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# Design, Synthesis, and Biological Evaluation of 16-Substituted 4-Azasteroids as Tissue-Selective Androgen Receptor Modulators (SARMs)

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**Abstract:** A novel series of 16-substituted-4-azasteroids has been identified as potential tissue-selective androgen receptor modulators. These ligands display potent hAR binding and agonist activity, low virilizing potential, and good pharmacokinetic profiles in dogs. On the basis of its in vitro profile, **21** was evaluated in the OVX and ORX rat models and exhibited an osteoanabolic, tissue-selective profile.



The androgen receptor[1] (AR[a]) is a member of the nuclear receptor superfamily and is responsible for mediating the physiological action of endogenous androgen ligands including dihydrotestosterone (DHT, **1**, Figure 1) and testosterone (**4**).[2] The AR is expressed in numerous tissues, and the recruitment of cofactors and subsequent ligand-mediated gene transcription results in the regulation of several physiological characteristics including bone formation, muscle mass, hair growth, acne, and sexual development. Androgen therapy has been used in the clinic to treat a variety of male disorders, including reproductive disorders and primary or secondary hypogonadism. Patients with androgen deficiencies often receive testosterone as a patch or gel because of its poor oral bioavailability. Side effects include hair loss, gynecomastia, and prostate hyperplasia.[3] A number of natural and synthetic AR agonists have been clinically investigated for the treatment of musculoskeletal disorders, including sarcopenia, which is characterized by a slow, progressive loss of muscle mass occurring with advancing age. In addition, the beneficial effects of combined estrogen/androgen therapy versus estrogen therapy alone on bone in women with postmenopausal osteoporosis have been documented.[4] This evidence provides strong rationale for our objective which is the development of a tissue-selective AR agonist that is anabolic on bone and muscle with reduced undesired andronizing effects on tissues, such as the prostate and skin, for the treatment of sarcopenia and osteoporosis.

From our previous work on the 5-α reductase program, we have identified **2**, a 4-aza analogue of **1**, as a full agonist for AR with reduced androgenizing or virilizing potential compared to the full androgen agonist DHT. In addition to moderate 5-α reductase activity (41% inhibition at 1000 nM), the in vitro profile of **2** is characterized by high binding affinity for human AR (hAR) ($IC_{50} = 7$ nM) in the competitive AR binding assay (ARBIND)[5a] and potent agonist activity ($EC_{50} = 5$ nM) in the transactivation assay of hAR (TAMAR),[5b] a cell-based transactivation assay that examines potential to stimulate bone formation. In the virilization assay (VIRCON),[6] a two-hybrid assay designed to measure virilizing potential, **2** displayed low agonist activity (4%) in contrast to the full agonist DHT (73%). The *N*-methyl group has a pronounced effect on the ARBIND affinity, as the compound that lacks this moiety has ARBIND $IC_{50} > 1000$ nM. The pharmacokinetic (PK) profile of **2** in dogs is typified by a short plasma half-life ($t_{1/2} = 42$ min) and a high clearance (CL) rate (32.3 (mL/min)/kg). An initial set of *N*-methyl-4-aza steroids[7] was evaluated for stability in the presence of female rat, male rat, dog, and human liver microsomes, and in general, there was good correlation between the observed $t_{1/2}$ in dog and human liver microsomes. Moderate stability was observed in the presence of female rat microsomes; however, high CL was generally observed in the presence of male rat microsomes because of species specific oxidation of the *N*-methyl group in male rats. Compounds with appropriate in vitro and PK profiles are studied in vivo in a female overiectimized (OVX) rat model for evaluation of osteoanabolism and tissue selectivity.[7] Compounds that demonstrate selectivity in the OVX rat model are then studied in the orchiectimized (ORX) male rat model to evaluate effects on ventral prostate (VP) and seminal vesicles (SV). For this initial class of compounds, we targeted a series of compounds that maintained partial to full agonist activity in TAMAR with minimal activity in VIRCON and improved PK based on the structure of **2** and a series of 16-substituted-4-azasteroids was investigated.

