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Tetrahydroquinolines as a novel series of nonsteroidal selective androgen receptor modulators: Structural requirements for better physicochemical and biological properties

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ABSTRACT

A rationally designed tetrahydroquinoline (**1**) for nonsteroidal selective androgen receptor modulators was modified for the exploration of promising compounds by Grieco three-component condensation using various dienophiles. Based on the in vitro effects and physicochemical properties of the synthesized compounds, compound **4c** was selected for further study. Compound **4c** increased the femoral bone mineral density as much as DHT, but it reduced the uterus effect compared with DHT in ovariectomized rats. Thus, compound **4c** has desirable osteoanabolic effects with weak undesirable effects on the uterus in a female osteoporosis model.

These days, calcium, vitamin D3 supplementation, and bone resorption inhibitors such as bisphosphonates, estrogens, and selective estrogen receptor modulators (SERMs) are used in the prevention and treatment of osteoporosis. Bisphosphonates and estrogens increase bone mineral density (BMD) by decreasing bone resorption. SERMs maintain bone mass without affecting the breast and uterus. On the other hand, androgens, which have been investigated by several pharmaceutical companies because of their many physiological roles,[1] are known to have positive effects on BMD by increasing bone formation.[2,3] Therefore, selective androgen receptor modulators (SARMs) for osteoanabolic activity without the virilizing effects of steroidal androgens could be alternative treatments for osteoporosis.

Many chemically distinctive nonsteroidal SARMs have been created for to avoid the undesirable effects of treatments for prostate diseases, osteoporosis, hormone replacement therapy, and muscle-wasting diseases. Several nonsteroidal androgen receptor (AR) agonists—LGD-2941, BMS-564929, and GTx-007—have shown anabolic effects with few virilizing effects in preclinical studies (Fig. 1).[1,4]

In our study focusing on the development of new SARMs, we reported that a tricyclic tetrahydroquinoline (THQ), compound **1**, had an advantageous characteristic for being an SARM.[4] Its structure featured our four-point pharmacophore hypothesis for the structural requirement of an AR agonist. Compound **1** exhibited not only

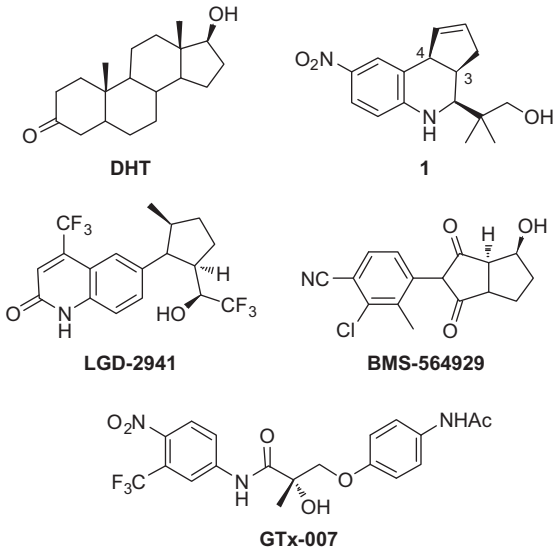

Figure 1. DHT and representative nonsteroidal AR modulators.

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strong AR agonistic activity but also the highest selectivity in binding affinity to the AR among steroid hormone receptors. The combination of nitro, methyl, and hydroxyl groups was indispensable for exerting agonistic activity and an anabolic effect on the levator ani of orchiectomized (ORX) rats in vivo.

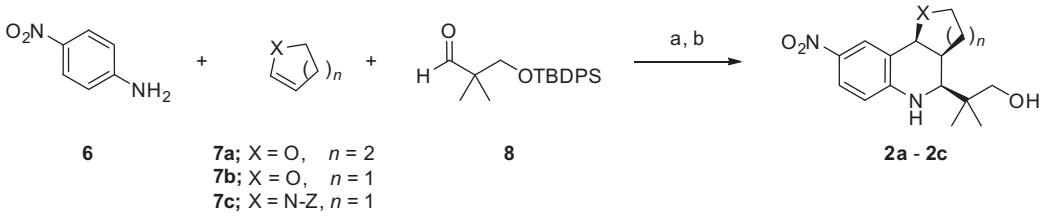
In this Letter, we report on our continuous effort to explore the ideal structural requirements of AR agonistic activity and to improve physicochemical properties simultaneously. We then describe the in vivo results of the best compound.

The calculated log*P* (*c*log*P*) of compound **1** was 2.57,[5] which appeared to be an appropriate value for drug likeness, but its water solubility was very low (0.23 μg/ml). Water solubility is generally related largely to the polarity of the molecule, and the AR, whose endogenous ligands are androgens, has an affinity for nonpolar compounds. Therefore, we had to create compounds with a special balance between water solubility and AR binding affinity. Moreover, the molecular volume of ligands was important for their AR agonistic activity.[4]

The cyclopentene moiety of **1**, a dienophile part of Grieco three-component condensation (Grieco 3CC),[6] seemed to be a preferable position from which to control physicochemical properties, for two reasons: first, this dienophile part would have a very small effect on the biological properties based on our initial hypothesis; second, various derivatives could be synthesized easily using commercially available dienophile reagents. The synthesized compounds were evaluated by measuring AR binding affinity and water solubility. The agonistic and antagonistic activities of the compounds were measured when they were needed.

