecular contact of these termini in the AR homodimer provides interaction surfaces unique to the classical AF-1 and AF-2 domains.

NUCLEAR RECEPTOR MODULATION

Certain NR ligands are known to exert their action in a tissue selective manner [18]. This selectivity stems from the particular ability of these ligands to function as agonists in some tissues, while having no effect or even an antagonist effect in other tissues. The term "selective receptor modulator" (SRM) has been given to these molecules. A synthetic compound that binds to an intracellular receptor and mimics the effects of the native hormone is referred to as an agonist. A compound that inhibits the effect of the native hormone is called an antagonist. The term "modulators" refers to compounds that have a spectrum of activities ranging from full agonism to partial agonism to full antagonism. The molecular basis for this tissue selective activity is not completely understood. Particular ligands put NRs in different conformational states. These states influence the ability of coactivators, corepressors, and other proteins to be recruited by the NR. These unique cofactor-NR ensembles are the gene transcription factors that are thought to modulate tissue selective effects.

AR ligand-mediated effects are not limited to the classical genotropic mechanism outlined above. It is thought that some, if not all, tissue selective effects can be explained by a particular ligand's ability to potentiate non-genotropic

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1568-0266/06 $50.00+.00

pathways [19]. An example of ligand-activated induction of non-genotropic pathways is found in the work of S. C. Manolagas *et al.* [20, 21]. The action of a sex steroid NR on osteoblasts and other cell types is shown to involve the Src/Shc/ERK signaling pathway. This activity is mediated through the LBD of the sex steroid nuclear receptor alone. The DNA-binding domain (DBD) is not required to attenuate etoposide-induced apoptosis in HeLa cells. An NR lacking the DBD cannot function in the classical mode, acting as a transcription factor.

ACTIVITY OF ENDOGENOUS AR LIGANDS

Steroidal NR ligands are known to play important roles in the health of both men and women. In regard to men's health, testosterone (T) and dihydrotestosterone (DHT) are endogenous steroidal ligands for the AR that likely play a role in every tissue type found in the mammalian body. During the development of the fetus, androgens play a role in sexual differentiation and development of male sexual organs. Further sexual development is mediated by androgens during puberty. Androgens play diverse roles in the adult including stimulation and maintenance of male sexual accessory organs and maintenance of the musculoskeletal system. Cognitive function, sexuality, aggression, and mood are some of the behavioral aspects mediated by androgens. Androgens affect the skin, bone, and skeletal muscle, as well as blood lipids and blood cells [1].

The study of androgen action and male reproductive dysfunction continues to expand significantly. In fact, only recently has the definition of a disease state been associated with hormonal changes that occur in aging men. This syndrome, previously referred to as "Andropause", has more recently been described as Androgen Deficiency in the Aging Male, or "ADAM" [22]. The onset of ADAM is unpredictable and its manifestations are subtle and variable. Clinical manifestations of ADAM include fatigue, depression, decreased libido, erectile dysfunction as well as changes in cognition and mood.

Published information indicates that androgen replacement therapy (ART) in men may have benefits in terms of improving body composition parameters (e.g. bone mineral density, lean muscle mass, and strength) as well as improving libido and mood in some men. Andrologists and other specialists are increasingly using ART for the treatment of the symptoms of ADAM. This use is with due caution given potential side effects of androgens. Nonetheless, there is increasing scientific rationale and evidence for androgen deficiency and treatment in the aging male.

CURRENT ANDROGEN THERAPIES/LIMITATIONS OF STEROIDAL ANDROGENS

Current testosterone-based ARTs including injections, skin patches, gel-based formulations, and oral preparations suffer from rather severe limitations. When dosed orally, unmodified T is highly absorbed, but quickly cleared by the liver. Therefore, it is not possible to achieve the exposures required to see pharmacologic effects. In addition to the *in vivo* conversion to inactive metabolites, T is also converted to the active metabolites, dihydrotestosterone (DHT) and estradiol (E2) (Fig. **1**). The two major strategies to circumvent the metabolic degradation of testosterone are the parenteral administration of C17-OH testosterone esters, and the preparation of 17-alpha alkylated derivatives. Esterified T preparations, such as testosterone propionate, act as a slow

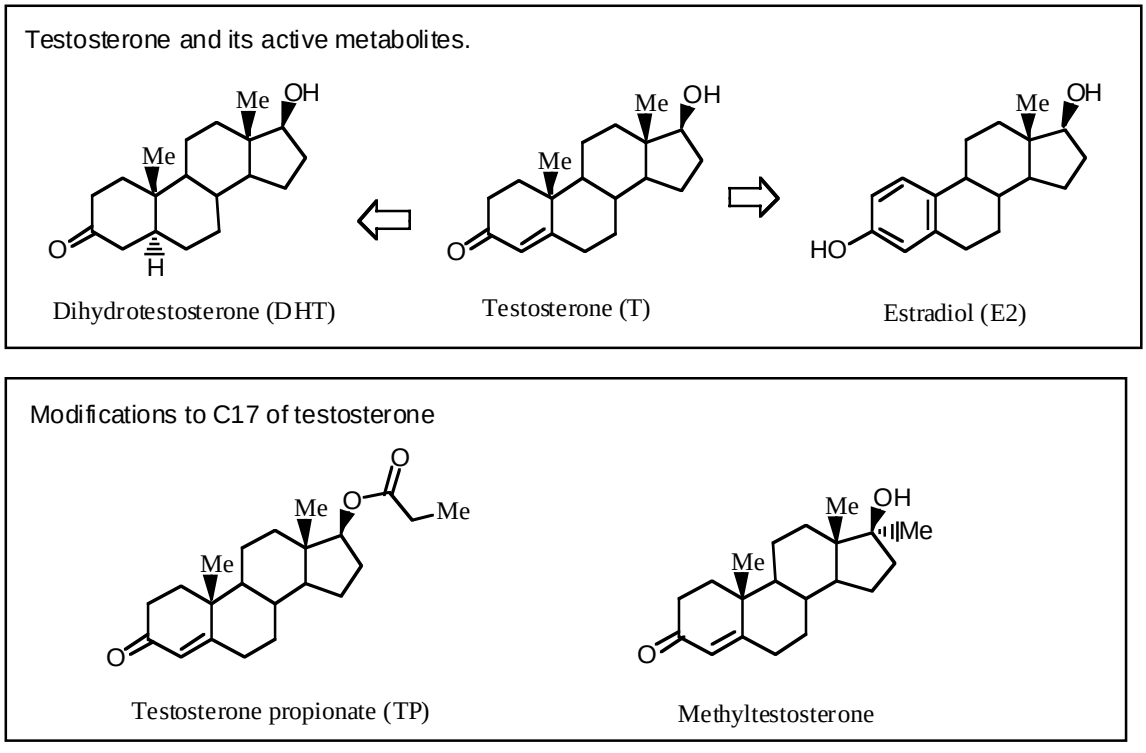


Fig. (1). Testosterone, active metabolites, and 17-position modifications.

release depots of testosterone when given as injections. Alkylated derivatives, such as 17-alpha methyl testosterone, are less prone to rapid hepatic metabolism, but are associated with hepatotoxicity.

In general, current ARTs fail to correctly mimic physiological testosterone levels and have potential side effects including exacerbation of pre-existing sleep apnoea, polycythemia (increased hematocrit), and/or gynaecomastia. Furthermore, the longer-term side effects on target organs such as the prostate or the cardiovascular system are yet to be fully elucidated. Importantly, the potential cancer promoting effects of testosterone on the prostate prevent many physicians from prescribing it to older men (i.e. age > 60 years) who, ironically, stand to benefit most from treatment. The need for a novel selective androgen receptor modulator (SARM) is obviated by the potential side effect profile manifested by conventional treatments. A SARM would ideally have all the beneficial effects of endogenous androgens, while sparing sexual accessory organs, specifically the prostate.

SARMs IN THE CLINIC

Currently there are no SARMs on the market, although a number of pharmaceutical companies have active research in this area including phase I starts. Animal studies with molecules that appear to have beneficial effects on muscle and bone, but spare the prostate have been disclosed [23, 24]. As our knowledge of tissue specific co-activator and co-repressor proteins increases, it is anticipated that the mechanisms of androgen receptor modulation will become greatly elucidated. Integration of this mechanistic understanding will facilitate the discovery of SARMs with increasing tissue specificity and improved safety and efficacy profiles.

SELECTIVE ANDROGEN RECEPTOR MODULATORS (SARMs)

The aim of this section is to provide a comprehensive overview and historical perspective of the different types of non-steroidal AR agonists (full or partial) that have been described in the peer-reviewed and patent literature.

While the focus of this review, and much of the AR medicinal chemistry literature in recent years, has been on tissue–selective AR agonists, the concept of tissue-selective activation of the AR was an integral part of the strategy of medicinal chemists in the 1980s involved in the discovery of AR antagonists for the treatment of prostate cancer. The goal of this earlier work was the discovery of a pure antiandrogen that would antagonize the effects of testosterone/DHT in the prostate, while showing little or no effect on the hypothalamic-pituitary axis (HPA). Research efforts by Tucker and coworkers at ICI ultimately led to the discovery of bicalutamide (Casodex), a currently marketed drug for the treatment of prostate cancer [25].

SARM MOLECULAR CLASSES

To facilitate the presentation, we have used an arbitrary classification of the different chemotypes according to characteristic chemical motifs, whether or not such motifs may represent pharmacophoric elements in these molecules (Table **1**). The discussion of each chemotype is further organized by company, beginning with the earliest published work for that chemical class.

1. N-Aryl Propionamides

The N-aryl propionamide series evolved from the antiandrogen bicalutamide (**3**), which is in turn a derivative of hydroxyflutamide (**2**), the active metabolite of flutamide (**1**) (Fig. **2**). Flutamide (**1**) was the first non-steroidal antiandrogen approved for the treatment of prostate cancer. Its antiandrogenic properties were discovered by Schering Corp., subsequently to its original preparation as a bacteriostatic agent. The structure of its active metabolite, hydroxyflutamide (**2**), became a lead molecule in the 1980s in the search for tissue-selective antiandrogens. In 1988, Tucker and co-workers at ICI reported the discovery of bicalutamide (**3**), an antiandrogen that displayed peripheral selectivity in rodent models. During the course of their investigations they also discovered a series of analogs that demonstrated mixed agonist-antagonist activity *in vivo* [25].

SAR studies around the hydroxyflutamide template included modifications to the nitrobenzene ring, the central amide region and incorporation of thioether substituents on the propionamide chain. Tucker *et al.* discovered that analogs in the thioether series, that incorporated a CF_3 group on the hydroxyl-bearing carbon, displayed agonist activity *in vivo* (as indicated by an increase in the prostate weight of castrated rats). Analogs **4** and **5** (Fig. **3**), in particular, demonstrated very strong agonist effects, comparable to Testosterone propionate (TP). In contrast, analogs with the corresponding alpha-methyl substituent displayed only antagonist activity [25].

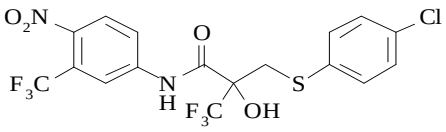
Tucker *et al.* hypothesized that the agonism (full or partial) observed with the alpha-CF_3 analogs could be attributed to the enhancement by the CF_3 group on the hydrogen bond-donor ability of the adjacent OH, which could result in tighter binding to the AR. Empirical data in other series and physicochemical studies by Morris *et al*. on this series of 2-hydroxypropionalides provided further support to the notion of a critical hydrogen bond interaction between these ligands and the receptor, similar perhaps to the C17-OH interaction with testosterone or DHT [26]. Furthermore, these physicochemical studies showed that the dominant conformation of the 2-hydroxy-carboxamide is that with the amide NH eclipsed with the OH group. This conformation will not only enhance the hydrogen bond donor ability of the OH group, but also ensure a planar arrangement, akin to the planar structures of the natural ligands.

Additional SAR findings by Tucker *et al.* in this series of anilide antiandrogens (which confirmed previous data with flutamide analogs) were found to be equally applicable to subsequent series of AR agonists that shared the A-ring aniline motif. These key structural features common to both agonists and antagonists can therefore be ascribed to important, if not critical, binding interactions between these ligands and the AR. The key SAR findings are summarized below [25, 27]:

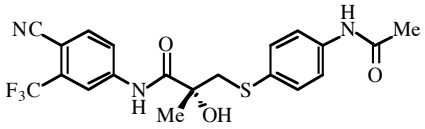
1) Optimal activity was generally found for 3, 4-disubstituted anilides with cyano or nitro in the 4-position and chloro or trifluoromethyl in the 3-position.

