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Design and synthesis of tricyclic tetrahydroquinolines as a new series of nonsteroidal selective androgen receptor modulators (SARMs)

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ABSTRACT

Some tricyclic tetrahydroquinolines (THQs) were found to have the potential of a new series of nonsteroidal selective androgen receptor modulators (SARMs). Compound **5b** was first designed and synthesized under our hypothesis based on a four-point pharmacophoric requirement of the 3-carbonyl, 18-methyl, 17-hydroxyl, and 13-quaternary carbon groups of dihydrotestosterone (DHT). It was revealed that this compound exhibits not only a strong androgen receptor (AR) agonistic activity (EC_{50} = 9.2 nM) but also the highest selectivity in binding affinity to AR among the steroid hormone receptors. Furthermore, this compound showed a weak virilizing effect with retention of the desired anabolic effect as compared with DHT in vivo.

The androgen receptor (AR) is a member of the nuclear receptor superfamily, which consists of the receptors for estrogen, progesterone, glucocorticoids, mineralocorticoids, and androgens.[1] Physiologically, AR is activated by endogenous androgens, testosterone (TES), and its metabolite, dihydrotestosterone (DHT). TES and DHT play important roles in establishing and maintaining the male phenotype.[2] Their actions are essential for the differentiation and growth of male reproductive organs. In addition, androgens are important for the development of male characteristics in certain extragenital structures such as muscle, bone, hair, larynx, skin, lipid tissue, and kidney.[3] The activated AR forms a homodimer and subsequently recruits necessary coregulators and/or general transcription factors to mediate the enhancement or repression of transcription of the target gene.

Various synthetic steroidal AR ligands have been developed for the treatment of male hypogonadism, muscle wasting, anemia, benign prostate hyperplasia, and prostate cancer,[4] but the use of such steroidal AR ligands has been limited because of their poor oral bioavailability and the risks of serious side effects.[4,5] On the other hand, nonsteroidal AR modulators have also been developed by several research groups (Fig. 1).[6] Especially the compound **3** not only binds AR with high affinity but also demonstrates tissue selectivity in animal models.[7] This compound showed the possibility of developing selective AR modulators (SARMs) with receptor and tissue selectivity avoiding undesired side-effects derived from steroidal templates.

To create nonsteroidal AR agonists, we have designed tricyclic tetrahydroquinoline (THQ) derivatives by a four-point pharmacophore method. In this Letter, we would like to report a nonsteroidal SARM lead compound **5b** which has a strong binding affinity and an agonistic activity to AR. The in vivo effect of the compound **5b** was also shown in the latter part of this Letter.

To design nonsteroidal AR agonists, the common pharmacophore points of AR modulators were extracted by structural comparison of DHT, tricyclic quinolinones (**1** and **2**),[8,9] and diaryl propionamides (**3** and **4**)[7,10] (Fig. 1). The nitro group of **3** and cyano group of **4** are well known as bioisosteres of the 3-carbonyl group of DHT.[11] Compounds **1** and **3** have been reported as agonists[7,8] while **2** and **4** as antagonists.[9,10] Before superimposition of these five compounds, their three-dimensional (3D) structures were built by ab initio full geometry optimizations using Jaguar and selected the most stable conformation.[12]

Upon superimposition of these 3D structures, we paid attention to the 3-carbonyl, the 18-methyl groups and 13-position's carbon atom of DHT at the beginning. This was based on the following five factual data obtained from the solved crystal structure of the AR ligand-binding domain bound with DHT,[13] and the common features of DHT and tricyclic quinolinones (**1** and **2**): (1) the 3-carbonyl and 17-hydroxyl groups of DHT are two major functional groups playing a key role for the binding to the receptor, (2) the 18-methyl group and the 13-carbon atom stipulating the distance and the angle of 18-methyl group, being settled closely to the 17-hydroxyl group of DHT, are important for face recognition of AR, (3) the 6-ethyl group of **1** and the 8-dimethyl groups of **2** play important roles as the 18-methyl group of DHT, (4) the molecular volume

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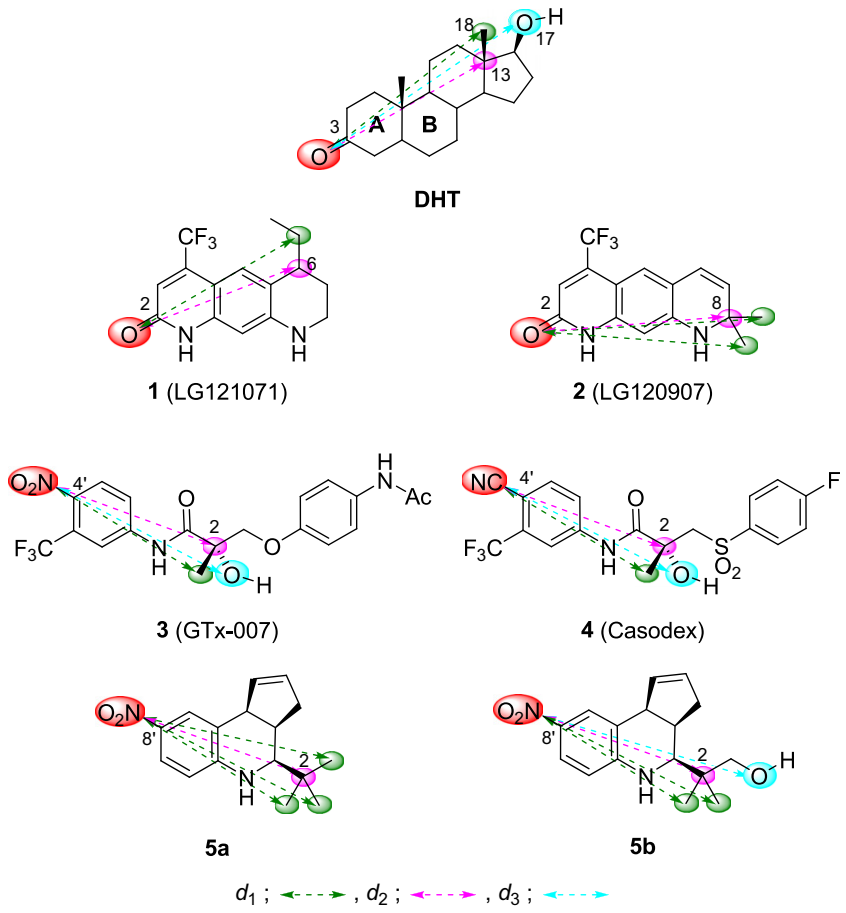

