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[2.2.1]-Bicyclic sultams as potent androgen receptor antagonists

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ABSTRACT

This letter describes the discovery, synthesis, SAR, and biological activity of [2.2.1]-bicyclic sultams as potent antagonists of the androgen receptor. Optimization of the series led to the identification of compound **25**, which displayed robust pharmacodynamic effects in rats after oral dosing.

Prostate cancer (CaP) is the second leading cause of cancer-related death in men.[1] The etiology and progression of prostate carcinoma can be attributed to many factors related to androgen production. The standard of care for many years[2] has been androgen ablation, by surgical or chemical castration, in combination with an antiandrogen such as bicalutamide (**1**).[3] However, after a treatment period of 18 months, most patients progress to unresponsive castration resistant prostate cancer (CRPC).[4] The androgen receptor (AR) belongs to the nuclear hormone superfamily of ligand-induced transcription factors and is a key player of the signaling pathway leading to prostate carcinoma. In CPRC, there is sustained signaling due to overexpression, activation of the AR and the presence of AR mutations.[5] In addition, CPRC tumors express the necessary cytochrome P450 enzymes for intratumoral androgen production[6] suggesting that CPRC remains AR- dependent. Thus, effective new therapies must target AR signaling directly. Several new therapies have been recently approved by the FDA to treat CPRC, including enzalutamide (**2**)[7] and abiraterone acetate (**3**)[8] (Fig. 1). Both agents have shown promise in treating CPRC patients, however, most patients go on to develop resistance to enzalutamide or abiraterone acetate.[9] Thus, finding a novel antiandrogen with distinct interactions in the AR ligand binding domain might lead to more effective therapy for the treatment of CRPC.

Previous work from our laboratories described a series of bicyclic imide[10,11] and hydantoin-based[12,13] AR antagonists. We recently disclosed [2.2.1]-oxabicyclo imide-based AR antagonists, such as BMS-641988 (**4**).[14] Compound **4** exhibits higher AR binding affinity and significantly increased functional antagonist potency to both wild type and mutant AR compared to bicalutamide (Table 1). Compound **4** was advanced into clinical development based on its promising profile.[14] This letter describes an alternate approach for optimization of the [2.2.1]-bicyclic core with a view to identify potent AR antagonists with good metabolic stability and robust pharmacodynamic effects.

One potential issue associated with cyclic imides, such as compound **4** is that a pH-dependent equilibrium exists between open imide form and the closed form.[15] Thus, one of our goals within the program was to improve the chemical stability observed with compound **4**. Based on extensive SAR, neither of the imide carbonyls appeared to be essential for potent AR antagonist activity in the lead series. Analysis of the available crystal structures of the T877A AR ligand binding domain (LBD) with a variety of imides further confirmed that the imide moiety generated no significant interactions within the LBD.[11] It was our assumption that the imide portion of the molecule serves only to constrain the bicyclic and aniline portions of the molecule into a geometry that optimizes binding. Therefore, the [2.2.1]-bicyclic sultam was proposed which should maintain structural geometry similar to the bicyclic imide and offer improved chemical stability.

The first sultam compound **5** (Fig. 2) displayed potent binding affinity (K_i 3 nM) and good functional antagonist activity with an

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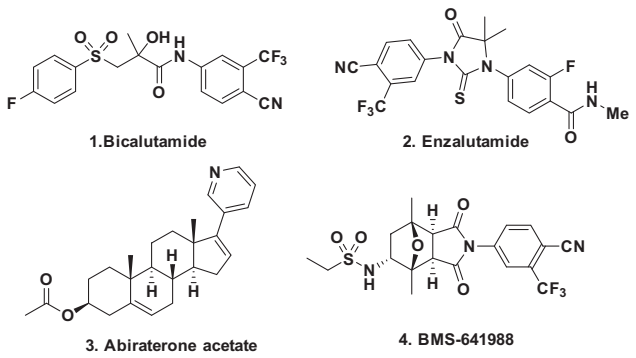

Figure 1. Known modulators of androgen receptor mediated signaling.

Table 1
Androgen receptor binding (K_i) and functional antagonist activity (IC_{50}) of sultam analogs

Compound no.	MDA-MB-453 K_i (nM)[20]	MDA-MB-453 IC_{50} (nM)[21]
1	37	173
4	2	16
5	3	130
10	12	219
11	3	73
12	2	30

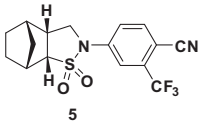

Figure 2. Initial [2.2.1]-bicyclic sultam.

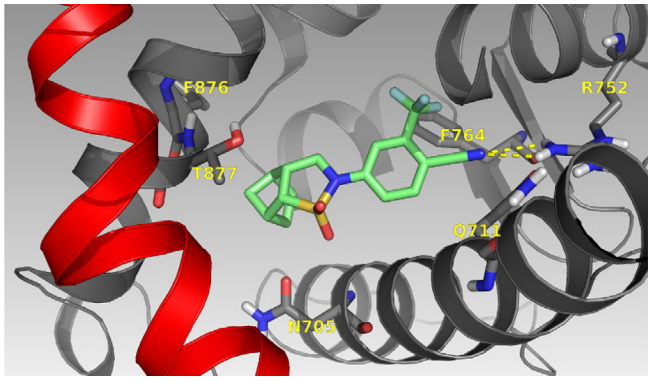

Figure 3. Compound **5** docked into WT AR Ligand Binding Domain. Helix-4 is hidden to facilitate visualization of the ligand. Helix-11 is colored in red.