Table 1. Examples of SARM Chemotypes

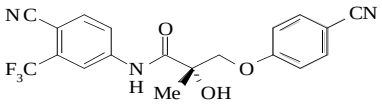
1. N-ARYL PROPIONAMIDES (BICALUTAMIDE DERIVATIVES)



4, ICI (1988)

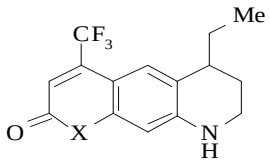


114, University of Tennessee (1998)

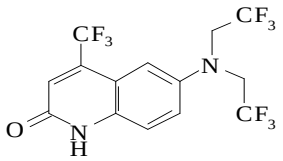


11, GTx (2005)

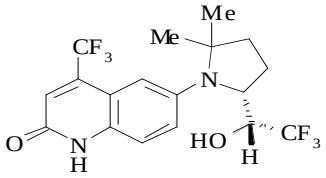
2. QUINOLONES AND COUMARINS



X = NH **(22)**, O **(38)**
Ligand Pharmaceuticals (1996)

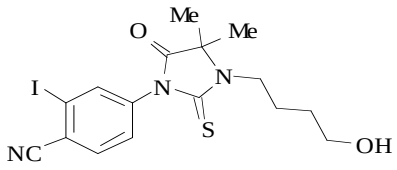


26, Ligand Pharmaceuticals (2001)

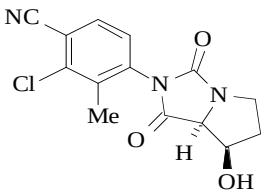


29, Ligand Pharmaceuticals (2005)

3. HYDANTOIN AND SUCCINIMIDE DERIVATIVES

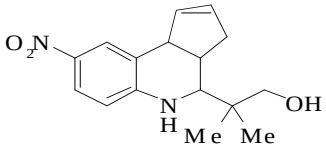


55, University of Michigan (2000)

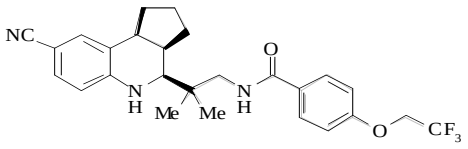


59, Bristol-Myers Squibb (2003)

4. 6-NITRO(CYANO)TETRAHYDROQUINOLINES

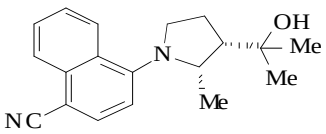


64, Kaken Pharmaceuticals (2001)

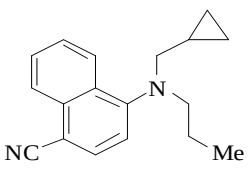


72, Kaken Pharmaceuticals (2004)

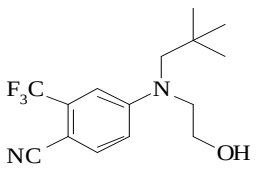
5. 4-CYANO(NITRO)ARYLAMINES



76, Takeda Pharmaceuticals (2004)



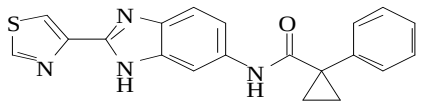
79, GlaxoSmithKline (2004)



82, GlaxoSmithKline (2005)

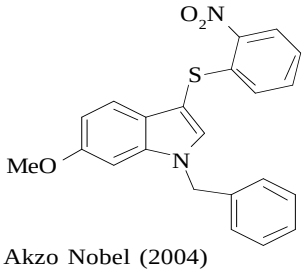
(Table 1) Contd….

6. CARBONYLAMINOBENZIMIDAZOLES



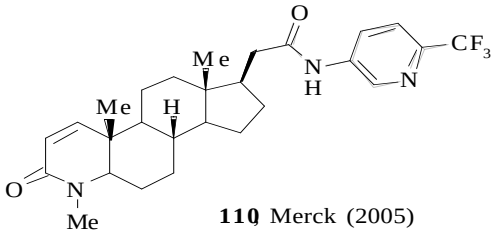
96, Merck (2004)

7. 3-(2-NITROPHENYL)THIOINDOLES

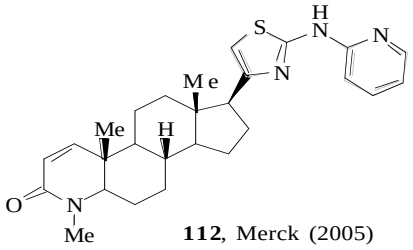


105, Akzo Nobel (2004)

8. 4-AZASTEROIDS



110, Merck (2005)



112, Merck (2005)

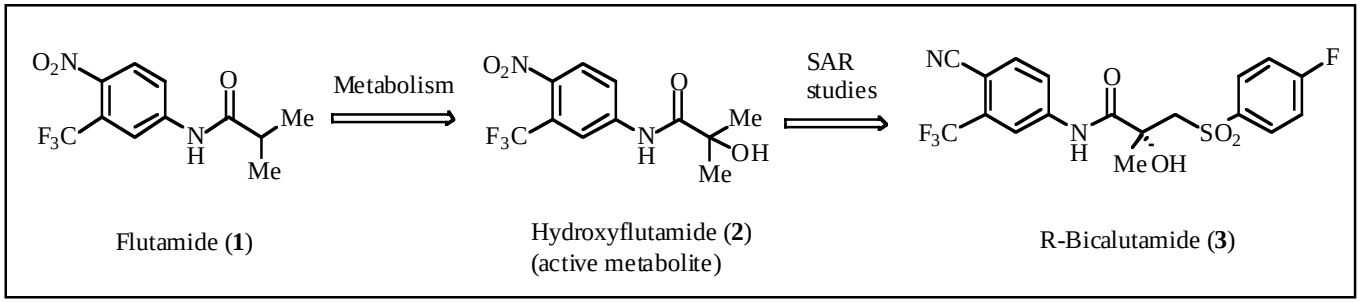


Fig. (2). Nonsteroidal antiandrogens.

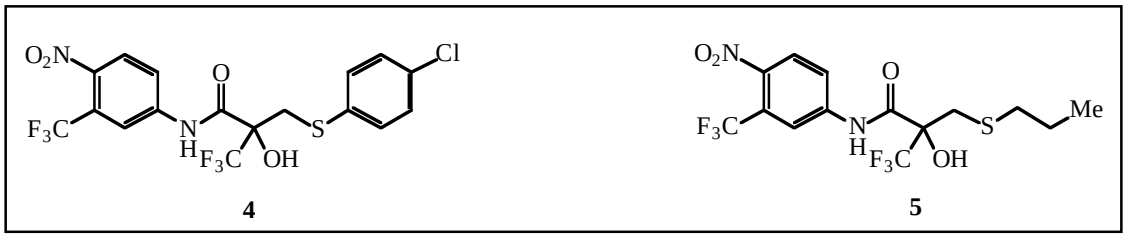


Fig. (3). α-Trifluoromethyl bicalutamide analogs with *in vivo* AR agonist activity.

2) The amide and the tertiary carbinol were critical for activity in this series.

3) The nature and stereochemistry (R preferred in the bicalutamide template) of the substituents attached to the hydroxyl-bearing carbon greatly influenced the biological profile.

4) The sulfoxide and sulfone analogs (that formed readily *in vivo*) have similar antiandrogenic activity to their thioether counterparts.

Because ICI scientists were pursuing molecules with antagonist properties, this series of N-aryl-propionamides with agonist activity was not further pursued.

Ten years later, in 1998, Dalton *et al*. at the University of Tennessee, came across a series of potent AR N-aryl propionamide agonists during studies of electrophilic affinity ligands for the AR [28]. The thioether **6** was the most potent analog with a K_i of 1.7 nM (DHT = 0.3 nM; bicalutamide = 11 nM) and full agonist response in a transactivation assay (at 100 nM, **6** produced the same maximal response as DHT at 1nM) (Fig. **4**). The smaller bromo intermediate **7** showed even tighter binding (0.3 nM), but lower cellular potency (83% maximal response at 500 nM). Similar to observations with the previous bicalutamide analogs, the (R)- enantiomers showed greater activity than the (S)-enantiomers.

These results represented a significant break from the SAR delineated by Tucker *et al*. since none of the previously reported α-methyl analogs displayed agonist activity.

Over the last 7 years, J. T. Dalton, D. D. Miller and collaborators at the University of Tennessee, The Ohio State University, and GTx Inc. have investigated extensively the SAR of the N-aryl propionamide template and have pioneered efforts to investigate the biological activities of this class of SARMS and their multiple potential therapeutic applications [3]. Highlights of their published SAR and PK findings are summarized below.

A-ring (Anilide)

1) The preferred substitution pattern is analogous to the antiandrogen series, with NO_2 and CN optimal at the 4-position. NO_2 affords slightly tighter binding, but undergoes metabolic reduction, which could explain the higher *in vivo* clearances of these analogs [3, 30].
2) Replacement of the 3-CF_3 with Cl or iodo maintains high binding affinity [29].
3) Certain heterocyclic derivatives of the anilide ring show poor binding affinity [3].

Propionamide

1) Thioether analogs generally showed 2 to 3-fold better binding affinity and significantly better functional potency than the corresponding sulfone analogs [31].
2) Replacement of sulfur with oxygen maintains high binding affinity, enhances transcriptional activity in functional assays, and improves metabolic stability [32, 33].
3) Enantiomers with the S-configuration are ~40-fold more potent than R-enantiomers (note: enantiomer assignment changes when S is replaced with O) [34].
4) Replacement of the α-methyl with CF_3 (racemic mixtures) maintains high binding affinity [31].

B-Ring (Aryl Ether/Thioether)

1) Proper substitution is critical for agonist activity. Para or/and meta substitution seems optimal, with F, Cl, CN, NO_2 and NHAc affording some of the highest activities [3, 35].
2) In a series of para-substituted halogen derivatives binding affinities decreased with increasing halogen size [32]. Interestingly, PK studies demonstrated lower clearances, longer $t_{1/2}$s, and higher AUCs as the size of the halogen increased [3, 36].

The biological activity and therapeutic potential of lead molecules in this class has been investigated by Dalton *et al*. in different animal models of androgen-associated conditions such as osteoporosis, muscle wasting, benign prostatic hyperplasia and male contraception [24, 30, 32, 37-40]. For example, studies with **8** and **9** (Fig. **5**) in castrated rats demonstrated agonist activity in the levator ani muscle (LA) (anabolic effect), while exerting reduced activity in prostate (P) and seminal vesicles (SV) (androgenic effect) [24, 30, 32].

Compound **10** was also evaluated *in vivo* [39, 40]. In castrated rats, **10** demonstrated very potent, dose-dependent selective androgenic and anabolic effects. Recently, analog **11** was reported as displaying the highest *in vivo* AR pharmacological activity to date [29, 36]. In castrated rats, **11** demonstrated strong anabolic and androgenic effects with ED_{50}s of 0.03, 0.12 and 0.39 for LA, P and SV, respectively. Several molecules in this chemical class are reportedly at various stages of preclinical and clinical development (GTx Inc, Ortho Biotech).

Recently Dalton at al. solved the x-ray co-crystal structure of the antagonist R-bicalutamide complexed with the LBD of a W741L AR mutant isoform [41]. It is anticipated that this binding mode is representative of the orientation of the structurally-related N-aryl proprionamide agonists. Further support for this hypothesis comes from the fact that R-bicalutamide displays agonist activity in cells transfected with the mutant AR. Comparison by Dalton *et al* of their crystallographic data with that previously described for DHT bound to the wild type AR LBD revealed the following key observations:

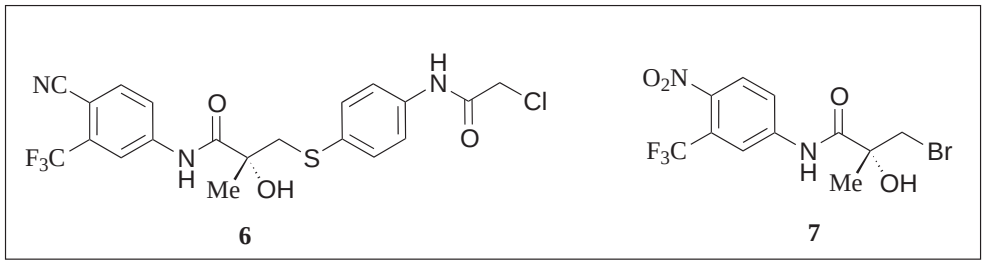
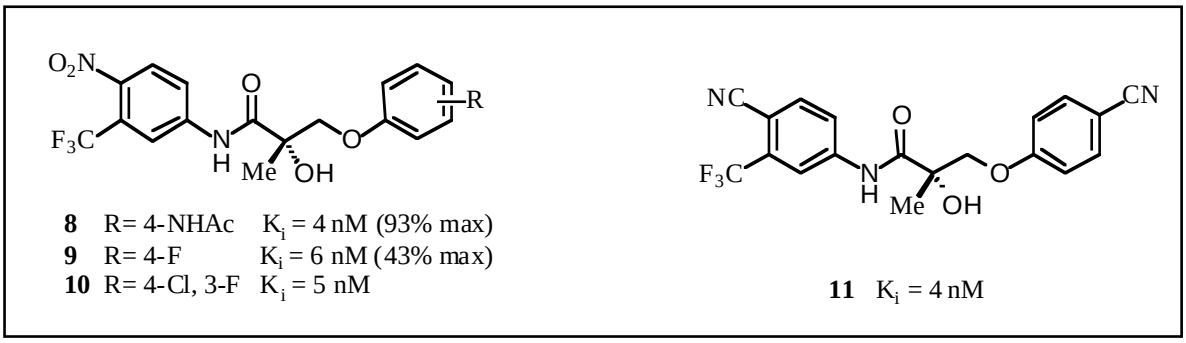


Fig. (4). First α-methyl bicalutamide analogs demonstrating *in vitro* AR agonist activity.



8 R= 4-NHAc K_i = 4 nM (93% max)
9 R= 4-F K_i = 6 nM (43% max)
10 R= 4-Cl, 3-F K_i = 5 nM

11 K_i = 4 nM

Fig. (5). N-Aryl propionamide SARMS.

1) The 4-cyano group mimics the 3-carbonyl of DHT (H-bonding interactions with Arg-752 and possibly Gln-711).
2) The A-ring of bicalutamide partially overlaps the region occupied by the AB rings of DHT (establishes hydrophobic interactions with surrounding amino acid residues).
3) The 3-CF_3 group occupies a hydrophobic space unoccupied by DHT.
4) The amide NH appears to H-bond with the backbone oxygen of Leu-704
5) The hydroxyl group H-bonds with Asn-705, but not with Thr-877 (both of these residues interact with C-17 OH of DHT).
6) The N-aryl-carboxamide fragment of the molecule effectively mimics the planar arrangement of the steroidal ligand.
7) The extended substituent containing the aryl-sulfone moiety bends out of the planar arrangement and lies alongside helix 12, establishing hydrophobic interactions with the receptor.
8) The sulfone moiety seemingly causes displacement of Met-895, an interaction that would be detrimental for the wild type AR agonist conformation, since the presence of nearby Trp-741 in the wild type AR further increases the bulk in this area.

This last observation has led Dalton *et al.* to suggest that steric impingement could be responsible for the antagonist profile displayed by sulfone analogs in the wild type AR.

