Bioorganic & Medicinal Chemistry Letters 20 (2010) 4491–4495

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Design and synthesis of 4-[3,5-dioxo-11-oxa-4,9-diazatricyclo[5.3.1.0^{2,6}]undec-4-yl]-2-trifluoromethyl-benzonitriles as androgen receptor antagonists

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ARTICLE INFO

Article history:
Received 22 April 2010
Revised 3 June 2010
Accepted 7 June 2010
Available online 10 June 2010

Keywords:
Androgen receptor
Prostate cancer
Antagonist
Diazatricycloundecane

ABSTRACT

A novel series of 4-[3,5-dioxo-11-oxa-4,9-diazatricyclo[5.3.1.0^{2,6}]undec-4-yl]-2-trifluoromethyl-benzonitriles has been synthesized. The ability of these compounds to act as antagonists of the androgen receptor was investigated and several were found to have potent activity in vitro and in vivo.

Carcinoma of the prostate (CaP) is one of the leading causes of cancer related death in men in the United States.[1] The androgen receptor (AR) is a ligand binding transcription factor in the nuclear hormone receptor super family and is a key molecular target in the etiology and progression of prostate cancer. Binding of androgens, such as dihydro-testosterone (DHT), to the AR provides the mitogenic signal for growth of prostate cancer cells. Androgen ablation via surgical castration or by chemical castration with a luteinizing hormone releasing hormone agonist, in combination with an antiandrogen,[2] is currently the treatment of choice for advanced CaP. Although this therapy initially shows an 80–90% response rate,[3] approximately 50% of patients progress to fatal androgen independent CaP (AI-CaP) after about 18 months of treatment.[4] Recent advances in the field have shown that reactivation of the AR signaling pathway is the root cause for the development of AI-CaP.[5] The identification of the role of the AR in AI-CaP suggests that new agents which act at the level of the AR may be effective in the treatment of this disease. For this reason, we are interested in identifying novel small molecule antagonists of the AR that are more effective than the current AR antagonists at targeting the AR in AI-CaP.

Our initial screening and optimization efforts led to a series of hydantoin[6] and cyclic imide[7]-based AR antagonists, exemplified by compounds **1** and **2** (Fig. 1), that bound tightly to the AR and functioned as antagonists to the wild-type (WT) and the mutant (MT) isoforms of the AR in vitro.

Figure 2 shows the structures of flutamide (**3**), nilutamide (**4**), and bicalutamide (**5**)—the nonsteroidal AR antagonists that have been used in the treatment of prostate cancer.

Of the compounds outlined in Figures 1 and 2, the 3,4-disubstituted aniline amide structure is very intriguing. It appears that this motif of the molecules is essential for high affinity binding to the AR. We reasoned that combining the 3,4-disubstituted aniline moiety with a symmetric bicyclic system similar to our lead compounds (**1**) and (**2**), as shown for the generic structure (**6**) in

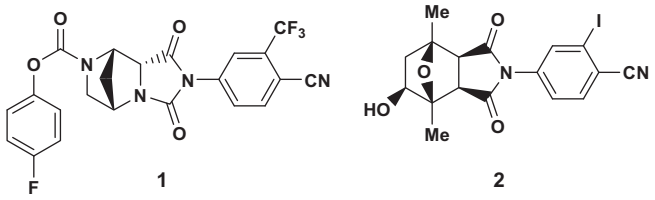

Figure 1. Our lead antiandrogens.

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doi:10.1016/j.bmcl.2010.06.034

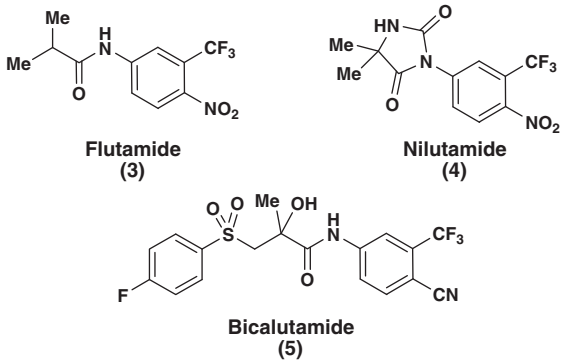


Figure 2. Clinically used antiandrogens.

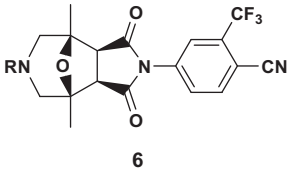


Figure 3. Proposed diazatricyclic antiandrogens.