IC_{50} of 130 nM (Table 1). Notably, this compound was found to be stable under a wide pH range. Previous efforts from our laboratories led to the first crystal structures of the AR with DHT, as well as several small molecule agonists from our earlier bicyclic imide series.[16] Using the available crystal structure of an AR modulator (PDB1XNN), we constructed a model (Fig. 3) of compound **5** bound to the AR ligand binding domain (LBD) using the software Glide[17] followed by Macro Model[18] energy minimization. We explored potential sites to increase interactions between compound **5** and the AR LBD protein backbone to improve antagonist activity.

In this model, phenylalanine 764 (F764) forms an edge-face interaction with the aromatic ring of compound **5**. The interactions between arginine 752 (R752) and the aryl nitrile of compound **5** are also evident. Furthermore, there is a lipophilic pocket between threonine 877 (T877) and the bicyclic ring of the sultam. It is believed that the orientation of Helix-12 is, in part, responsible for agonist/antagonist function of nuclear hormone receptors.[11] Therefore we investigated substitutions on the bicyclic sultam ring at C_5 to take advantage of the lipophilic pocket and potentially perturb Helix-12 to a more favorable antagonist conformation.

A series of sultams was synthesized by the methods shown in Scheme 1. Dienophile **6** was synthesized according to literature precedent[19] and subsequent Diels–Alder reaction with cyclopentadiene in dichloromethane at room temperature resulted in formation of the desired bicycle **7** as a 95:5 ratio of *endo* and *exo* isomers in 75% yield. Fortuitously, the endo and *exo* isomers were easily separated by silica gel chromatography. The endo isomer was then reduced to the corresponding alcohol **8** by treatment with sodium borohydride. At this stage, normal phase chiral HPLC (AD column, Hexane/IPA/DEA 73%/27%/0.1%) was performed to give enantiomers **9A** and **9B** in >99% ee. Antipode **9A** which is shown in Scheme 1, led to the active series whereas the enantiomer **9B** led to inactive analogs (Data not shown). The absolute stereochemistry was confirmed by single crystal X-ray diffraction measurement. With enantiomerically pure alcohol **9A** in hand, the sultam ring was closed by an intramolecular Mitsunobu reaction with triphenylphosphine and diisopropyl azodicarboxylate which afforded **10** in 76% yield over 2 steps. Catalytic hydrogenation (Pd/C) of **10** led to formation of the saturated analog **5**. Treatment of either **5** or **10** with lithium bis (trimethylsily) amide followed by methyl iodide yielded C_5 methylated analogs **11** and **12**.

The data in Table 1 reveals some exciting results with C_5 methyl substituted compounds **11** and **12**, both of which have improved functional antagonist potency compared to compounds **5** and **10**. This was in line with prediction from our models. Most notable was compound **12**, which was comparable to our clinical compound **4** in terms of in vitro potency.

Based on this promising profile, compound **12** was evaluated in the immature rat prostate weight (IRPW) PK/PD model, where the compound effect on AR dependent growth of the prostate and seminal vesicles was measured.[22] In this model, compounds were dosed orally once daily for 4 days with plasma concentrations of drug measured 2 h post-dose on day 4. Agents that effectively block the proliferative effect of the AR in these tissues would result in a decrease in the total weight of organs relative to a control group. While the exposure of compound **12** was very low (0.05 ± 0.014 μM) compared to compound **4**, it still had a robust PD effect (35 ± 5% at 25 mg/kg) compared to the castration control (32% ± 4%). Therefore, compound **12** was progressed into an efficacy study in the CWR22-LD1 human prostate cancer xenograft model which has been shown to be refractory to treatment with bicalutamide.[14] In this study (Fig. 4), **12** and bicalutamide (**1**) were administered with daily oral dosing at 150 mg per kg for 20 days. As shown in Figure 4, **1** had modest activity (39% Tumor Growth Inhibition). Animals receiving compound **12** exhibited tumor stasis during the course of treatment (87% TGI on the last day of dosing). There was no observed toxicity in this study.

Similar to the results from the IRPW study where the robust PD effects could not be rationalized on the basis of the observed very low exposures in animals, the observed efficacy in tumor models was not consistent with the very low exposure of compound **12** (Not detected) in mouse serum. To investigate this further, we performed mouse liver microsome incubations of compound **12**. In this study, multiple oxidative metabolites were observed, suggesting the possible presence of multiple active agents in vivo. Previous experience in our lab suggested that sustained drug exposure over 24 h was necessary for an AR antagonist to be effective. Based on the metabolic profile of [2.2.1]-bicyclic imides from our lab,[10,11]