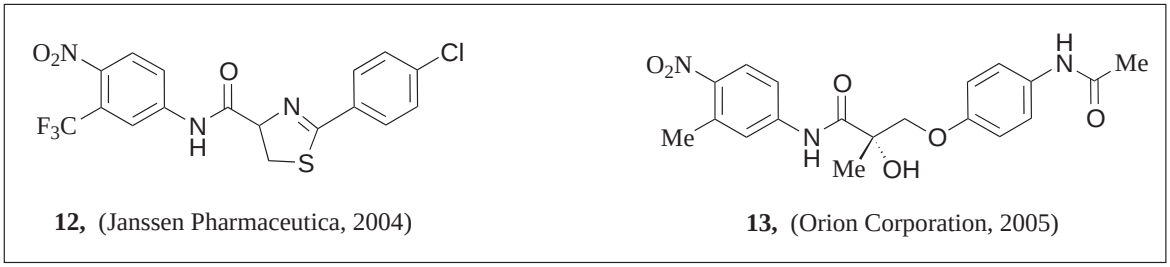
Two other publications have recently appeared concerning the N-aryl proprionamide chemical class. In 2004, a patent application by Janssen Pharmaceutica described a series of thiazoline derivatives as SARMs (Fig. **6**) [42]. The thiazoline ring constraint in the linker region is the distinguishing feature. AR binding was reported for three compounds (no agonist data) with **12** as a representative example (61% inhibition of ^{3}H R1881 at 1μM).

In 2005, a patent application by Orion Corporation described N-aryl propionamide derivatives with a chemical scaffold very similar to those published by Dalton and Miller [43]. The only distinction in this series is the 3-substituent in the anilide ring claimed as alkyl, hydroxyalkyl or alkylformyl. Ninety-three compounds were exemplified with preferred molecules having a 4-nitro-3-methyl (or ethyl) aniline motif. Compound **13** (103% inhibition of ^{3}H mibolerone at 0.2 μM) was evaluated in immature male rats and demonstrated tissue-selective anabolic and androgenic activity.

2. Quinolone and Coumarin Derivatives

Ligand Pharmaceuticals first described this entirely novel class of SARMS in a patent application in 1996 [44]. Screening efforts against several nuclear receptors led to the discovery of the lead molecule **14** which displayed AR antagonist activity (IC_{50}= 43 nM) (Fig. **7**). Initial SAR studies around this template led to improvements in AR antagonist potency and selectivity [45]. Several members of this chemical series demonstrated oral activity, with efficacy superior to flutamide in animal models (analog **15**, Fig. **7**).

In the pursuit of molecules with an agonist profile, Ligand Pharmaceuticals carried out an extensive and elegant SAR investigation of this chemical scaffold. These efforts have led to the discovery of very potent and selective AR agonists across diverse chemical templates. Publications by Ligand and recent AR reviews have described detailed



12, (Janssen Pharmaceutica, 2004)

13, (Orion Corporation, 2005)

Fig. (6). N-Aryl propionamide derivatives.

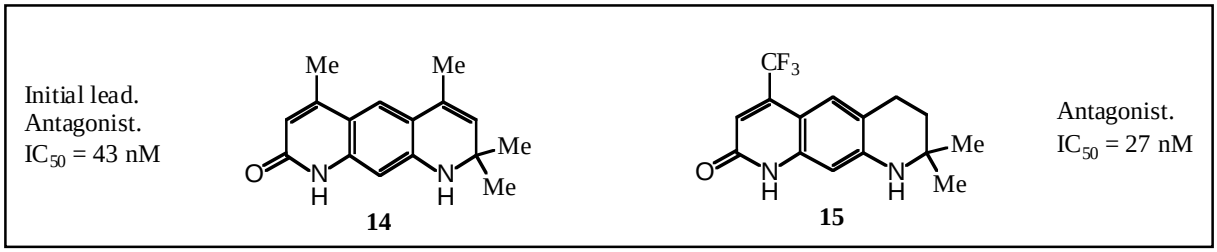


Fig. (7). Quinolone AR antagonists.

aspects of the SAR and biological activities of compounds in this class [4]. A summary of those studies and highlighted specific examples from each chemical series are described below.

The basic Ligand chemical motif is characterized by a bicyclic quinolone or coumarin template that can be viewed as mimicking the AB ring system of testosterone. Further substitution on the scaffold's aryl ring mimics the CD ring system of testosterone. In essence, the diverse polycyclic chemical series exemplified by Ligand in recent years are differently constrained modifications of 6-substituted quinolone or coumarin derivatives (Fig. **8**).

2a. Linear Tricyclic and Tetracyclic Analogs

Ligand scientists investigated extensively the SAR around the piperidine moiety of the lead molecule **14**, exploring different substitution patterns and replacing the piperidine ring by other heterocycles (general structure **17**, Fig. **8**). These investigations led to the discovery of tricyclic and tetracyclic quinolone derivatives that displayed full agonist activity on the AR, with potencies comparable to or higher than DHT. Some of the more interesting molecules in this series are shown in Fig. (**9**).

Key features of the SAR and PK properties of the quinolone and coumarin series are summarized below [46-50]:

1) The 4-CF_3 substituent generally improved PK properties and solubility *vs.* the corresponding 4-methyl analogs [45].
2) Proper substitution at the 2-, 3-, and 4-position of the piperidine ring (or 2- and 3-position of the pyrrolidine) is tolerated.
3) Geminal substitution adjacent to the piperidine nitrogen (as in **14** and **15**) is associated with antagonist activity.
4) The size, positioning, and stereochemistry of the substituents on the C-ring heterocycles strongly influenced the agonist profile of the molecule, with a preference for short alkyl and cyclic derivatives. The subtle SAR reported for this region reflects the SAR for steroids, where structural modifications around the steroid D-ring confer dramatic shifts in potency and functional activity.
5) Selectivity against other steroidal receptors (e.g. GR, MR, PR) was generally good, although some analogs also displayed moderate PR antagonist activity.
6) The piperidine ring can be replaced with a variety of other heterocycles (for ex. pyrrolidine, pyran, morpholine, oxazine and thiazine). When properly substituted, these novel tricyclic analogs displayed good potency and full agonist activity.

Compound **22** (LGD-121071) was reportedly the first known orally-active nonsteroidal AR agonist [48]. In a two-week study in castrated rats, at a dose of 20 mg/kg, **22** was fully efficacious at suppressing the castration-induced elevation of luteinizing hormone (LH), an *in vivo* measurement of AR agonist activity. Ligand later reported the *in vivo* evaluation of other analogs in this series, including the oxazino derivative **25** [50]. In the castrated rat model, **25** demonstrated 300% growth of the levator ani over vehicle treated castrates without significant effects on ventral prostate.

2b. Bicyclic Analogs

In a 2001 patent application, Ligand described a series of structurally simplified bicyclic quinolone derivatives [51]. The most potent analogs were derivatized at the 6-position with small disubstituted amines (exemplified by **26**, Fig. **10**) or with small cyclic amines (exemplified by pyrrolidine **27**

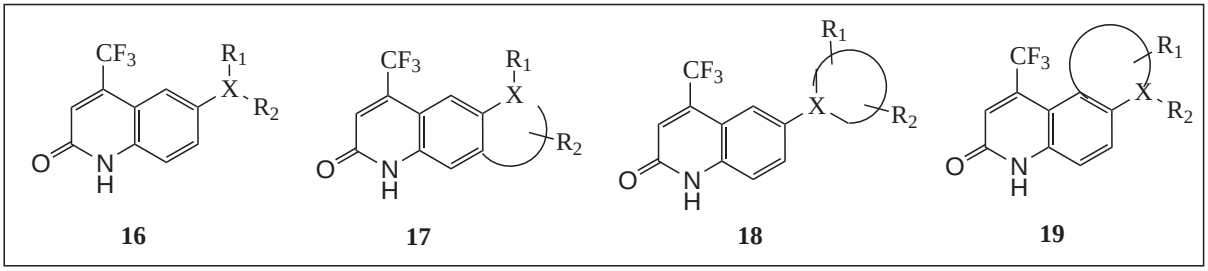


Fig. (8). Quinolone templates explored by Ligand Pharmaceuticals.

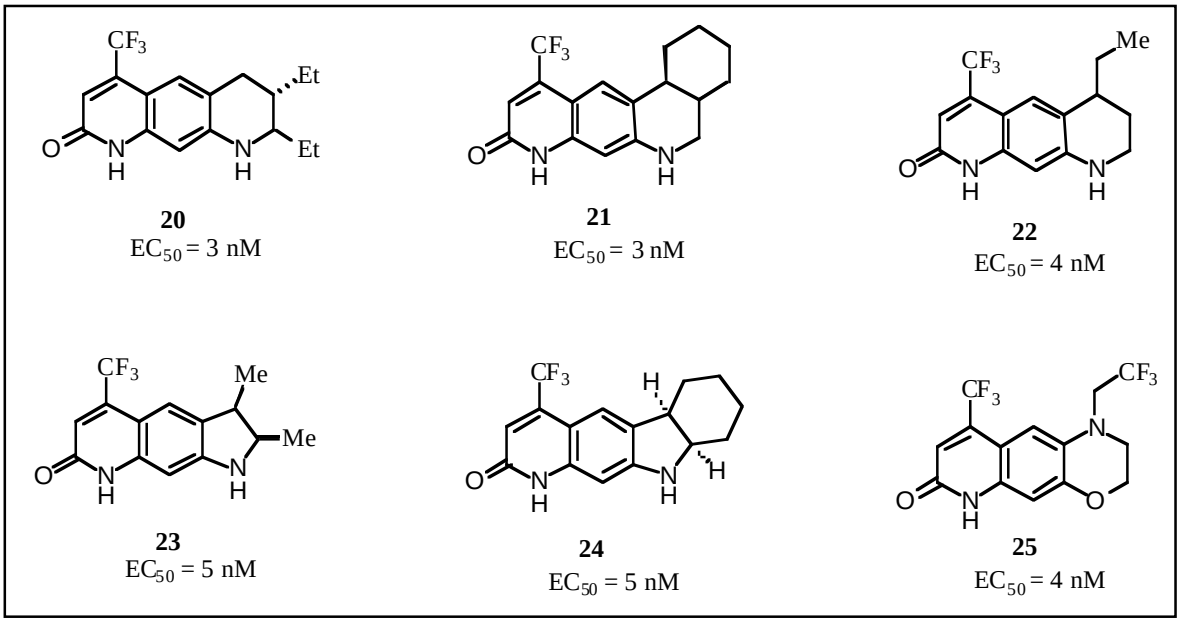


Fig. (9). Linear tricyclic and tetracyclic quinolone AR agonists (Ligand Pharmaceuticals).

and piperidine **28**).

Analogous to the sensitive SAR observed in the tricyclic template, functionalization of the amine moiety with small alkyl or fluoroalkyl substituents is critical for potency and full agonist activity. Other analogs incorporated hydroxyl groups, likely targeting the H-bonding interactions enjoyed by the 17-OH of testosterone. The biological activity of **26** (LGD-2226) was further investigated in several animal models of androgen-deficiency [52].

2c. Angular Tricyclic and Tetracyclic Analogs

Angular tricyclic and tetracyclic analogs were described by Ligand in two patent applications in 2002 [53, 54]. A variety of 5,6-fused heterocyclic derivatives were prepared that yielded novel tricyclic and tetracyclic AR agonists, such as indoline **30**, indole **31**, and oxazine **32** (Fig. **11**). Substitution on the C-ring is tolerated, with small alkyl or fluoroalkyl substituents imparting the best potencies and full agonist activity. The oxazine analog **32** was one of the most potent compounds described (10 times more potent than DHT in a functional assay).

2d. Coumarin and Quinolone Analogs

Ligand also investigated structural modifications to the pyridone portion of the quinolone system (some examples illustrated in Fig. **12**) [51]. Below is a summary of the most salient SAR features:

1) The 4-CF_3 group can be replaced with methyl (see **26** and **34**). CF_3, however, has been reported to enhance PK and solubility properties.

2) Fluorine on the 3-position yields equipotent analogs.

3) Methylation of the quinolone nitrogen generally results in a substantial loss of potency and/or a switch to an antagonist profile (**26** vs. **35**).

4) The quinolone NH can be replaced with oxygen (coumarin template; as in **33**).

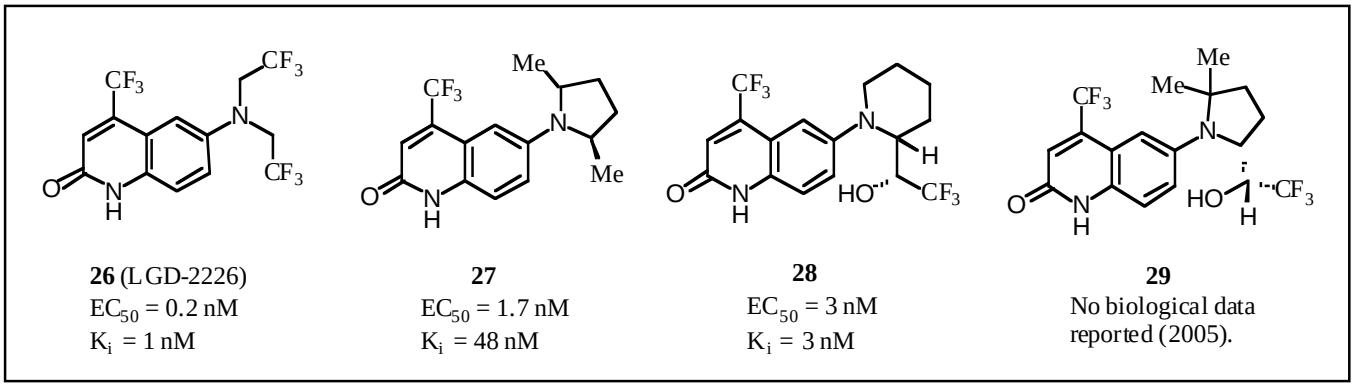


Fig. (10). Bicyclic quinolone AR agonists (Ligand Pharmaceuticals).