16-Alkyl and 16-alkenyl analogues were prepared by the synthetic sequences shown in Scheme 1. The A-ring of testosterone **4** was oxidatively cleaved with potassium permanganate[8] to give keto acid **5**. Conversion to the lactam was facilitated by treatment with methylamine[9] in ethylene glycol at 180 °C, followed by platinum-catalyzed hydrogenation of the 5,6-olefin to afford intermediate **6**. The 1,2-olefin was installed by a four-step, two-pot procedure involving silylation of the 17-alcohol with TESOTf and 2,6-lutidine, alkylation of the 2-position with phenylmethylsulfinate[10] and KH to afford the sulfoxide, thermal elimination in refluxing toluene, and desilylation via treatment with HF in MeCN to afford 1,2-ene **7**. Swern oxidation[11] of the 17-alcohol afforded ketone **8**, which was subsequently treated via one of two sequences. For 16-alkyl substitution, ketone **8** was deprotonated with LDA at −78 °C and then treated with the requisite alkyl halide at −20 °C to afford ketone **9**. Reduction of the ketone with LAH (or $NaBH_4$) at low temperature afforded the targeted alcohols **10**−**12** in reasonable overall yields. For 16-alkenyl

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[a]Abbreviations: AR, androgen receptor; DHT, dihydrotestosterone; hAR, human androgen receptor; OVX, overiectimized; ORX, orchiectimized; ARBIND, androgen receptor binding assay; TAMAR, transactivation assay of endogenous human AR; VIRCON, virilization assay; hERG, human ether-a-go-go-related gene; SV, seminal vesicle; VP, ventral prostrate; UW, uterine weight; PK, pharmacokinetics; $t_{1/2}$, half-life; CL, clearance; BFR, bone formation rate; SC, subcutaneous.

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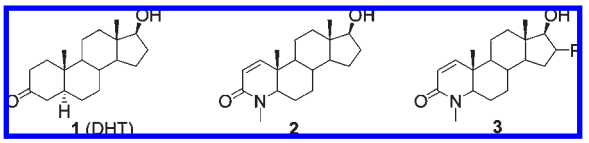
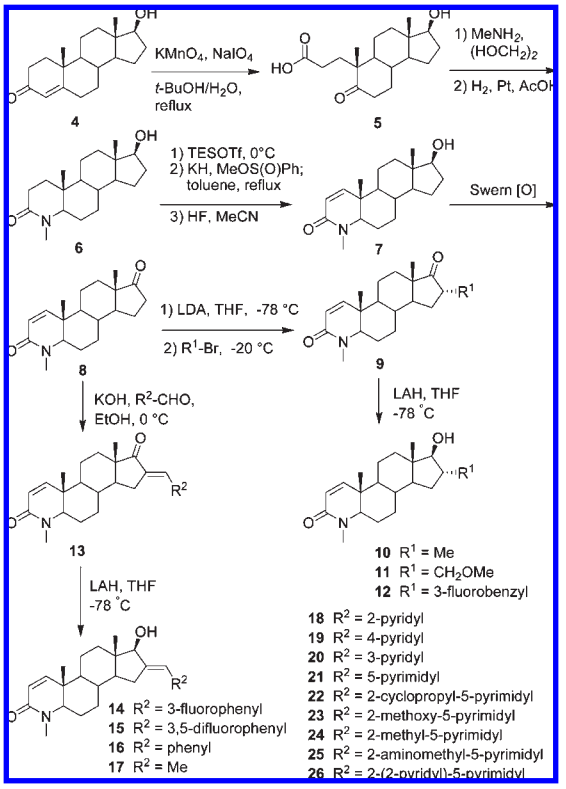



**Figure 1.** Structure of AR leads.

**Scheme 1.** Synthesis of AR ligands.




substitution, ketone **8** was treated with the appropriate aldehyde and KOH in ethanol to afford *trans*-enone[12] **13**, which was also reduced with LAH at low temperature to afford styrenyl analogues **14**–**26**.