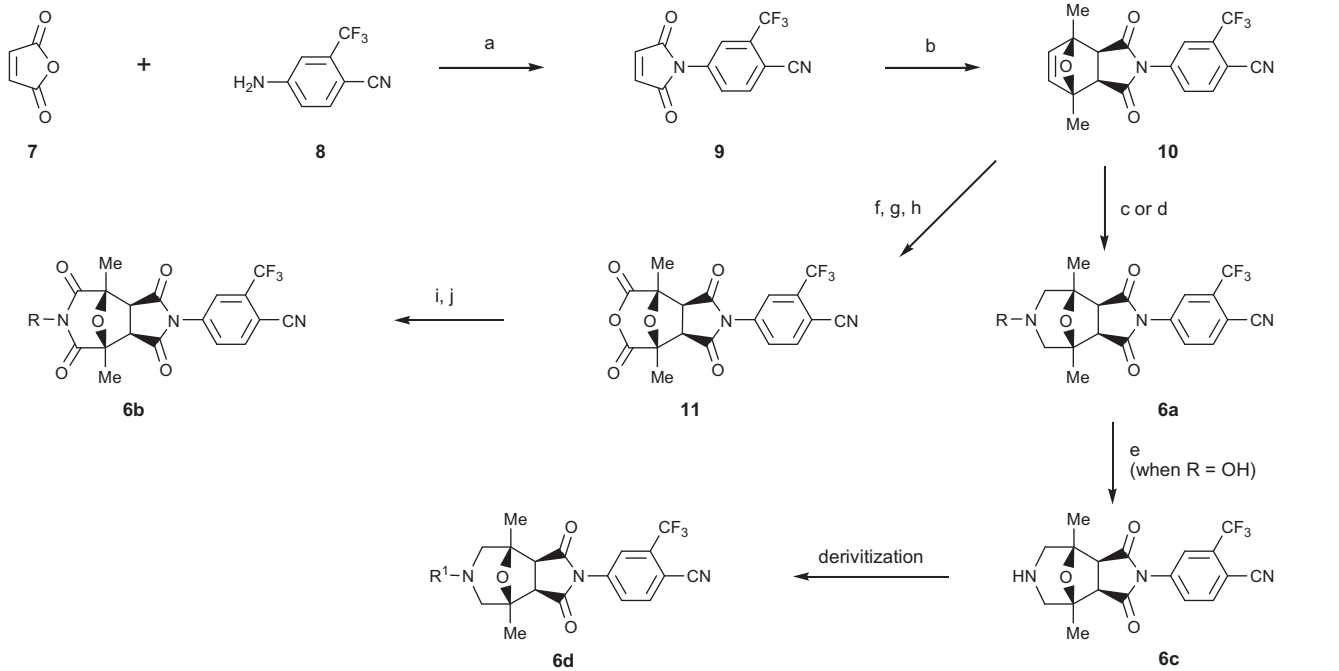
Figure 3, would allow us to rapidly explore the SAR in a novel series of compounds.

The synthetic pathway[8] utilized in the preparation of analogs of compound **6** is outlined in Scheme 1. Furan-2,5-dione (**7**) and 4-amino-2-trifluoroenzonitrile (**8**) were heated together in the presence of acetic acid to yield 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2-(trifluoromethyl)benzonitrile (**9**). Diels–Alder reaction of **9** with 2,5-dimethylfuran gave exclusively the exo adduct (**10**) that precipitated out from the reaction mixture. Ozonolysis of the Diels–Alder adduct (**10**), reduction and reductive amination with sodium cyanoborohydride afforded the desired compounds. *N*-Aryl analogs of **6a** were successfully synthesized employing aryl amines in the presence of acetic acid. When aliphatic amines were used, the reaction did not proceed due to the protonation of the amine by acetic acid. To synthesize aliphatic amine analogs, ozonolysis was carried out in anhydrous dichloromethane and the ozonide was reduced with dimethylsulfide to give the dialdehyde intermediate that was then subjected to reductive amination conditions to provide the desired *N*-alkyl analogs. The parent amine (**6c**) was synthesized from the hydroxylamine intermediate (**6a**, R = OH) via reduction with titanium trichloride. A number of analogs were synthesized from (**6c**) employing acylation and reductive amination protocols. The ozonide was also oxidized[9] to give the diacid that was converted into imides (**6b**) via the anhydride (**11**).

To evaluate the activity of this new series, we investigated the ability of compounds to bind to (K_i) and functionally antagonize (IC_{50}) the WT AR found in the MDA-453 cell line as well as antagonize the MT AR (T877A) found in the LNCaP cell line.[11]

Modification of the tricyclic core has dramatic effect on the activities. The data in Table 1 clearly shows that although the binding potency is maintained with the imides (**12, 13**), the functional potency in the MDA-453 assay is significantly reduced compared to bicalutamide (**5**). However, the tertiary amine analog (**15**) was significantly more potent than bicalutamide across all the in vitro assays examined and was the subject of further SAR studies as outlined in Table 2.

The parent amine (**6c**) and *N*-hydroxyl analog (**16**) had similar binding and wild-type functional activity compared to bicalutamide, although both compounds are significantly less potent in the LNCaP functional assay. However, the *N*-methoxy analog (**17**) had significantly improved activity versus bicalutamide in all three of the in vitro assays. The SAR trend in Table 2 appears to suggest that lipophilic substitution in general improved potency across all three in vitro assays (**23** vs **24**; **30** vs **31**; **32** vs **34**; **36** vs **37**). Aryl substitution improved potency in amides (**22** vs **20**) and ureas (**28** vs **27**) series. Carbamate and sulfonamide analogs were better than



Scheme 1. Synthesis of compound **6**. Reagents and conditions: (a) AcOH, 120 °C; (b) 2,5-dimethylfuran, PhMe, 60 °C, 3 h, 90%; (c) O_3, MeOH, CH_2Cl_2, −78 °C, then $NaBH_3CN$, $ArNH_2$, HOAc, 20–50%; (d) O_3, CH_2Cl_2, −78 °C, then SMe_2, then RNH_2, $NaBH_3CN$, TEA, DMF, 20–40%; (e) $TiCl_3$, MeOH, H_2O, 70–90%; (f) O_3, CH_2Cl_2, −78 °C; (g) Jones' reagent, acetone; (h) Ac_2O; (i) RNH_2, THF; (j) Ac_2O, KOAc, HOAc; 20–50% yield for steps f–j.