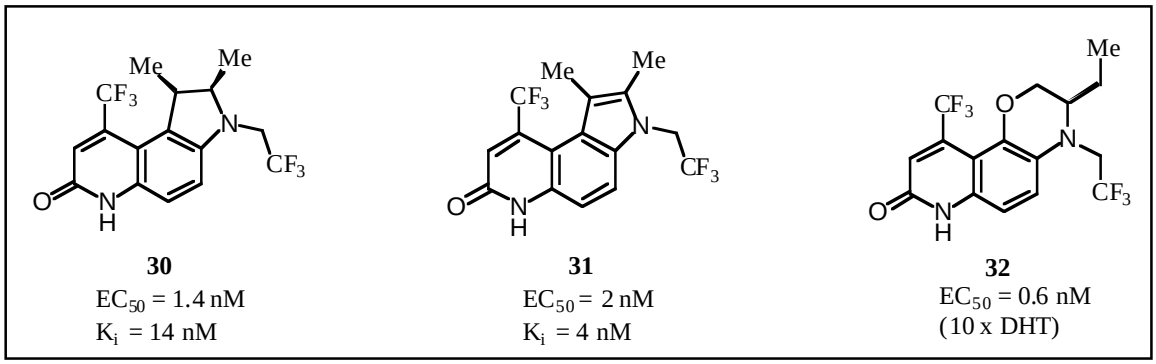


Fig. (11). Angular tricyclic quinolone AR agonists (Ligand Pharmaceuticals).

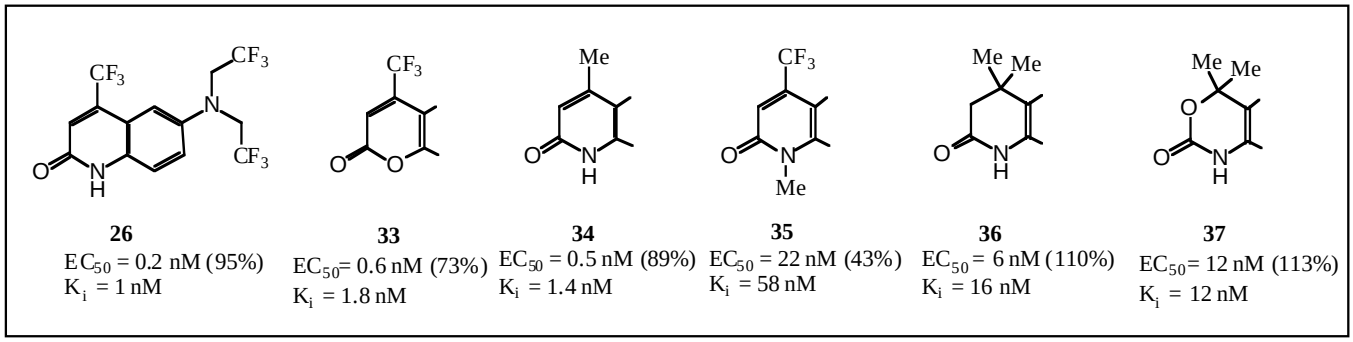


Fig. (12). Modifications to the A-ring lactam of bicyclic quinolones.

5) Replacement of the pyridone carbonyl with a thiocarbonyl resulted in a 10-fold drop in potency.

Analogs in the coumarin series are among the most potent AR agonists in this chemical class (Fig. **13**) [55, 56].

In some instances, the A-ring lactone altered significantly the agonist/antagonist profile of these molecules. For example, lactone **40**, a direct analog of the quinolone antagonist **15**, is a 9 nM agonist with 64% efficacy of DHT.

Ligand also investigated the replacement of the lactam moiety by 2-substituted pyridines. These studies indicated that a strong hydrogen-bond acceptor in the 2-position of the A-ring is likely optimal for AR activity. For instance, in an antagonist scaffold (see Fig. **14**), the 2-cyano pyridine analog **41** was the best isostere for the lactam ring, although the 2-fluoro analog **42** and a 2-chloro-substituted analog (not shown) also displayed good binding affinities [57]. In another series, 2-CN and 2-Br pyridine analogs (**43** and **44**) displayed good potencies although with partial agonist activity [58].

A 2005 patent application by Ligand Pharmaceuticals described 6-pyrrolidinyl- and 6-piperidinyl-quinolinones, exemplified by **29** (Fig. **10**), in which the SAR around the pyrrolidine or piperidine moieties were further explored (no biological data) [59].

In the last few years, other companies have reported derivatives in this quinolone and coumarin class. Pfizer, in a 2000 European patent application, described the preparation of the (-)-enantiomer of the coumarin analog **38** (Fig. **13**) [60]. The racemic mixture of **38** had been reported in a 1996 patent application by Ligand Pharmaceuticals [56]. In the Ligand patent, **38** was described as a potent AR agonist in cellular assays (EC_{50}= 2 nM, 119% efficacy; K_i = 0.3 nM). The binding IC_{50} for the enantiopure isomers reported by Pfizer were 5 nM for the (-) enantiomer and 112 nM for the (+) enantiomer.

Kaken Pharmaceuticals, in a 2003 patent application, described a series of carboxyaminocoumarins as AR agonists and antagonists [61]. These molecules are hybrids of coumarins, hydroxyflutamide and bicalutamide analogs. Modifications to the lactone ring included saturated and unsaturated derivatives and replacement of the 4-CF_3 with H or Me. The propionamide substituent was positioned at either the 6- or 7-position and was additionally substituted with aryl ethers or benzamides. Biological data was reported for compounds **45**, **46** and **47** (Fig. **15**), displaying 58%, 49% and 64% inhibition of T binding, respectively.

In a 2003 patent application, Merck described a series of quinolones and coumarin derivatives with a fused 7-member azepine ring which was optionally substituted [62]. Compounds **48**-**50** (Fig. **16**) are representative examples (no biological data reported).

Ortho-McNeil Pharmaceuticals, in a 2003 patent application, described a series of quinolone derivatives that incorporated other fused heterocycles, such as dioxane and thiomorpholine [63]. These analogs, exemplified by

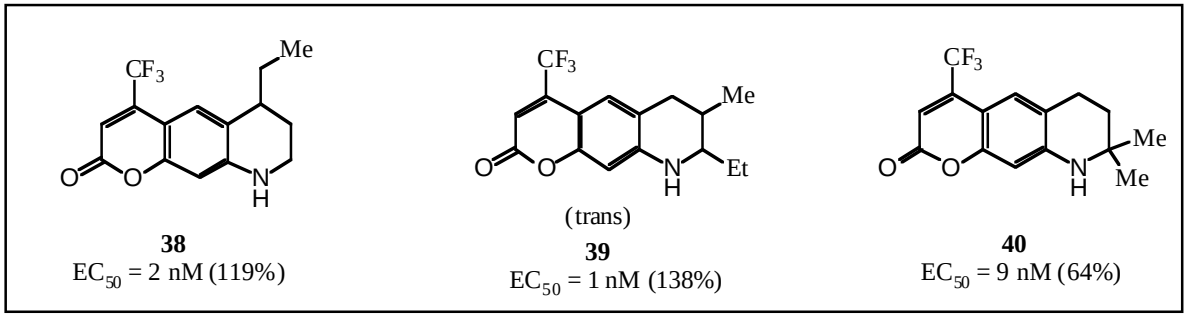


Fig. (13). Coumarin AR agonists (Ligand Pharmaeuticals).

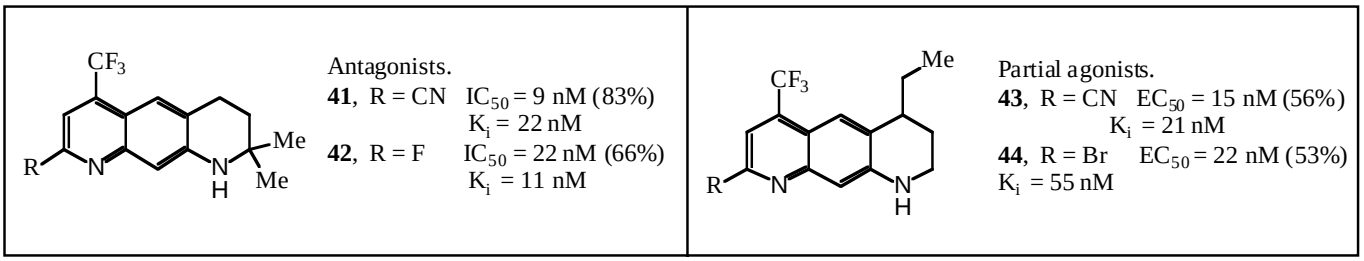


Fig. (14). A-ring pyridine derivatives. Antagonist and partial agonists.

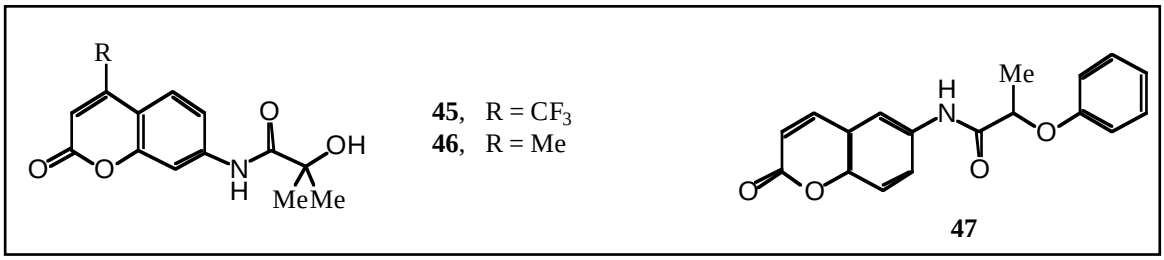


Fig. (15). Hybrid analogs of coumarins and hydroxyflutamide. Kaken Pharmaceuticals (2003).

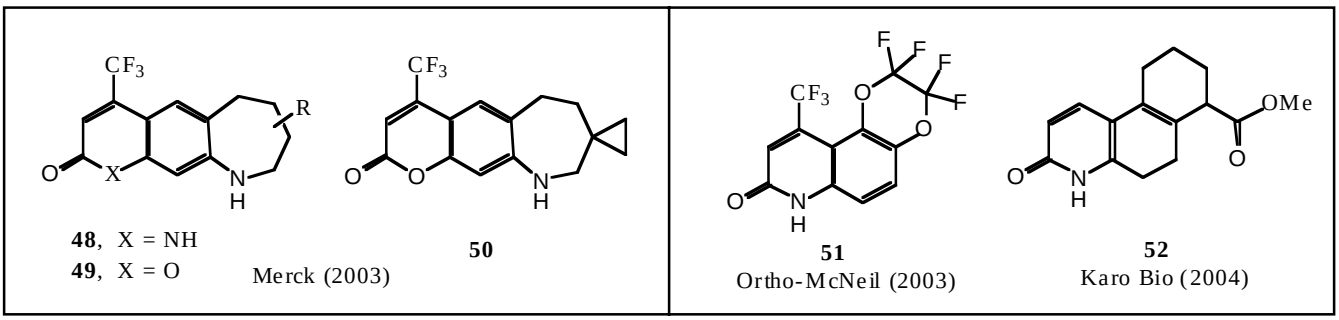


Fig. (16). Other coumarin and quinolone analogs.

compound **51**, displayed binding affinities for the AR in the μM range.

Karo Bio AB, in a 2004 patent application, described a small number of pyridone derivatives, exemplified by compound **52**, that are ligands for several of the steroid receptors, including AR, with IC_{50}s in the range of 1 to 100 μM [64].

3. N-Aryl Succinimide and Hydantoin Derivatives

The N-aryl succinimide and hydantoin class of molecules also evolved from known antiandrogen structures, such as nilutamide (**53**) and RU-59063 (**54**) (Fig. **17**).

AR-mediated transcriptional activation by molecules in this class was first reported by Van Dort *et al.* at the University of Michigan in 2000 [65]. In their search for

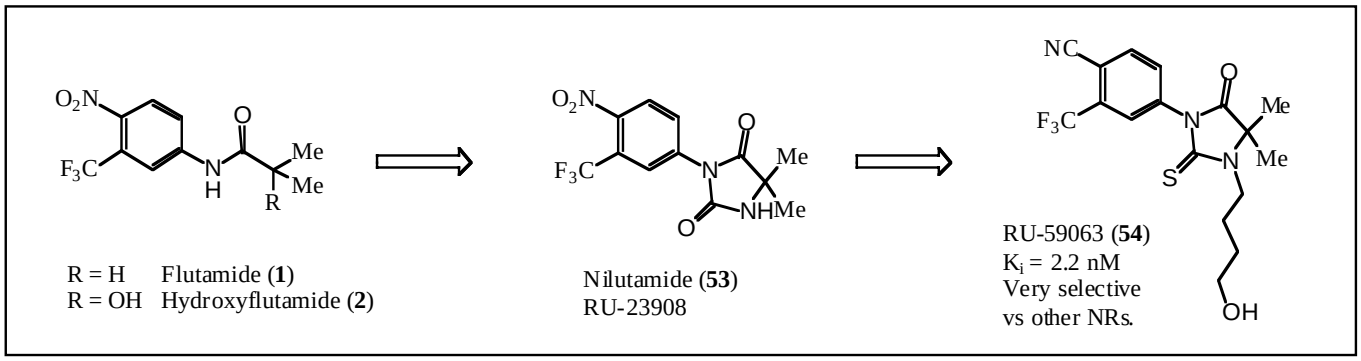


Fig. (17). Antiandrogen compounds.

radioiodinated AR ligands, they synthesized the thiohydantoin **55** (Fig. **18**), a direct analog of RU-59063 (**54**), with iodo replacing the 3-CF_3 group. **55** displayed subnanomolar AR binding affinity and, most surprisingly, it displayed potent agonist activity in cotransfection assays (mouse AR). Iodo for CF_3 replacement enhanced binding affinity three-fold. Interestingly, however, and in contrast to the potent antiandrogenic activity reported in rodent models, RU-59063 displayed dose-dependent agonist activity in these cotransfection assays, albeit with inferior efficacy to DHT and the iodinated analog **55**.