A series of compounds were designed and synthesized and their in vitro profiles evaluated with the aim of optimizing agonist potency, minimizing virilizing potential, and improving $t_{1/2}$ in dogs. Compounds with sufficient affinity in ARBIND ($IC_{50} < 200$ nM) were tested in the TAMAR and VIRCON assays, counterscreened for human ether-a-go-go-related gene (hERG) $K^+$ ion channel[13] affinity to assess a compound's ability to affect heart through QT prolongation, and then evaluated for PK in beagle dogs.

A series of 16-alkylated analogues (**10**–**12**; see Table 1) displayed only 3- to 5-fold weaker binding affinity than lead **2**; however, methyl and methoxymethyl analogues **10** and **11** exhibited a significant loss of agonist activity and potency in TAMAR with $EC_{50}$ values of 119 and 612 nM and EMAX values of 54% and 43%, respectively. In contrast, 3-fluorobenzyl analogue **12** maintained potency and partial agonist activity in TAMAR ($EC_{50} = 14$ nM, EMAX = 40%) while at the same time exhibiting minimal agonist activity in the VIRCON assay (1%). In addition, when **12** was evaluated for dog PK, it displayed a modest increase in $t_{1/2}$ (3 h) and a lower CL (22.0 (mL/min)/kg) compared to the lead **2**. Styrenyl analogue **14**, exhibited improved PK with a $t_{1/2}$ of 4.9 h and a lower CL (15.2 (mL/min)/kg). The monofluoro analogue **14** displayed partial agonist activity in the TAMAR assay ($EC_{50}$ = 12 nM, EMAX of 65%), minimal agonist activity in the VIRCON assay (1%), and potent undesirable hERG affinity (KI = 29 nM). The addition of a second fluoro substituent to afford **15** restored full agonist activity in the TAMAR assay (EMAX = 98%) and further improved dog PK ($t_{1/2}$ = 9.1 h; CL = 6.8 (mL/min)/kg); however, no improvement was observed in the hERG affinity (KI = 46 nM). Removal of the substituents to afford styrene **16** maintained full agonist activity but only afforded a modest improvement in the hERG affinity (KI = 225 nM). Further truncation to afford ethylene analogue **17** again maintained full agonist activity and reduced hERG affinity (KI = 8050 nM) but resulted in poor dog PK with a short $t_{1/2}$ (1.0 h) and high CL (42.8 (mL/min)/kg).

To address the undesirable hERG activity and restore the improved PK observed with the styrenyl analogues, the more basic pyridine and pyrimidine analogues **18**–**26** were identified and evaluated. A general potency trend in ARBIND was observed for the pyridyl analogues in that 3-pyridyl **20** was more potent than 4-pyridyl **19**, which was more potent than 2-pyridyl analogue **18**, with ARBind $IC_{50}$ values of 62, 129, and 292 nM, respectively. The 4-pyridyl analogue **19** exhibited partial agonist activity in TAMAR ($EC_{50}$ = 138 nM, EMAX = 69%) with low VIRCON activity; however, hERG affinity was not improved. The 3-pyridyl **20** restored full agonist activity in TAMAR, maintained low VIRCON activity (3%), and had reduced hERG affinity (KI = 3600 nM) and improved dog PK ($t_{1/2}$ = 17.1 h, CL = 5.0 (mL/min)/kg, and 21% oral bioavailability). It was also observed that the addition of a second nitrogen to the aryl ring, i.e., on moving from pyridine **20** to pyrimidine **21**, afforded at least a 3-fold increase in TAMAR agonist potency; i.e., 3-pyridyl **20** had an $EC_{50}$ of 62 nM, whereas pyrimidines **21** and **24** (which differ in structure by only one methyl group) had TAMAR $EC_{50}$ values of 17 and 8 nM, respectively, while maintaining the full agonist activity in TAMAR. The unsubstituted pyrimidine **21** displayed low agonist activity in VIRCON (6%), a $t_{1/2}$ of 2.3 h, and a CL rate of 15.3 (mL/min)/kg. When dosed orally from an aqueous 0.5% methylcellulose suspension to dogs, **21** afforded 51% bioavailability. The addition of substituents to the 2-position of the pyrimidine structure resulted in significant changes in these parameters including significant increases in VIRCON activity, increased TAMAR potency, and improved PK in dogs. Both alkyl (**22**, **24**) and polar (**23**, **25**) substituents were tolerated; however, larger substituents such as a 2-[2-pyridyl] analogue **26** were not tolerated and resulted in a loss of binding activity. These changes are typified by the methylpyrimidine **24**, a potent full agonist in TAMAR ($EC_{50}$ = 8 nM, EMAX = 137%), high agonist activity in VIRCON (82%), a longer $t_{1/2}$ of 18.7 h, and a lower CL (1.5 (mL/min)/kg) in dogs. This methyl group also resulted in a lower water solubility for **24** (0.23 mg/mL at pH 2) than for **21** (0.57 mg/mL at pH 2); however, both were still reasonable. Importantly, all pyrimidine analogues **21**–**25** had significantly weaker hERG activity with KI between 4650 and 22 500 nM. Compounds **21** and **24** exhibited good selectivity against other nuclear receptors including glucocorticoid, mineralocorticoid, progesterone, and estrogen receptors ($IC_{50} > 1000$ nM), and the addition of the 16-olefin resulted in a loss of the 5-α reductase activity.