Figure 1. DHT and nonsteroidal AR modulators, and the distances between the functional groups (d_1, d_2 and d_3).

of the ligand is also important for AR agonistic activity,[14] (5) tricyclic quinolinones (**1** and **2**) have strong AR binding activity though they have no hydroxyl group in their structure.[8,9]

We have constructed three-point pharmacophore hypothesis which consists of a carbonyl isostere for the 3-carbonyl group of DHT, one methyl group corresponding to the 18-methyl group of DHT and an aliphatic carbon corresponding to the 13-carbon atom of DHT which we think is very important to place and direct properly the methyl group just mentioned above.[15] The distances are defined; d_1 is denoted by a green dashed arrow and d_2 as a magenta dashed arrow (Fig. 1). All these distances were measured by Maestro molecular modeling package.[12] The distance between the 3-carbonyl oxygen and 18-methyl carbon atoms of DHT (d_1) was 9.55 Å (Table 1). The distance between the 2-carbonyl oxygen and the 6-methylene carbon atoms of **1** (d_1) was 8.42 Å, while that between the 2-carbonyl oxygen and one of the 8-methyl carbon atoms of **2** (d_1) was 9.47 Å. The distances (d_1) of **1** and **2** were close to the d_1 of DHT. The distance between the 3-carbonyl oxygen and 13-quaternary carbon atoms of DHT (d_2) was 9.80 Å. Similarly, the distance between the 2-carbonyl oxygen and 6-tertiary carbon atoms of **1** (d_2) and the distance between the 2-carbonyl oxygen and 8-quaternary carbon atom of **2** (d_2) were found comparable to the distance of DHT (d_2) (**1**: 7.93 Å, **2**: 8.44 Å versus DHT: 9.80 Å). The distances, d_1 and d_2, of the diaryl propionamide **3** (d_1: 8.49 Å, d_2: 8.09 Å) and **4** (d_1: 9.60 Å, d_2: 9.23 Å) were also close to each corresponding distance of DHT.

The tricyclic THQ derivatives obtained by the Grieco three-component condensation (3CC) satisfied the above hypothesis (Scheme 1).[16] This reaction was very attractive for the introduction of appropriate substituents in the scaffold of THQs to design new AR agonists. As shown in Scheme 1, THQs can be synthesized only one step by reacting a substituted aniline, an electron-rich olefin, and a substituted aldehyde in the presence of an equimolar amount of trifluoroacetic acid (TFA) in acetonitrile (MeCN).

First, *p*-nitroaniline (**6a**) and trimethylacetaldehyde (**8a**) were selected for the 3CC reaction as the aniline and aldehyde components. The distances between the one oxygen atom of the nitro group and the carbon atom of the side-chain methyl groups of **5a** (d_1) were calculated to be 8.90, 9.22 and 9.78 Å. These distances were close to those of DHT (d_1: 9.55 Å). Cyclopentadiene (**7**) was chosen as a dienophile part which could react with the above-mentioned two components to give THQ with the molecular volume around 900 Å^3 comparable to that of DHT.[12] The reaction with **6a**, **7**, and **8a** proceeded smoothly and gave the corresponding *endo*-isomer **5a** (Scheme 1).

Although **5a** satisfied our three-point pharmacophoric requirement with its molecular volume similar to DHT, the AR binding affinity was moderate. Our initial hypothesis did not focus on the distinctive 17-hydroxyl group of DHT, because tricyclic quinolinones (**1** and **2**) do not have the corresponding hydroxyl group. We assumed the weak AR binding affinity should be due to the lack of a hydroxyl group at appropriate distances from the 3-carbonyl and 18-methyl groups. The distance between the 3-carbonyl and 17-hydroxyl groups of DHT (d_3) was 10.69 Å (Table 1). The distance (d_3) denoted by a cyan dashed arrow (Fig. 1). The diaryl propionamides, **3** and **4**, have a hydroxyl group with the corresponding distances (d_3) of 9.80 and 10.10 Å, respectively, from the 4-nitro or 4-cyano group by the calculations (Table 1). In the result, we adopted the four-point pharmacophoric requirements; the corresponding hydroxyl group was added to the initial hypothesis.