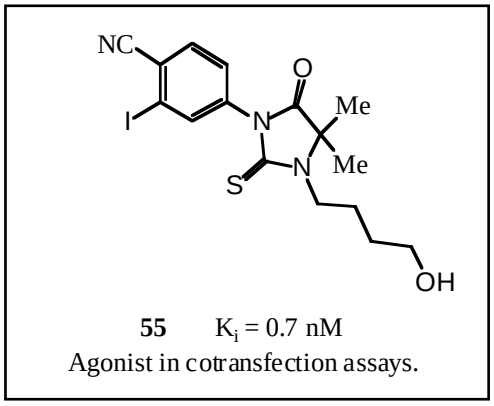


Fig. (18). Thiohydantoin AR agonist *in vitro.*

In 2001, Bristol Myers Squibb (BMS) reported the first X-ray co-crystal structures of the LBDs of the AR and its T877A mutant (the LNCaP mutation) complexed with DHT [66]. BMS scientists utilized this crystallographic information in a program originally aimed at the discovery of AR antagonists for the treatment of prostate cancer. They also utilized the structural motifs from known antiandrogens, and the structures of lead molecules derived from initial screening effort to design AR ligands that would antagonize the wild type and mutant AR isoforms common to metastasized prostate cancers [67]. Ultimately, a combination of empirical SAR studies and computer modeling led to the identification of AR ligands with a spectrum of functional activities.

In 2002 and 2003 a series of patent applications by BMS described the preparation of tricyclic, bicyclic and monocyclic succinimide and hydantoin derivatives as modulators of the AR or modulators of nuclear hormone receptor function [68-76]. Although no biological data was disclosed in the patent applications, details about the SAR and biological activity of members of this chemical class have recently been reported. These reports included the synthetic progression from an antagonist to an agonist scaffold and biological and crystallographic data on an antagonist series.

The lead chemical template for the antagonist program was provided by a series of bridged tricyclic succinimide derivatives (exemplified by **56**, Fig. **19**) that were identified in initial screening efforts as well as a closely related series of hydantoin analogs (exemplified by **57**).

Modifications of the bridged structure to a smaller bicylic system and appropriate placement of a hydroxyl group led to the discovery of a series of AR agonists exemplified by analog **58**. The smaller bicyclic structures minimize steric crowding in the binding site, while the hydroxyl substituent mimics the C-17 OH of DHT and establishes a critical interaction with Asn 705. The anilide region was also optimized to eliminate toxicity concerns related to the mutagenicity of some of these anilide derivatives or their metabolites [77]. These optimization efforts led to the discovery of BMS-564929 (**59**), a very potent and tissue-selective AR agonist. In the castrated rat model, BMS-564929 displayed 160-fold selectivity for levator ani vs. prostate growth (ED_{50} 0.9 *vs* 141 μg/kg, respectively), compared to 2-fold selectivity for testosterone (ED_{50}s 210 and 420 μg/kg, respectively). BMS-564929 has been progressed into Phase 1 clinical studies and is being developed as a potential therapy for age-related diseases, including androgen deficiency in males, and osteoporosis and sexual dysfunction in men and women.

A 2004 patent application by BMS described the preparation of bicyclic compounds structurally similar to BMS-564929 [78]. A small number of bicyclic urea moieties, including the bicyclic hydantoin fragment present in BMS-564929, are matched against a diverse set of aryl and heteroaryl structures. Other patent applications in 2004 and 2005 have described open chain analogs of these hydantoin compounds, exemplified by compounds **60** and **61** (Fig. **20**) [79, 80].

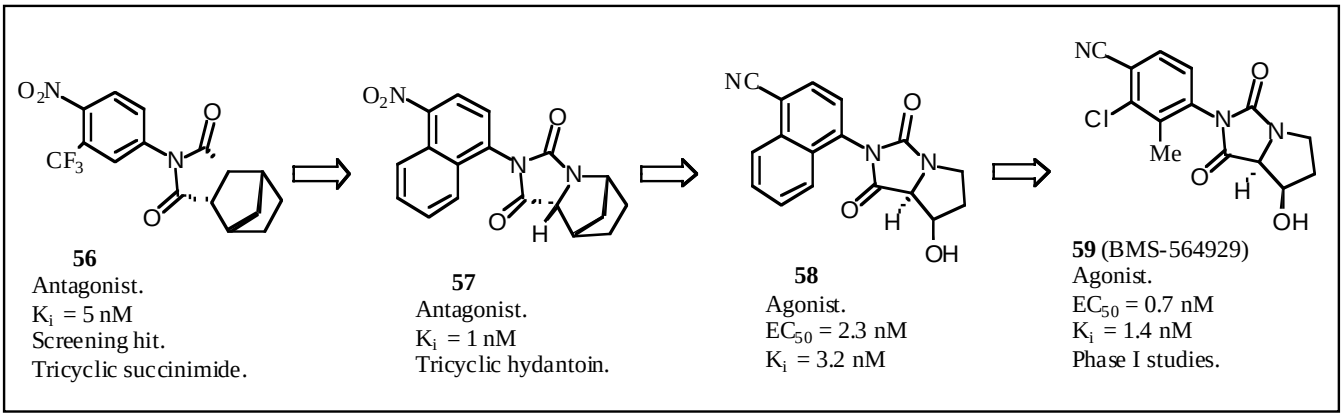


Fig. (19). Progression from AR antagonist leads to agonists in a hydantoin series.

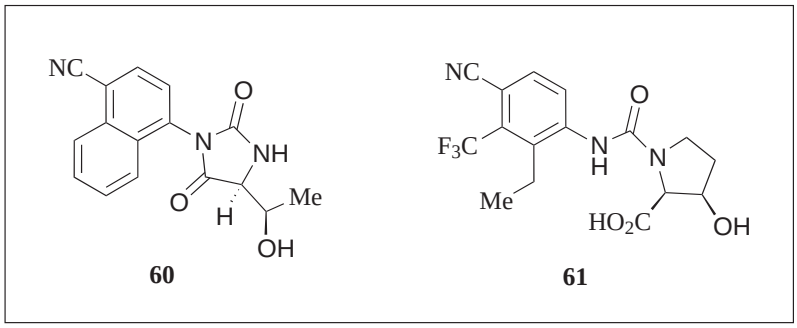


Fig. (20). Monocyclic hydantoins and open chain urea analogs.

Some additional insight into the SAR of the agonist ligands can be gained from the structural data and biological activities recently reported for members of the antagonist series [81]. Investigation of the SAR around the anilide portion in a series of tricyclic succinimides revealed that, analogous to the findings with previous antiandrogens, binding affinities (and functional activities) were critically determined by proper substitution on this ring. Electron withdrawing substituents at the 3- and 4-position (the most critical) give optimal activity and have additive effects. Small substituents, such as halogen or methyl, at the 2-position are also tolerated and can yield additive effects. The 4-nitro-naphthalene analog **62** showed the highest binding affinity in the series (Fig. **21**).

The crystal structure of the tricyclic succinimide antagonist **63** bound to the LBD of the AR mutant T877A has recently been reported and provides further insight on the binding mode of this type of molecules [82]. It revealed that the 4-nitro group mimics the C-3 carbonyl of DHT, making similar contacts with arginine 752 and glutamine 711 (a bridging water molecule observed with DHT, was not present). The fused benzene ring occupies a hydrophobic pocket, not occupied by DHT, and the lipophilic bridge moiety of **63** occupies similar space as the CD rings in DHT. Interestingly, the carbonyl groups in the imide moiety, which lie orthogonal to the naphthalene system, do not establish any significant interactions, what has led BMS scientists to postulate that the imide moiety serves simply as a geometric constraint that optimizes binding.

4. 6-Nitro(Cyano)Tetrahydroquinolines

Kaken Pharmaceuticals designed non-steroidal compound libraries based on the structures of bicalutamide, hydroxyflutamide and steroidal androgens. The first series of analogs, exemplified by compound **64** (Fig. **22**) was reported in a 2001 patent application [83]. The molecules were described as AR agonists or antagonists with specific and strong binding affinities for the AR. A 2002 patent application described modifications to the tetrahydroquinoline template where the fused cyclopentene ring of **64** was replaced with 4-substituted ethers, thioethers, and amines [84]. The corresponding 4-thioethyl and 4-ethyl ether analogs displayed the highest relative binding affinities (RBA= 2355 and 958, respectively, compared to RBA 100 for hydroxyflutamide). The 4-dimethylamine analog **65** (S-40503) also displayed high relative binding affinity (RBA= 710; K_i = 15 nM) and was selected for ORX and OVX studies.

In 2003 and 2004, two more patent applications by Kaken described additional structural modifications to the tetrahydroquinoline template [85, 86]. Analogous to the SAR in the bicalutamide series, a nitro or cyano group appears optimal in the para-position of the anilide moiety. Other 3, 4-fused ring analogs contained cyclopentane, cyclopentene, and tetrahydrofuran moieties. Modifications to the 2-substituent of the tetrahydroquinoline ring (central linker) were also explored. The majority of the compounds exemplified share the same gem dimethyl motif as hydroxyflutamide. Most of the modifications entailed

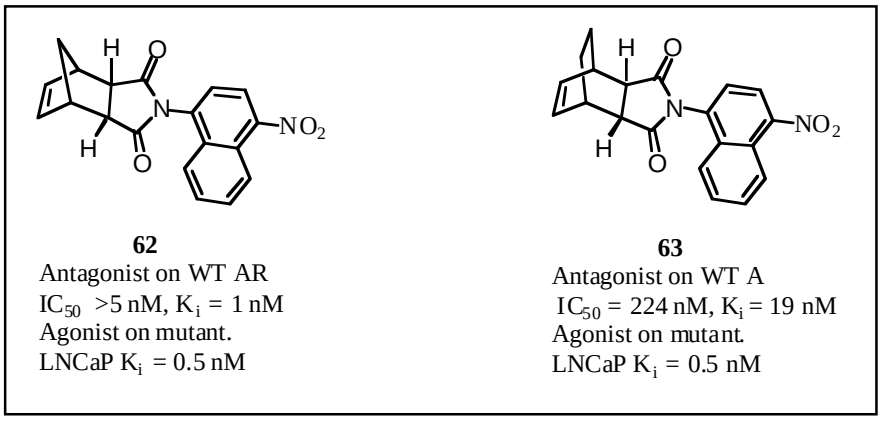


Fig. (21). Antagonists on wtAR (MDA-453), but agonists in T877A mutant (LNCaP).

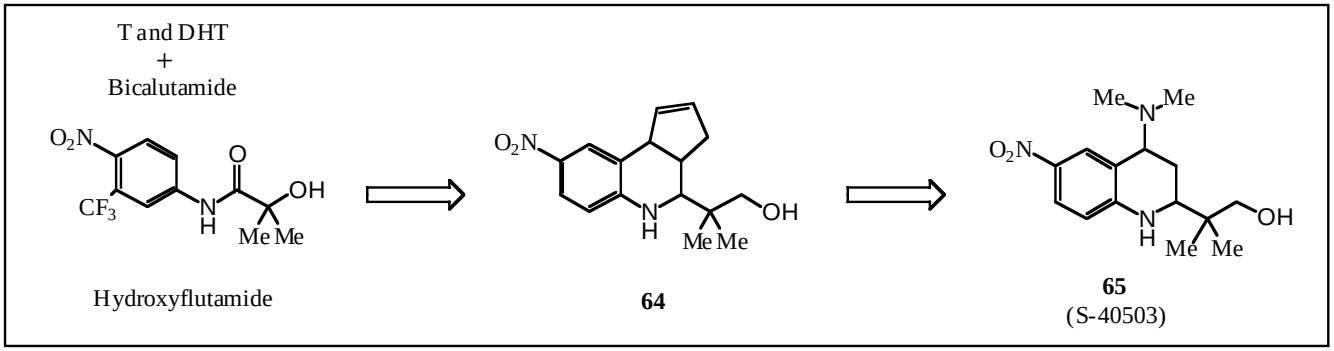


Fig. (22). Tetrahydroquinoline AR ligands.

functionalization at the terminal portion of the molecule, where they investigated substituted benzamides, as well as heteroaryl and alkyne replacements. The relative binding affinities for some compounds were reported and the more promising molecules were progressed into ORX studies. Selected examples based on this information are shown in Fig. (**23**, **24**).

Since the structures of bicalutamide and hydroxyflutamide were used in the design of these tetrahydroquinoline ligands, it is not surprising that ligands in both series share key structural motifs and may also share similar binding modes. Interestingly, the highest relative binding affinities reported in this series correspond to the methyl ether **66** and the alkyne derivative **69**.

5. 4-Cyano(Nitro)Aryl Amines

Takeda Chemical Industries, in a 2004 patent application, disclosed a series of fused benzene derivatives possessing pendant heterocyclic moieties [87]. These compounds were described as AR agonists or AR modulators for use in the treatment or prevention of hypogonadism, osteoporosis, and hormone-resistant cancer, including prostate cancer. Binding activity at a given concentration of 100 nM was reported for some of the more than 150 compounds prepared. Examples of analogs showing some of the AR highest affinities are shown in Fig. (**25**).

The 4-cyano and 4-nitro-naphthalene scaffold was the most represented fused ring system, but in a small number of analogs the unsubstituted benzene was replaced with cycloalkanes and heterocycles. Substituted pyrrolidines and piperidines comprised most of the groups attached to the fused system, although a small number of other heterocycles or carbocycles were also described. These derivatives have obvious structural similarities to previously discussed series. The functional activity and potency of these compounds is likely being further modulated by the substituents on the cyclic amine scaffold that may act as a steroidal C/D ring mimetic.

GlaxoSmithKline, in a 2004 patent application, described a series of 1-naphthalene amines that are modulators of the AR receptor [88]. The majority of the compounds exemplified contain a 4-nitro (or 4-cyano)-1-naphthaleneamine scaffold. The amine components are mainly acyclic and most commonly they are disubstituted with small alkyl (straight, branched or cyclic), fluoroalkyl, hydroxyalkyl or aminoalkyl groups. Representative examples are shown in Fig. (**26**) (no biological data reported).