This subtle structural change that resulted in a significant shift in virilizing potential and PK profile made analogues **21** and **24** attractive for further investigation. Thus, pyrimidines

**Table 1.** Binding Affinity, Transcriptional Activities, and PK Data for Agonists **1**, **2**, **10**−**12**, and **14**−**26**

| ligand | ARBind $IC_{50}$ (nM) | TAMAR $EC_{50}$ (nM) (% EMAX) | VIRCON % at 300 nM | hERG affinity KI (nM) | dog iv $t_{1/2}$ (h)[b] | dog CL ((mL/min)/kg)[b] | dog *F* (%)[c] |
|---|---|---|---|---|---|---|---|
| **1** | 1 | 2 (100) | 73 | –[a] | –[a] | –[a] | |
| **2** | 7 | 5 (105) | 4 | 130000 | 0.7 | 32.3 | |
| **10** | 31 | 119 (54) | < 1 | 20000 | 1.0 | 20.2 | |
| **11** | 24 | 612 (43) | 2 | 39000 | 1.5 | 11.0 | |
| **12** | 23 | 14 (40) | 1 | 240 | 3.0 | 22.0 | |
| **14** | 27 | 12 (65) | 1 | 29 | 4.9 | 15.2 | |
| **15** | 41 | 8 (98) | 1 | 46 | 9.1 | 6.8 | |
| **16** | 116 | 26 (140) | 1 | 225 | –[a] | –[a] | |
| **17** | 35 | 17 (92) | 1 | 8050 | 1.0 | 42.8 | |
| **18** | 292 | –[a] | –[a] | –[a] | –[a] | –[a] | |
| **19** | 129 | 138 (69) | 1 | 320 | –[a] | –[a] | |
| **20** | 62 | 62 (93) | 3 | 3600 | 17.1 | 5.0 | 21 |
| **21** | 59 | 17 (141) | 6 | 9400 | 2.3 | 15.3 | 51 |
| **22** | 51 | 26 (140) | 50 | 4650 | –[a] | –[a] | |
| **23** | 11 | 2 (158) | 79 | 7900 | 12.7 | 4.6 | |
| **24** | 43 | 8 (137) | 82 | 15000 | 18.7 | 1.5 | |
| **25** | 31 | 5 (148) | 87 | 22500 | 10.9 | 0.8 | |
| **26** | 715 | –[a] | –[a] | –[a] | –[a] | –[a] | |

[a] Not tested. [b] The iv injection of 0.2 mpk compound in DMSO to two male or female beagle dogs as PK cocktails. [c] The po administration of 1 mpk compound in 0.5% aqueous methylcellulose to two male or female beagle dogs as single compounds.

