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Novel androgen receptor full antagonists: Design, synthesis, and a docking study of glycerol and aminoglycerol derivatives that contain *p*-carborane cages

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ABSTRACT

Based on the co-crystal structure of bicalutamide with a T877A-mutated androgen receptor (AR), glycerol and aminoglycerol derivatives were designed and synthesized as a novel type of carborane-containing AR modulators. The (*R*)-isomer of **6c**, whose chirality is derived from the glycerol group, showed 20 times more potent cell inhibitory activity against LNCaP cell lines expressing T877A-mutated AR than the corresponding (*S*)-isomer. Docking studies of both isomers with AR suggested that (*R*)-**6c** is in closer spatial proximity to helix-12 of the AR than (*S*)-**6c**, which is the most important common motif in the secondary structure of AR for the expression of antagonistic activity.

1. Introduction

Worldwide, prostate cancer (PC) is one of the major causes of cancer-related death in men.[1] The molecular basis of this disease involves an irregular behavior of the functions mediated by the androgen receptor (AR), which belongs to the nuclear receptor (NR) superfamily of transcription factors that regulate gene transcription upon ligand binding.[2] Synthetic AR modulators can be structurally classified as either steroidal or non-steroidal, and may exhibit various types of functional (androgenic, anti-androgenic, or anabolic) activity.[3] The non-steroidal ligand flutamide (**1**),[4] which is metabolized into the more potent AR antagonist hydroxyflutamide (OH-Flu, **2**),[4] is a well-known AR antagonist used for the treatment of PC (Fig. 1), while bicalutamide (Bic, **3**) is used for the treatment of D2-stage metastatic PC (Fig. 1).[5] In contrast to steroidal ligands, these two typical non-steroidal AR antagonists exhibit a high selectivity for AR.

Anti-androgens are particularly useful for the early-stage treatment of PC. However, PC often advances to a hormone-refractory state, in which the disease progresses despite continued androgen ablation or anti-androgen therapy due to the appearance of androgen-independent PC cells or the ability of adrenal androgens to support tumor growth.[6] Instances of anti-androgen-withdrawal syndrome (AWS), i.e., a clinical improvement upon withdrawal of the anti-androgen therapy, have also been reported after prolonged treatment with anti-androgens.[7] Thus, the development of pure AR full antagonists which are effective for AWS represents an attractive drug discovery goal in the context of AR.[8] Although the molecular mechanism of operation for AR is not fully understood yet, one proposed mechanism is based on the hypothesis that AR may be subject to a mutation, which has been discovered in patients treated with flutamide.[9] AR mutations that result in receptor promiscuity and the ability of anti-androgens to exhibit agonist activity might at least partially account for this phenomenon. In particular, a point mutation at T877 has been discovered in the AR-ligand-binding domain (AR LBD) in AWS patients, and this mutation has since been considered as a hotspot for the critical pathology.[9] Bic, which is the most widely used pure anti-androgen agent, acts as an anti-androgen for the T877A-mutated AR. However, Bic also exhibits significant androgenic activity towards W741L- or W741C-mutated AR, which is known as Bic-withdrawal syndrome (BWS).[9]

Carborane-containing ligands are of interest in medicinal chemistry, as they exhibit a different spectrum of ligand responsiveness relative to other therapeutic agents due to their unique chemical and structural features.[10] We have reported several *in vivo* drug candidates, such as estrogen-receptor modulators[11] and retinoid-X-receptor antagonists[12] that contain a carborane cage as a hydrophobic pharmacophore. Moreover, we have obtained several useful carborane-containing AR ligands as PC-treatment-drug candidates and AR-related biochemical tools, e.g. BA341 (**4**) and BA632 (**5**).[13,14] Compound **4** showed more

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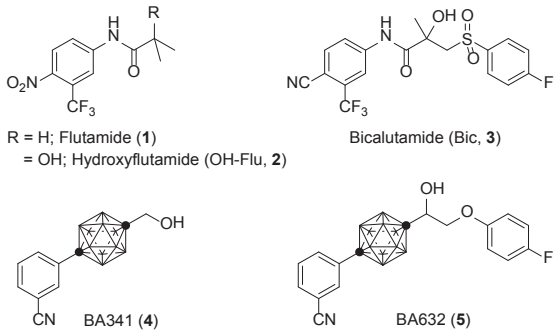

Fig. 1. Structures of non-steroidal and carborane-containing AR ligands.

potent AR-binding and AR-antagonistic activity levels than **2**, but acted as an agonist toward LNCaP cells, which express the T877A-mutated AR ($EC_{50} = 6.3 \times 10^{-7}$ M). Compound **5**, which contains a Bic-like side chain, acted as an AR full antagonist for LNCaP cells, i.e., the carborane cage acted as an effective hydrophobic pharmacophore for the AR LBD for both agonist and antagonist.