The tricyclic derivatives (**2a**–**2c**), whose heterocyclic ring was a substitute for the cyclopentene ring, were synthesized so as to add some polarity into the molecule while keeping the overall shape intact (Scheme 1, Table 1). The corresponding products were produced by the reaction of 4-nitroaniline (**6**), *O*-TBDPS-protected aliphatic aldehyde (**8**), and each cyclic dienophile (**7**) in the presence of an equimolar amount of TFA in MeCN followed by desilylation with TBAF in THF. Compound **2c** required an extra Z-deprotection step. The tricyclic derivative having an endocyclic oxygen atom **2a** had better water solubility and *c*log*P* compared with **1**, but the AR binding affinity and agonistic activity of compound **2a** decreased by approximately 12-fold and 40-fold, respectively. In addition, compound **2b**, which also had an endocyclic oxygen atom, had 100-fold higher water solubility, but its AR binding affinity and agonistic activity were moderate. The AR binding affinity of compound **2c** with a nitrogen atom in place of the oxygen atom in **2b** disappeared. It is difficult to precisely explain why the AR binding affinity was gone, but it may be said that the very polar hydrogen attached to the pyrrolidine amino group makes it difficult for the compound to approach the AR. The polarity of the tricyclic framework appeared to be incompatible with AR binding affinities and agonistic activities; thus, we focused our efforts on changing the tricyclic framework.

We planned to synthesize 4-heteroatom-substituted derivatives with several molecular volumes (Scheme 2, Table 2). These derivatives were sought to achieve an ideal balance between water solubility and AR binding affinity on the assumption that a polar functional group attached to the bicyclic framework through a single bond could be freely oriented to a region out of the way for AR binding affinities. In order for this assumption to be realized, we focused on 4-*N*-substituted amino derivatives because of the ease of synthesizing various kinds of derivatives from the common starting material, *N*-formyl vinylamine (**10**). The synthesis of 4-heteroatom-substituted derivatives proceeded smoothly. The 4-ethoxy bicyclic derivative **3a** was synthesized using vinyl ethyl ether as the dienophile. 4-*N*-Substituted amino-derivatives (**4a**–**4c** and **4f**–**4i**) were synthesized from 4-*N*-protected THQ (**4d**). The deformylation of **4d** with HCl afforded the 4-amino derivative **4e** as an HCl salt. 4-*N*-Monoalkylamino (**4a** and **4i**) and 4-*N*,*N*-dialkylamino derivatives (**4b** and **4c**) were synthesized by reductive *N*-alkylation of **4e** with appropriate aldehydes. The 4-amide, urea, and thiourea derivatives (**4f**–**4h**) were synthesized by isobutyryl chloride, isopropyl cyanate, and isopropyl thiocyanate, respectively. The 4-ethoxy bicyclic derivative **3a** was as water-soluble as **2b**. Moreover, the AR binding affinity and agonistic activity of **3a** were parallel with those of **2b**. The 4-amino derivative **4a**, which was thought to structurally correspond to **2c**, showed disappointing AR binding affinity. However, the addition of another *n*-propyl group onto the 4-*n*-propylamino moiety bestowed a moderate but clear binding affinity to the AR on **4b**. These



6 **7a;** X = O, *n* = 2; **7b;** X = O, *n* = 1; **7c;** X = N-Z, *n* = 1 **8** **2a - 2c**

Scheme 1. Reagents and conditions: (a) TFA, MeCN; (b) TBAF, THF.

Table 1
AR binding affinities, agonistic and/or antagonistic activities, solubilities, *c*log*P*, and molecular volumes of THQs

Compound	X, *n*	Binding affinity IC_{50}[a] (nM)	Agonistic activity EC_{50}[a] (nM)	Antagonistic activity IC_{50}[a] (nM)	Solubility (μg/mL)	*c*Log*P*[b]	Molecular volume (Å^3)[b]
DHT		3.1	0.97	—[c]		3.66	982
1		5.1	2.3	—[c]	0.23	2.57	920
2a	X = O, *n* = 2	59	95	61,000	4.20	2.00	944
2b	X = O, *n* = 1	38	190	1,500	22.51	1.77	904
2c	X = NH, *n* = 1	>1,000	—[c]	—[c]	—[c]	1.11	921

[a] Binding affinity (IC_{50}) was determined by the rat AR competitive binding assay. Agonistic (EC_{50}) and antagonistic activities (IC_{50}) were determined by an AR reporter assay.[4]
[b] Predicted octanol/water partition coefficient (*c*log*P*) and molecular volume were calculated using QikProp.[5]
[c] Compounds were not tested.