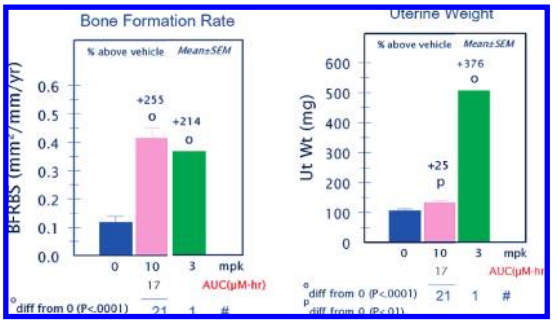



**Figure 2.** In vivo BFR and UW data for **21** in OVX rat.

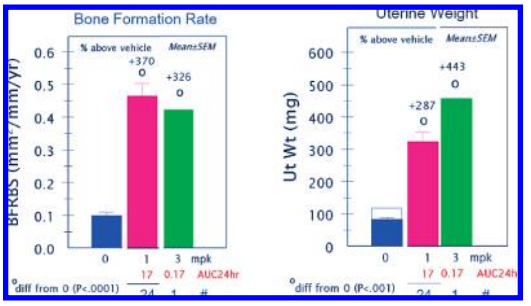



**Figure 3.** In vivo BFR and UW data for **24** in OVX rat.

**21** and **24**, in addition to DHT as a positive osteoanabolic and virilization control, were evaluated in the bone formation assay. In this assay, nine female Sprague−Dawley rats are OVX, to cause bone loss and simulate estrogen deficient, osteopenic adult human females. Following pretreatment with a low dose of an antiresorptive,[14] the rats are then dosed with the test compounds subcutaneously (sc)[15] once daily for 24 days. On the 5th and 15th days of treatment, a single sc injection of calcein (8 mg/kg) is given (measures increase in bone formation, shown by increased fluorochrome labeling at the periosteal surface of the femur). The osteanabolic effect (versus vehicle in blue; see Figures 2 and 3) is calculated from these data and is reported as a bone formation rate (BFR) as a % of the effect of DHT (set to 100%) at a standard dose (see Table 2). Virilizing effects are evaluated in two organs: the uterus and the skin. Increase in uterine weight (UW) is determined by measuring the isolated wet weight (vs vehicle in blue; see Figures 2 and 3), and the data are reported as a % of the effect caused by DHT (set to 100%; see Table 2). The effect on skin is determined by removal of sections of skin from the back of the rats, extraction of the RNA, and amplification and quantification by quantitative real-time RT-PCR analysis of two genes involved in sebum secretion. The skin data are also reported as a % of the effect caused by DHT (set to 100%). At an AUC of 17 $\mu$M·h, the low VIRCON pyrimidine **21** exhibited a BFR equal to that of DHT (120%), with minimal effects on skin (6% of DHT) and minimal change in UW (7% of DHT).

**Table 2.** Normalized OVX Data for **21** and **24**[a]

| ligand | dose, mpk | AUC, $\mu$M·h | BFR,[b] % DHT | UW change,[c] % DHT | skin effect,[d] % DHT |
|---|---|---|---|---|---|
| DHT | 3 | 0.02 | 100 | 100 | 100 |
| **21** | 10 | 17 | 120 | 7 | 6 |
| **24** | 1 | 17 | 113 | 65 | 61 |

[a] For complete details, refer to Supporting Information. [b] Assessed for total periosteal surface, single fluorochrome label, double fluorochrome label, interlabel distance, and a BFR is then calculated and reported as % activity to DHT. [c] The uterus is located, blunt dissected free, blotted dry, and weighed. [d] Skin QRT-PCR: Sections of skin are collected, RNA is extracted, and two genes are amplified and quantified.

In contrast, when dosed to achieve the same AUC, the high VIRCON pyrimidine **24** exhibited a BFR equal to that of DHT (113%) but also significant virilizing effects. Pyrimidine **24** caused a 65% increase in UW and a similar 61% effect on skin compared to DHT. To confirm the attenuated virilizing potential of **21**, it was evaluated in male ORX rats by dosing sc once daily for 17 days and then determining the change in VP and SW weights compared to DHT (set to 100%) (see Figure 4 and Table 3). Higher doses were required in the male ORX rat model because of metabolism of the *N*-Me group; therefore, a dose of 30 mpk was required to achieve an exposure similar to that obtained in the OVX model. At 16.2 $\mu$M·h, **21** exhibited a 3% increase in VP weight and a 21% increase in SV weight compared to DHT, confirming its tissue selectivity.