In 2005, another patent application by GlaxoSmithKline described a closely related series of compounds in which the naphthalene template was replaced by substituted benzenes [89]. The 4-cyano (or 4-nitro)-3-trifluoromethyl motif of bicalutamide was common in many of these analogs. In other examples the 3-CF_3 group was replaced by NO_2, CN, Cl or

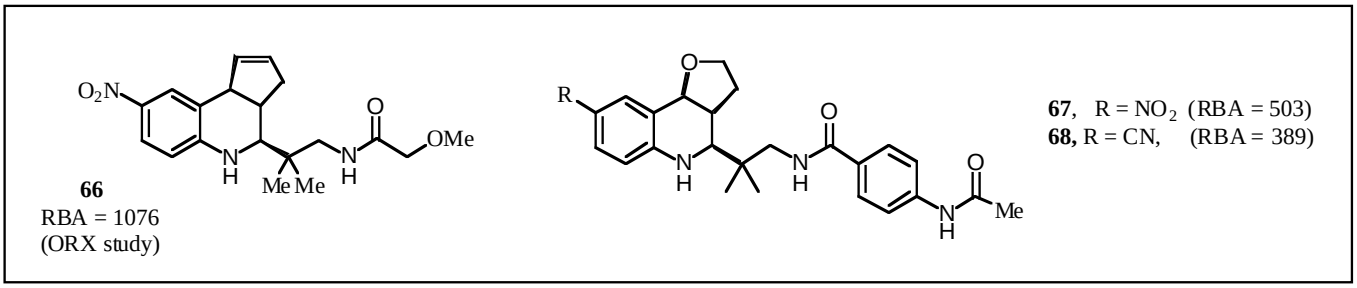


Fig. (23). Tetrahydroquinoline SARMS. Kaken Pharmaceuticals (2003).

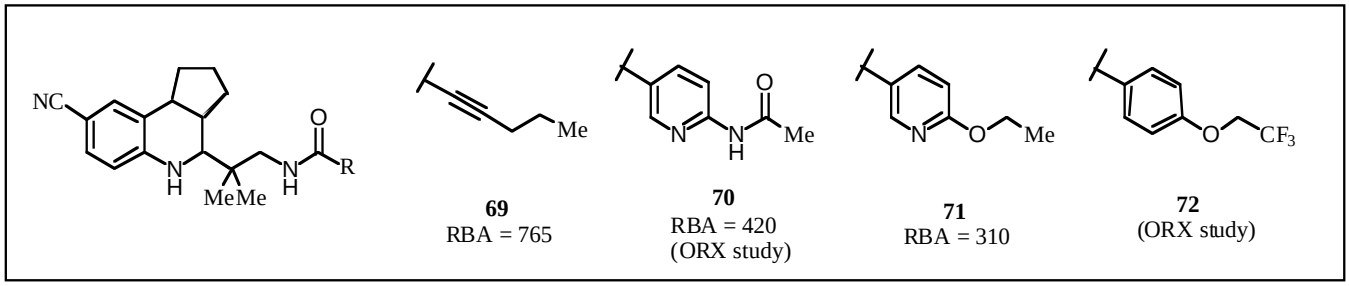


Fig. (24). Tetrahydroquinoline SARMS. Kaken Pharmaceuticals (2004).

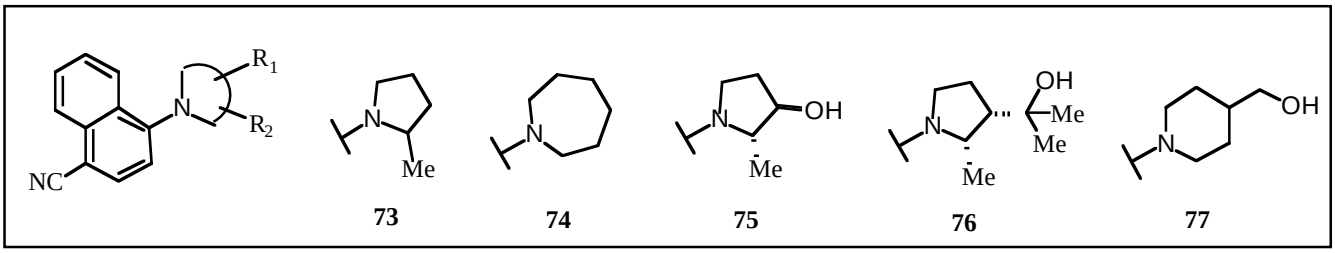


Fig. (25). 4-Cyano(cyclic amino)naphthalene derivatives. Takeda (2004).

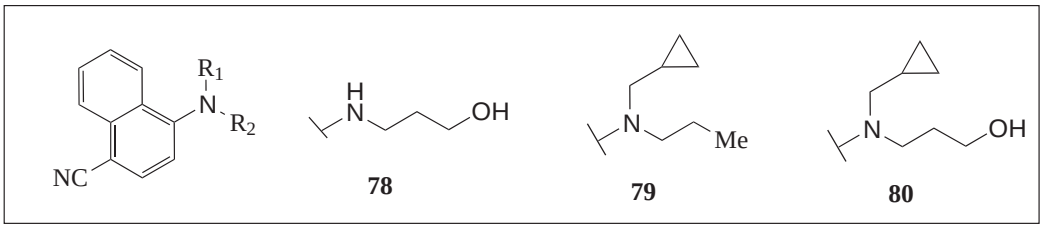


Fig. (26). 4-Cyano-1-aminonaphthalene derivatives. GlaxoSmithKline (2004).

Me. Cyano and nitro were the most common substituents in the arene 4-position. Representative examples are shown below in Fig. (**27**) (no biological data reported).

Pfizer, in a 2005 patent application, described a series of 5-cyano-2-amino-pyridines as androgen receptor modulators [90]. The most distinctive feature is the replacement of the common A-ring benzene with pyridine. The classic CN-ortho-CF_3 motif is prevalent, but a more novel 1,2,3-trisubstituted pattern, Cl-CN-CF_3 motif is also described. This unique substitution pattern enhanced AR binding affinities 3 to 20-fold (for example, **85** vs **86**, Fig. **28**). As in the previously described analogs, disubstituted amines are appended to the heteroaryl scaffold. Binding affinities in this series are also significantly affected by minor structural changes to the amine substituents. For example, a 27-fold improvement in binding was gained by incorporating an α-methyl substituent with an R-configuration (compounds **87** and **89**, Fig. **27**). A similar enhancement in activity was realized by replacement of an ethyl with a cyclopropyl (not shown).

Several of the analogs described bound AR with high affinity but displayed poor activity in an antagonist cellular assay (> 1 μM) (no agonist data were reported). Compounds that displayed good antagonist activity in the cellular assay

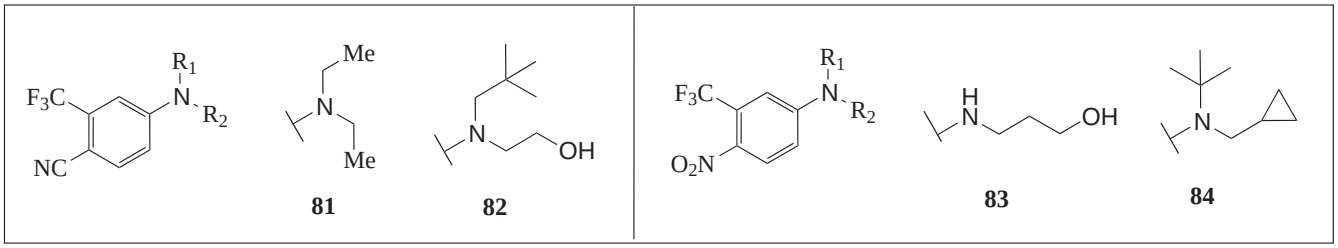
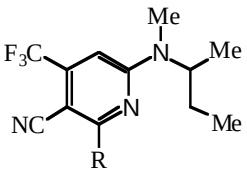
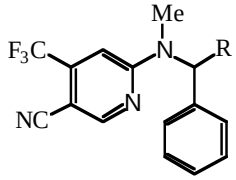


Fig. (27). 4-CN (NO2)-aniline derivatives. GlaxoSmithKline (2005).



	R	K_i (nM)	Antagonist IC_{50} (nM)
85	H	10	
86	Cl	0.5	> 1 μM



	R	K_i (nM)	Antagonist IC_{50} (nM)
87	H	538	
88	Me	123	
89	(R)-Me	20	45

Fig. (28). 2-Aminopyridine analogs. Pfizer (2005).

were further evaluated in a rodent model of alopecia. Analog **89**, applied topically twice a day for 30 days, demonstrated good efficacy in this model.

In a 2005 patent application, Karo Bio described a series of (phenyl/pyridyl) amino-alkanols and related compounds as AR modulators [91]. Over 100 compounds were prepared and binding and transactivation data were reported for 14 examples. The most commonly exemplified chemical scaffold consists of an aromatic A-ring (phenyl or pyridyl) condensed with a primary aminoalkanol fragment. A common substitution pattern on the A-ring is the classic CN/NO_2/ortho CF_3 motif. Other modifications to the A-ring included the following: replacement of the NO_2 or CN with fluoro, acetyl, methylsulfonyl, etc.; replacement of the CF_3 with Me or H; and incorporation of additional substituents (typically methyl). The most commonly exemplified substituent for the pendant amine was an ethanolamine backbone incorporating various substituents. The compounds, for which biological data was reported, displayed either an antagonist profile or partial agonist activity. Selected examples are shown in Fig. (**29**).

In this particular set of analogs, binding affinities and transactivation activities are negatively affected by replacement of the ortho-CF_3 with methyl and introduction of nitrogen in the phenyl ring. These modifications also significantly enhanced the antagonist profile. Incorporation of an extended benzylthioether substituent led to a large improvement in binding affinity within an antagonist profile.

6. Carbonylaminobenzimidazoles

Merck, in a 2004 patent application, described a novel series of carbonylaminobenzimidazoles as AR modulators [92]. The chemical scaffold in this series is a 5-amino-2-thiazole-benzimidazole template, which is connected to a second aromatic unit *via* an amide or urea linker. More than 150 derivatives were prepared, all of which contain the thiazole benzimidazole motif. While no biological data was reported, they were described as tissue selective AR modulators with agonist activity in muscle and/or bone and antagonist activity in prostate or uterus. A preferred set of ureas and amides was claimed and selected examples are shown in Fig. (**30**).

The preferred amide analogs share a benzyl or phenethyl motif with hydroxyl or small alkyl substituents in the linker. The geminal methyl/hydroxyl derivatives share the central amide motif of hydroxyflutamide and its derivatives, however the thiazolebenzimidazole moiety is unlike any other A-ring arrangement previously described. The preferred urea derivatives are similarly substituted either directly on nitrogen or in the linking unit.

Additional information on this chemical class was subsequently disclosed by Merck [93]. The series arose from a screening hit (compound **102**) that displayed good AR potency (IC_{50} = 77 nM), but had P450 liabilities (Fig. **31**).

SAR studies revealed that the amide carbonyl was critical for activity and that the thiazole was an optimal heterocycle. Modifications to the benzyl carbamate led to a series of urea and amide analogs from which the cyclopropane derivative **96** was identified (IC_{50} = 55 nM; 20% bioavailability in dog, $t_{1/2}$ = 1.5 hr, Cl = 6.7 mL/min/kg). *In vivo*, at 10 mg/kg, the compound demonstrated tissue selective effects, increasing bone formation with little effect on uterine weight (10% of DHT). An important liability of this chemical class is the finding that the amino-benzimidazole-thiazole that could result from hydrolysis of the amide bond was positive in an AMES genetic toxicity assay, while the corresponding des-amino benzimidazole-thiazole was negative.

7. 3-(2-Nitrophenyl)Thioindoles

In a 2004 patent application, Akzo Nobel N.V. described a series of indole derivatives useful in the treatment of AR related diseases [94]. The core scaffold in this chemical class is an indole ring substituted in the 3-position with a

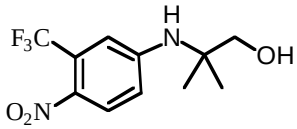
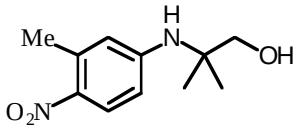
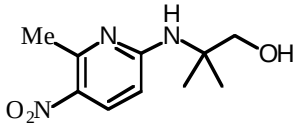
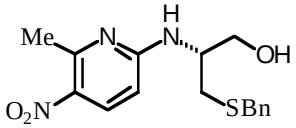
	Cpd	Binding IC_{50}	Agonist EC_{50}	% Maximal activation	Antagonist IC_{50}	% Maximal activation
	**90**	23 nM	27nM	52%	2 nM	33%
	**91**	38 nM	82 nM	29%	7 nM	61%
	**92**	241nM	374 nM	11%	22 nM	83%
	**93**	6 nM	1867 nM	7%	78 nM	89%

Fig. (29). Phenyl/pyridinyl aminoalkanols. Karo Bio (2005).

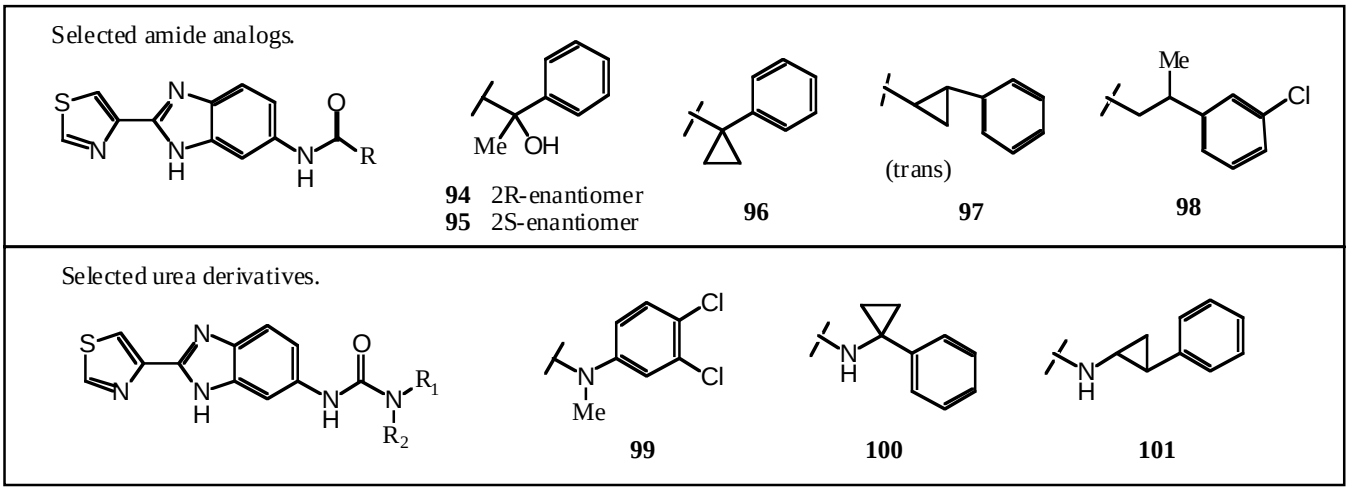


Fig. (30). Carbonylaminobenzimidazoles. Merck (2004).

phenylsulfanyl fragment and in the N-position with benzyl-like substituents. Some 125 compounds were prepared and biological data was reported (agonist and antagonist activity in functional assays). This chemical series evolved from a screening hit (3-[(2-nitrophenyl)thio]-1-(phenylmethyl)-1H-indole) which displayed micromolar activity in a functional assay. The majority of the compounds exemplified contain a nitro group in the ortho-position of the phenylsulfanyl moiety, although a few analogs are alternatively substituted with cyano, hydroxymethyl, $CONH_2$ or CONHMe. In other analogs, the sulfide linker is replaced with sulfoxide or sulfone. Compounds displaying some of the highest agonist activities (agonist EC_{50} < 5 nM, >80% efficacy vs 100 nM DHT) are shown in Fig. (**32**).