It seems that the steric repulsion between the carborane cage and several amino acid residues around helix-12 is able to directly control helix-12, which is crucial for expressing AR-antagonistic activity.[2] Our strategy for the development of AR full antagonists is based on a permanent AR antagonistic activity that is unaffected by the point mutation of AR LBD, using the direct repulsion between helix-12 and the carborane cage. Bohl et al. have reported that the cyano group of Bic interacts with the amino-acid residues Arg752, Glu711, and Met745 of AR LBD via a water molecule in co-crystal structure (Fig. 2a).[15]

Glycerol and aminoglycerol groups contain three hydrogen-bond acceptors and two or three hydrogen-bond donors, respectively. We anticipated that compounds with these groups could effectively bind to the target protein through the formation of multivalent hydrogen bonds. Although Hosoda et al. have reported that diphenylmethane derivatives with glycerol and aminoglycerol groups bind to the vitamin D receptor (VDR) and AR LBD, the specific roles of glycerol and aminoglycerol remain unclear.[16] Thus, we designed novel *p*-carborane derivatives with glycerol (**6**) and aminoglycerol groups (**7**) at the *para* position to mimic the binding mode of Bic with AR LBD containing a water molecule, and to bring the *p*-carborane cage closer to helix-12 in the AR (Fig. 2). In this paper, we describe the synthesis of novel *p*-carborane derivatives with glycerol (**6**) and aminoglycerol groups (**7**) at the *para* position and their biological activity, i.e., AR binding, their effect on AR-dependent proliferation of SC-3 and LNCaP cells, and an AR-ligand docking simulation study.

2. Results and discussion

2.1. Chemistry

Scheme 1 summarizes the synthesis of the target molecules **6** and **7**. *p*-Carborane derivative **8**,[11] which is protected with a *tert*-butyldimethylsilyl (TBS) group was consecutively treated with *n*-BuLi and CuCl to afford the corresponding Cu reagent, which was reacted with 4-iodoanisole or 4-iodonitrobenzene under Ullmann coupling conditions to furnish the corresponding aryl-*p*-carborane derivatives **9** and **11** in 54% and 80% yield, respectively.[17] The methoxy and TBS groups of **9** were deprotected with BBr_3 to afford phenol derivative **10**, in which a phenol group between two hydroxy groups is selectively transformed with 3-chloro-1,2-propanediol to generate the corresponding glycerol derivative **6a** in 91% yield over two steps. The reduction of the nitro group of **11** was accomplished by a catalytic hydrogenation using Pd/C under an atmosphere of hydrogen. The thus quantitatively obtained aniline (**12**) was reacted with glycidol, and the TBS group was subsequently deprotected with tetra-*n*-butylammonium fluoride (TBAF) to furnish the corresponding aminoglycerol derivative (**7**) in 29% yield over two steps.

Scheme 2 summarizes the synthesis of **6b**, **6c**, and **14**, whereby the

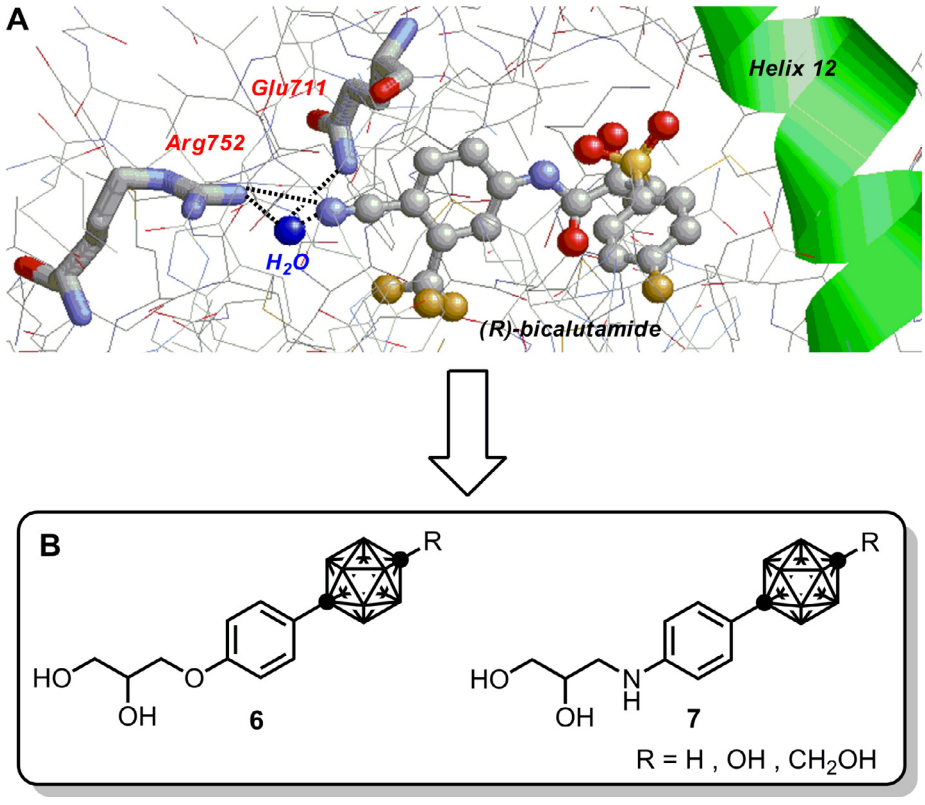

Fig. 2. (A) X-ray crystal structure of bicalutamide with AR-LBD (PDBID: 1Z95); (B) Design of novel carborane-containing AR full antagonist drug candidates **6** and **7**.