In summary, we have identified a novel series of 16-substituted 4-azasteroids as potent and selective AR modulators.

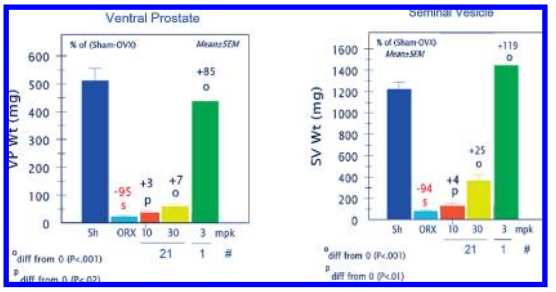



**Figure 4.** In vivo VP and SV wt data for **21** in ORX rat.

**Table 3.** Normalized ORX Data for **21**[a]

| ligand | dose, mpk | AUC, $\mu$M·h | VP wt change,[b] % DHT | SW wt change,[c] % DHT |
|---|---|---|---|---|
| DHT | 3 | 0.08 | 100 | 100 |
| **21** | 10 | 4.3 | 4 | 8 |
| **21** | 30 | 16.2 | 3 | 21 |

[a] See Supporting Information for complete details. Six male Sprague–Dawley rats are ORX followed by 17 days of q.d. sc dosing. PK collected on day 17. [b] VP is located, blunt dissected free, blotted dry, and weighed. [c] SV is located, dissected free, blotted dry, and weighed.

The introduction of polar styrenyl pyridine and pyrimidine moieties to the 4-azasteroid scaffold resulted in a series of compounds with good potency in TAMAR, reduced agonism in VIRCON, reduced affinity for the hERG $K^+$ channel, and good dog PK. In addition, this work demonstrated that a good in vitro/in vivo correlation between potency in TAMAR and BFR and the percent agonism in the VIRCON assay and the effects observed on the skin and uterus in OVX rats exists for this series. And finally, we have identified pyrimidine **21** as having an attractive osteoanabolic and tissue-selective in vivo profile.

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**Supporting Information Available:** Experimental procedures and characterization data of final compounds and details for the biological evaluation of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) (a) Negro-Vilar, A. Selective AR modulators (SARMs): a novel approach to androgen therapy for the new millennium. *J. Clin. Endocrinol. Metab*. **1999**, *84*, 3459–3462. (b) Liu, P. Y.; Swerdloff, R. S.; Veldhuis, J. D. The rationale, efficacy and safety of androgen therapy in older men: future research and current practice recommendations. *J. Clin. Endocrinol. Metab*. **2004**, *89*, 4789–4796. (c) Gao, W.; Dalton, J. T. Expanding the therapeutic use of androgens via selective AR modulators (SARMs). *Drug Discovery Today* **2007**, *12*, 241–248.

(2) (a) Gao, W.; Reiser, P. J.; Coss, C. C.; Phelps, M. A.; Kearbey, J. D.; Miller, D. D.; Dalton, J. T. Selective AR modulator treatment improves muscle strength and body composition and prevents bone loss in orchidectomized rats. *Endocrinology* **2005**, *146*, 4887–4897. (b) Swerdloff, R. S.; Wang, C.; Cunningham, G.; Dobs, A.; Iranmanesh, A.; Matsumoto, A. M.; Snyder, P. J.; Weber, T.; Longstreth, J.; Berman, N. Long-term PK of transdermal testosterone gel in hypogonadal men. *J. Clin. Endocrinol. Metab*. **2000**, *85*, 4500–4510. (c) Jockenhovel, F. Testosterone supplementation: what and how to give. *Aging Male* **2003**, *6*, 200–206.