The N-benzyl substituent is tolerant of some substitution and of replacement with heterocycles. The 6-position of the indole can accommodate a variety of electron donating or withdrawing substituents of various sizes and still retain high activity. While a nitrophenyl moiety is a common motif in this series and a few analogs contain an additional cyano or nitro substituent on the indole ring, the geometrical arrangement of the substituents on this scaffold is unlike any other previously described and may be indicative of an alternative binding mode to the AR.

8. 4-Azasteroid Derivatives

These azasteroid SARMs share their chemical scaffold with the family of 5-alpha-reductase inhibitors previously

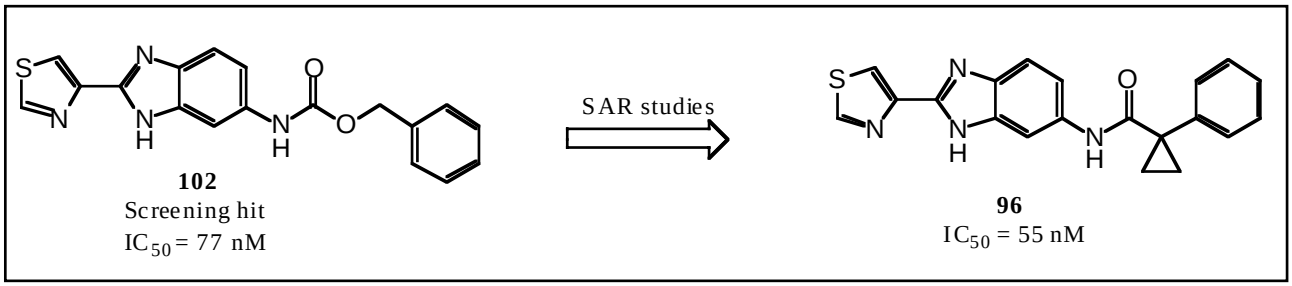


Fig. (31). Progression of carbonylaminobenzimidazoles series.

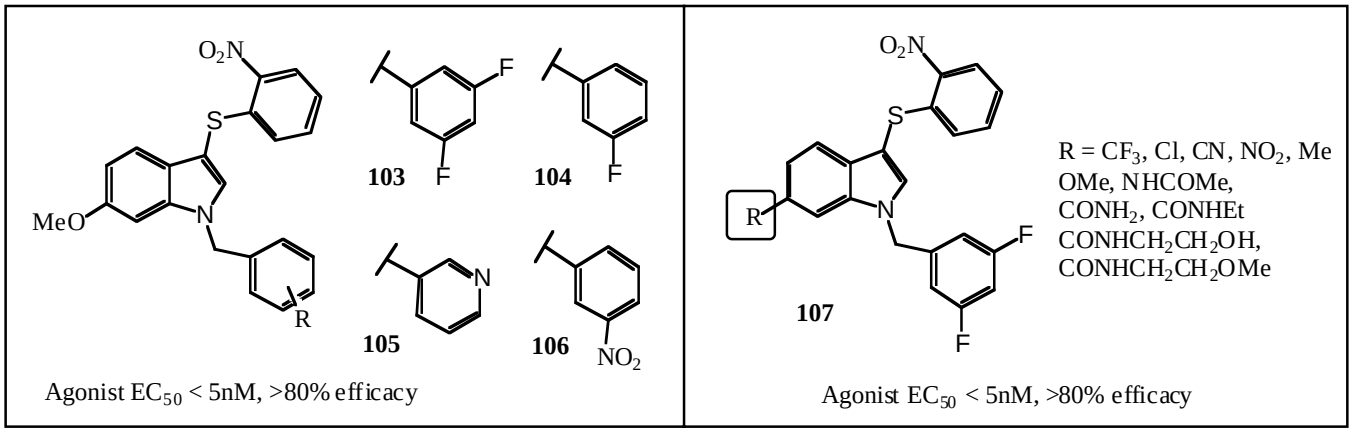


Fig. (32). 3-(2-Nitro-phenyl)thioindoles. Akzo Nobel N.V. (2004).

discovered by Merck and typified by Finasteride (**108**) (Fig. **33**). The affinity of these analogs for the AR is profoundly increased by methylation of the N-4-position [95]. In 2003, a series of patent applications by Merck described 4-azasteroid derivatives as androgen receptor modulators [96-98]. No biological data was reported in the patent applications, but the compounds were described as tissue selective, with agonist activity in bone or muscle and antagonist activity in prostate or uterus. The first set of analogs described were C-17 carboxamides, exemplified by compound **109** (an analog that had previously been reported as a 5-α-reductase inhibitor). The C-17 amide region was the most extensively modified, with smaller changes made on the A- and B-rings (for example, replacement of the 4-Me with small alkyls or incorporation of a spirocyclopropane at C-6).

Homologated amide derivatives (C-17 acetamides), exemplified by compound **110**, were described in several patent applications in 2005 [99-102]. Amide substitution was again explored extensively, with additional modifications on the A-ring (2-F analogs) and C-20 (incorporation of F, OH or NH_2).

In 2004, another patent application by Merck described C-17 amine derivatives, exemplified by the reverse amide **111** (an analog that had also been previously reported as a 5-α-reductase inhibitor) [103]. Carbamates, ureas, and sulfonamides were also explored.

Analogs in which the C-20 or C-21 amide moieties are replaced by heterocycles were the subject of Merck's most recent 2005 patent applications exemplified by **112** and **113** (Fig. **34**) [104-106].

THERAPEUTIC OPPORTUNITIES FOR SARMS

General

SARMs are currently in the early stages of development. The publication frequency of preclinical data is rapidly increasing. A clear portrait of the viable therapeutic potential for SARMs is beginning to emerge from these studies. Much of our preclinical and clinical understanding of the therapeutic promise of SARMs stems from work using anabolic steroids. Because of their highly selective anabolic properties and demonstrated prostate sparing activity, SARMs could be used for prevention or treatment of many diseases, including sarcopenia (muscle wasting), osteoporosis, frailty, and other conditions associated with aging or androgen deficiency. SARMs also show promise in the areas of hormonal male contraception and benign prostatic hyperplasia (BPH). As testosterone therapy also provides the benefits of its metabolites, E2 and DHT, it is unknown whether SARMs will suffice as stand alone therapies. The therapeutic potential of SARMs for treatment of androgen deficient disorders in women is a far less studied field. This review primarily focuses on the use of SARMs for the treatment and prevention of disease in males, but many of these therapies could theoretically apply to both genders.

Treatment of Male Hypogonadism

Male hypogonadism represents a state of impaired testosterone production. There are two general types of hypogonadism: primary hypogonadism is due to testicular failure, while secondary hypogonadism is due to malfunction at the hypothalamic/pituitary level. Gonadotropins can be

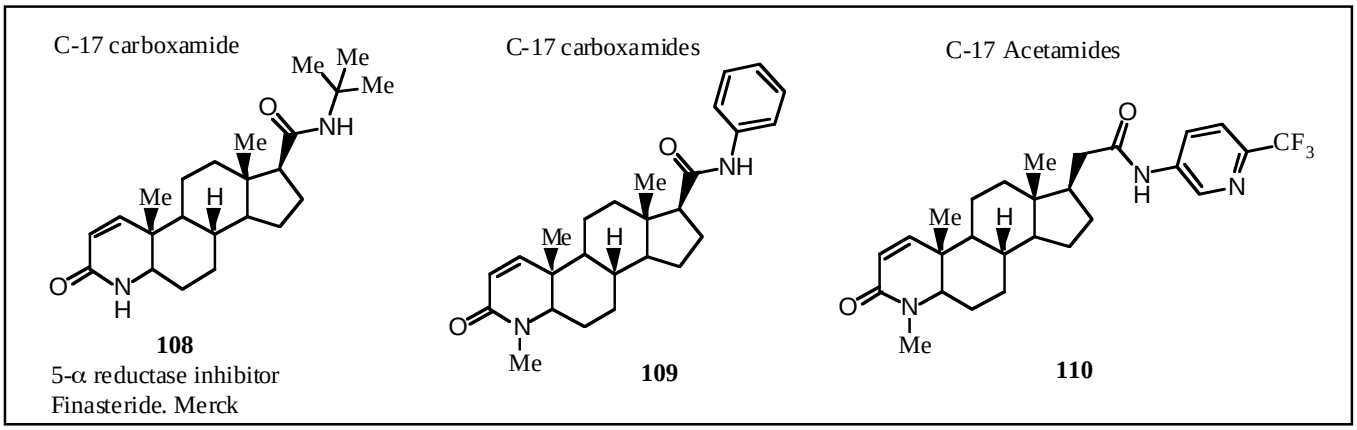


Fig. (33). Finasteride and 4-azasteroid AR ligands.

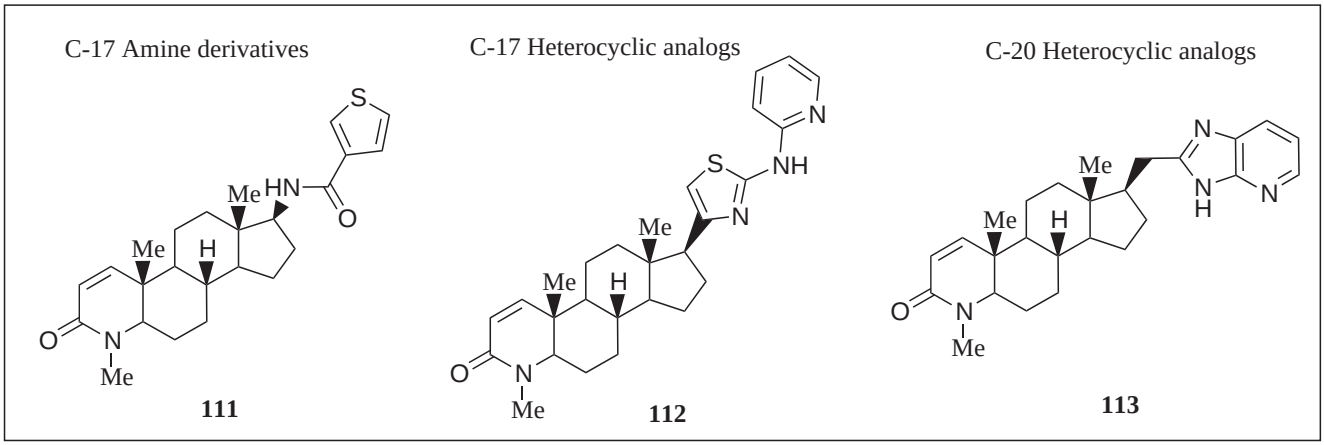


Fig. (34). 4-Azasteroid AR ligands.

elevated or decreased depending on the localization of the condition. Severe symptoms are associated with the hypogonadal state. Symptomatic profiles differ depending on the time of onset of the condition. Symptoms in patients who experience hypogonadism after normal virilization include decreased muscle mass, osteopenia/osteoporosis, decreased fertility, increased visceral fat, and sexual dysfunction [107].

A SARM in hypogonadal men would ideally function by providing the anabolic effects of testosterone with the convenience of oral administration. Prostate drive is usually not a concern for young hypogonadal males, but the sparing effects of a SARM may still prove beneficial. When designing clinical studies, the hypogonadal male population represents an excellent testing cohort. Clinical studies in hypogonadal males using testosterone have provided compelling efficacy data [108]. Despite the emergence of clinical studies with T, there is still a paucity of accepted clinical endpoints. Most studies with T simply measure hormone levels to provide exposures in the normal physiological range. T naïve or washed hypogonadal males would serve as a viable cohort for clinical studies with a SARM. Physiological markers such as an increase in muscle mass and function, a decrease in visceral fat, and an increase in bone mineral density would serve as endpoints. The challenge for a SARM is to correlate drug exposures to these concrete clinical endpoints.

Treatment of Androgen Deficiency in the Aging Male (ADAM)

Over 80% of all illness, morbidity, and medical costs are concentrated in the years after age 65. With increased survival to more advanced ages, the absolute numbers of senior citizens will increase markedly in coming years. According to the United Nations World Health Organization report on Aging, it is anticipated that by 2030 one in five American will be over the age of 65 [109]. Though decline in organ function is inevitable in this population, it may be possible to extend organ function, thereby increasing quality of life (QOL) in older people. Therapeutic interventions that reduce organ decline and increase QOL will clearly be widely accepted, both for their ability to decrease overall health care costs and to improve the length of functional life.

There is still disagreement within the scientific community about what does or does not constitute androgen deficiency in the aged population [110, 111]. Some of the disagreement concerning testosterone deficiency stems from the failure to distinguish between total T, and bioavailable T (testosterone not sequestered by sex hormone binding

globulin, SHBG). T must be free and unbound for uptake in target tissues [112]. Specialists increasingly focus on bioavailable T, which is emerging as a standard measure for ADAM. Total T levels decline with increasing age at a rate of approximately 2% per year after age 50 [113, 114]. Concomitant increases in SHBG levels further exacerbate the decline in bioavailable T.