(3) (a) Vermeulen, A. Androgen replacement therapy in the aging male—a critical evaluation. *J. Clin. Endocrinol. Metab*. **2001**, *86*, 2380–2390. (b) Tan, R. S.; Culberson, J. W. An integrative review on current evidence of testosterone replacement therapy for the andropause. *Maturitas* **2003**, *45*, 15–27. (c) Wang, C.; Swerdloff, R. S. Editorial: Should the nonaromatizable androgen dihydrotestosterone be considered as an alternative to testosterone in the treatment of the andropause? *J. Clin. Endocrinol. Metab*. **2002**, *87*, 1462–1466. (d) Sharma, V.; Perros, P. The management of hypogonadism in aging male patients. *Postgrad. Med*. **2009**, *121*, 113–121. (d) Miner, M. M.; Sadovsky, R. Evolving issues in male hypogonadism: evaluation, management, and related comorbidities. *Cleveland Clin. J. Med*. **2007**, No. Suppl., 3, S38–S46.

(4) Hofbauer, L. C.; Khosla, S. Androgen effects on bone metabolism: recent progress and controversies. *Eur. J. Edocrinol*. **1999**, *140*, 271–286.

(5) Refer to Supporting Information. (a) Characterized by the displacement of [$^3$H]methyltrienolone by compounds in the hAR from MDA-MB-453 cells. (b) Measured by the ability of test compounds to control transcription from the MMTV-LUC reporter gene in MDA-MB-453 cells. (c) Quantified by the ability of agonists to induce stable assembly of an AR N-terminal /C-terminal interaction. Values are % of agonism of R1881.

(6) He, B.; Kemppainen, J. A.; Wilson, E. M. FXXLF and WXXLF sequences mediate the NH2-terminal interaction with the ligand binding domain of the androgen receptor. *J. Biol. Chem*. **2000**, *275*, 22986–22994.

(7) A full description of the correlation between TAMAR, VIRCON, and observed in vivo effects are the subject of a separate manuscript.

(8) Gut, M.; Uskokovic, M. 4-Aza-17$\alpha$-methyl-17$\beta$-hydroxyandrost-5-en-3-one and methyltestosterone-4-C14. *J. Org. Chem*. **1961**, *26*, 1943–1944.

(9) Rasmusson, G. H.; Johnston, D. B. R; Arth, G. E. 4-Aza-17$\beta$-substituted-5$\alpha$-androstan-3-one-reductase Inhibitors. U.S. Patent 4377584, 1983.

(10) Monteiro, H. J.; De Souza, J. P. New synthesis of $\beta$-keto phenylsulfoxides. *Tetrahedron Lett*. **1975**, *11*, 921–924.

(11) Mancuso, A. J.; Huang, S.-L.; Swern, D. Oxidation of long-chain and related alcohols to carbonyls by dimethyl sulfoxide "activated" by oxalyl chloride. *J. Org. Chem*. **1978**, *43*, 2480–2482.

(12) El-Rayyes, N. R.; Ramadan, H. M. Heterocycles. Part X. Synthesis of new pyrimidine systems. *J. Heterocycl. Chem*. **1987**, *24*, 589–596.

(13) (a) Pearlstein, R.; Vaz, R.; Rampe, D. Understanding the structure–activity relationship of the HERG gene cardiac $K^+$ channel. A model for bad behavior. *J. Med. Chem*. **2003**, *46*, 1–6. (b) Fermini, B.; Fossa, A. The impact of drug-induced QT interval prolongation on drug discovery and development. *Nat. Rev. Drug Discovery* **2003**, *2*, 439–447.

(14) In humans and rats, most of the hormonal bone resorption activity is controlled by ER$\alpha$ and not by AR. The OVX rats used in this experiment may have high bone turnover, and therefore, an antiresorptive agent was used to suppress bone resorption in order to increase the assay window. The effects of SARMs on cortical bone formation with and without an antiresorptive agent were compared (to be reported elsewhere).

(15) Other administration routes were also used. Compound **24** gave similar in vivo effects when dosed orally from a 0.5% aqueous methylcellulose suspension.