Clinical studies show that ART in men improves body composition parameters such as muscle mass, strength, and bone mineral density [111]. There is also evidence of improvement in less tangible parameters such as libido and mood. Andrologists and other specialists are increasingly using androgens for the treatment of the symptoms of androgen deficiency. ART, using T and its congeners, is available in transdermal, injectable and oral dosage forms. All current treatment options have contraindications (e.g., prostate cancer) and side-effects, such as increased hematocrit, liver toxicity, and sleep apnoea.

ART in older men with low testosterone has long been a topic of discussion, but only recently has become the focus of controlled clinical studies [113, 114]. These studies continue to build the case for treatment of ADAM. There is still significant controversy about hypogonadism being related to aging, despite the fact that its incidence increases with age. The signs and symptoms of androgen deficiency in the senescent male are defined as low levels of testosterone accompanied by of loss of libido, erectile dysfunction, loss of muscle mass, osteoporosis, fatigue, mood swings, and loss of energy. The lack of a definitive treatment strategy, resulting from the non-specific nature of the clinical features of ADAM, further fuels the andropause debate.

The key scientific opportunity for the treatment of ADAM is the development of non-steroidal molecules that act via the androgen receptor in a tissue specific manner. SARMs confer tissue specificity by acting as potent agonists in target tissues such as muscle, bone, and brain, while acting as partial agonists or antagonists in tissues such as the prostate. Within the therapeutic realm of ADAM lies a wealth of therapeutic indications. In order to focus a therapeutic strategy and define concrete clinical endpoints it is necessary to pull apart the multiple facets of androgen deficiency and understand how androgens may treat these more specific conditions. An understanding of the function of the classical anabolic steroids in treating androgen deficient disease states, in combination with the emerging preclinical data for SARMs, sets the stage for the successful therapeutic use of SARMs.

Treatment and Prevention of Muscle Wasting, Sarcopenia

Sarcopenia or muscle wasting is the aging-associated decline in neuromuscular function and performance [115]. Skeletal muscle atrophy and weakness are considered major contributing factors to the loss of mobility, independence, and frailty that affect many older adults [116]. Relative muscle loss in aging men and women is similar, but because men start with higher baseline values, their absolute loss of strength is greater. Epidemiological data support the relationship between the fall in testosterone and the decline in muscle mass [117, 118]. As mentioned above, many clinical studies with testosterone have demonstrated significant gains in muscle mass and function along with decreases in visceral fat [119, 120].

The actual mechanisms of androgen-promoted muscle anabolism are still not fully understood. It is generally believed that androgen-induced increases in muscle mass can be attributed to increases in muscle protein synthesis [121]. Muscle size increases associated with androgen therapy occur through the hypertrophy of both type I and type II muscle fibers. Studies have shown that androgens promote increases in satellite cell number as well as myonuclei [122]. Other studies have shown androgens to promote the commitment of pluripotent, mesenchymal cells into the myogenic lineage and to inhibit differentiation into the adipogenic lineage.

Many preclinical studies with SARMs to date have employed the classical Hershberger model of pharmacologic androgen activity on muscle and sexual accessory organs [24, 123]. The anabolic marker in this rodent model measures hypertrophy of the levator ani (LA), a muscle that is thought to be involved in tail raising and erectile function. Unlike the rat skeletal muscle tissue, the LA has a relatively high expression of the AR [124]. The differential AR expression and the fact that the LA is really a component of the sexual accessory organs, spawns questions regarding the validity of LA hypertrophy as being predictive of or relevant to anabolic skeletal muscle activity. In order to elucidate the effects of a SARM on skeletal muscle, Dalton *et al*. recently reported the effects of the SARM, S-4 (compound **8**, Fig. **5**), on the mass and strength of isolated soleus muscle in orchidectomized (ORX) rats [125]. Treatment with **8** significantly increased skeletal muscle strength, measured as peak titanic tension in ORX animals. The effect of **8** on skeletal muscle hypertrophy was not significant, yet the SARM restored castration-induced losses in lean body mass. DHT-treated animals showed similar changes in muscle size, muscle strength, and lean body mass. Interestingly, **8** did not change fat mass, whereas DHT showed a significant decrease.

Treatment and Prevention of Osteoporosis/Osteopenia

Men undergo a gradual reduction in bone mass in early to mid adulthood. In fact, when in their late 60's, men lose bone mass at a rate similar to women. There is increasing evidence that T plays an important role in the maintenance of bone [126, 127]. There have been multiple studies examining the relationship between bone mineral density (BMD) and related bone markers and T levels in men. Osteoporosis is common in men undergoing treatment for prostate cancer. Bilateral orchidectomy and gonadotropin-releasing hormone agonist treatment decrease BMD and increase fracture risk [128]. Testosterone therapy increases bone mineral density in men with low T [129, 130]. It is not entirely clear if both T and E2 are required for healthy bone maintenance. A combination therapy of estrogen and androgen increases BMD to a greater extent than does estrogen therapy alone [127].

Androgens are important for skeletal homeostasis, affecting bone mineral density (BMD) by regulating the bone breakdown and remodeling process. Androgen action

on AR-expressing osteoblasts inhibits osteoclastogenesis in the bone marrow cavity. Androgens increase cortical bone formation mainly by stimulating periosteal bone formation [126].

Clinically employed antiresorptive therapies such as estrogen replacement, selective estrogen receptor modulators (SERMs), bisphosphonates, and cathepsin K inhibitors, do not restore bone mass in patients already showing significant bone loss. The clinical use of intermittent parathyroid hormone (PTH) treatment to promote bone formation is limited because of side effects and possible association with osteosarcoma.

SARMs may provide a novel approach to the treatment of osteoporosis. Like T therapy, SARMs offer promise not only as antiresorptive agents, but also as osteoanabolic agents. A few preclinical studies demonstrating the promise of SARMs in the treatment of osteoporosis have been published [23, 131, 132]. SARMs were shown to significantly increased BMD and bone strength in ORX rats [23]. Administration of the SARM, S-40503 (compound **65,** Fig. **22**), ORX rats for 4 weeks increased bone mineral density (BMD) of femur and levator ani muscle weight as markedly as DHT. Prostate weight was not elevated over that for eugonadal rats at any doses tested. In order to further validate the bone anabolic effect, **65** was given to ovariectomized (OVX) rats over a 2 month period. The SARM significantly increased BMD and biomechanical strength of femoral cortical bone, whereas the antiresorptive estrogen did not. An increase in periosteal mineral apposition rate of the femur showed direct bone formation activity of **65**. The increase in BMD was not attributed to muscle anabolism as hind limb suspended rats showed like increases in BMD.

Treatment of BPH

Benign prostatic hyperplasia (BPH) affects the majority of men in the United States over the age of 50. Prostatic drive is determined by the local concentration of androgen. DHT, the androgen of the prostate, is produced in the prostate by the action 5-α-reductase on T. BPH can lead to many problems including acute urinary retention, recurrent bladder infection, bladder calcul, and a general decrease in a patient's quality of life [133, 134, 135].

SARMs that compete with prostatic binding of DHT, but that do not elicit an agonist response, may provide a therapeutic approach to the treatment of BPH. The true novelty of such a therapy is realized when prostate volume reduction is combined with the other desirable pharmacologic features of a SARM. Drug-related adverse events from 5-α-reductase inhibitors include erectile dysfunction, decrease libido, and decreased ejaculate volume [134]. When compared to a 5-α-reductase inhibitor, a SARM would likely have the opposite effects in terms of side-effects. A comparison study of the pharmacologic activity of a SARM to an antiandrogen, and a 5α-reductase inhibitor in intact male rats was recently reported [136]. The SARM, S-1 (compound **9,** Fig. **5**), selectively decreased prostate weight when dosed at appreciably high doses (5, 10, 25 mg/kg/day sc), with efficacy equal to finasteride (5 mg/kg/sc). After 9-days of treatment, no significant changes in LA muscle weight, plasma levels of testosterone, or follicle stimulating hormone (FSH) were observed in the SARM-treated group. Luteinizing hormone (LH) levels were, however, suppressed at these doses after 9-days. In contrast, the antagonist hydroxyflutamide decreased prostate and LA weight with no selectivity, while raising plasma hormone levels. It is important that the activity of a SARM in shrinking prostate volume not be from suppression of endogenous androgen production, but instead from the competitive binding to prostatic androgen receptors. These studies indicate that SARMs may be a viable treatment for BPH either as a single or combination therapy.

Male Contraception

Large studies investigating the use of high doses of testosterone as a means of male contraception have been and are currently being conducted [136, 137]. Testosterone is a necessary component in the generation of sperm, but high doses actually inhibit formation of mature sperm. Sperm maturation relies on the secretion of LH and FSH. LH regulates testicular testosterone production by the Leydig cells and FSH stimulates Sertoli cells to provide nutrients to maturing sperm. T production is regulated through a feedback loop that involves the hypothalamus and pituitary glands. Testosterone signals the hypothalamus and pituitary to decrease production of gonadotropin releasing hormone which in turn lowers the secretion of LH and FSH. Supraphysiological levels of testosterone serve to inhibit LH and FSH secretion through the feedback loop [138, 139]. Lowered intratesticular levels of T and FSH decrease sperm production [140].

A SARM's efficacy in male contraception is dependent on its ability to interfere with the HPT axis and also on its potential action on androgen receptors in the testes. Studies of the effects of SARMs on spermatogenesis are beginning to emerge. A SARM from the aryl-propionamide class, C-6 (compound **10**, Fig. **5**), exhibited significant gonadotropin suppression in castrated male rats [141]. Demonstrative of its tissue selective effects, treatment with **10** (0.3 mg/kg/day sc) showed LA muscle mass maintenance at a level close to intact controls, whereas the mass of the prostate was only partially maintained (30% of control). At this same dose the castration-induced elevated levels of LH were fully suppressed while those for FSH were partially suppressed. In addition, a pilot study of **10** in adult intact male rats showed significant inhibition of spermatogenesis at a subcutaneous dose of 1 mg/kg/day over 10 weeks, while maintaining anabolic effects in levator ani muscle and sparing the prostate. Testicular and epididymal weights were also significantly decreased. While this study focused on the central mediation of spermatogenesis, further investigation of the direct effects of SARMs on androgen receptors in the Sertoli, Leydig, peritubular myoid, and vascular smooth muscle cells of the testis would increase our understanding of spermatogenic inhibitory mechanisms [142]. Additional investigations into the particular stage of spermatogenic degradation influenced by SARMs would also be interesting.

Inhibition of spermatogenesis may not be a desired effect for individuals seeking the benefits of hormone replacement. In such cases, the most desirable SARM profile would show no effects on the endogenous hormone levels and/or

spermatogenesis, while still demonstrating marked anabolic effects in muscle and bone.

Treatment of Sexual Dysfunction

Hypoactive sexual desire disorder (HSDD) is prevalent in both men and women, though it is thought to be less common in men [143]. There are multiple factors contributing to HSDD in men. The two major components are decreased libido and erectile dysfunction. Libido decreases with aging in men. Adequate plasma T levels are required for maintenance of normal libido. Testosterone deficiency decreases libido, but the threshold level of testosterone under which libido problems may occur is relatively low (290 ng/dL) [144]. Low libido in aging men is associated with deficiency of bioavailable testosterone, whereas total testosterone showed no or only weak associations [145, 146]. Clinical studies investigating the effects of testosterone on male sexual dysfunction have been conducted [147-149]. Establishment of efficacy in these studies relies on the collection of soft data such as daily diary recordings and questionnaires regarding perceived libido. Testosterone replacement appears to have positive effects on libido, but the establishment of common clinically validated tools would serve to allow meaningful study interpretation and comparisons.

Incidence of erectile dysfunction increases with aging [150]. The etiology of erectile dysfunction is usually multifactorial, and late-onset hypogonadism is a contributing factor in a minor percentage (8-15%) of cases [150, 151] There is an association between serum testosterone level and frequency, duration and degree of spontaneous nocturnal erections [152]. Although some studies found no relationship with testosterone levels in older men [153, 154], other studies have reported reduced testosterone levels in patients with erectile dysfunction [151, 155].

Although no studies have been published to date, the use of SARMs for HSDD offers the potential to increase libido while not driving the stimulation of sexual accessory organs such as the prostate. Presumably SARMs amenable to this application will require brain penetration. T has been shown to aid in the treatment of erectile dysfunction and such promise should be offered by a SARM. Because the threshold value for T required to enhance libido is so low, it may be possible to give very low doses of a SARM in order to provide treatment.

Use of SARMs in Women

The use of androgens to alleviate the physiological consequences of testosterone deficiency is well recognized in men. The concept of androgen deficiency in women, however, is not readily embraced. The clinical manifestations of T deficiency in women are decreased libido, lowered mood, a diminished sense of well-being, blunted motivation, and persistent fatigue. Clinically, the use of androgens in women has been shown to enhance sexual function, maintain BMD, and increase fat-free mass [156].

SARMs have the potential to offer the same benefits in women as androgen therapies without the unwanted side effects. Side effects from androgen therapy in women include: acne, hirsutism, and lowering of high-density lipoprotein (HDL) cholesterol levels. Limited preclinical studies exploring the use of SARMs for female indications have been published. Most of these studies focus on OVX rat osteoporosis models [23, 125].

CONCLUSIONS

SARMs show great preclinical therapeutic potential for the treatment of androgen deficiency, sarcopenia, osteoporosis, and BPH, in addition to their potential use in male hormonal contraception. Emerging clinical studies will further reveal their true value. Demonstrated advantages over steroidal androgens such as tissue selective activity, oral administration, AR selectivity, and lack of androgenic effects poise SARMs for a bright future of therapeutic applications.

ABBREVIATIONS

SARMs	=	Selective androgen receptor modulators
NR	=	Nuclear receptor
LBD	=	Ligand binding domain
DBD	=	DNA binding domain
ART	=	Androgen replacement therapy
ADAM	=	Androgen deficiency in the aging male
Tp	=	Testosterone propionate
T	=	Testosterone
DHT	=	Dihydrotestosterone
E2	=	Estradiol
BMD	=	Bone mineral density
ORX	=	Orchidectomized
OVX	=	Ovariectomized
BPH	=	Benign prostatic hyperplasia
LH	=	Luteinizing hormone
FSH	=	Follicle stimulating hormone
HSDD	=	Hypoactive sexual desire disorder
HDL	=	High density lipoprotein

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