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

Hai-Yun Xiao [a,*], Aaron Balog [a], Ricardo M. Attar [a], David Fairfax [b], Linda B. Fleming [b], Christian L. Holst [b], Gregory S. Martin [b], Lana M. Rossiter [b], Jing Chen [a], Mary-Ellen Cvjic [a], Janet Dell-John [a], Jieping Geng [a], Marco M. Gottardis [a], Wen-Ching Han [a], Andrew Nation [a], Mary Obermeier [a], Cheryl A. Rizzo [a], Liang Schweizer [a], Thomas Spires Jr. [a], Weifang Shan [a], Ashvinikumar Gavai [a], Mark E. Salvati [a], Gregory Vite [a]

[a] Bristol-Myers Squibb Company, Research and Development, Princeton, NJ 08543-4000, USA
[b] Albany Molecular Research Institute, Albany, NY 12203, USA

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

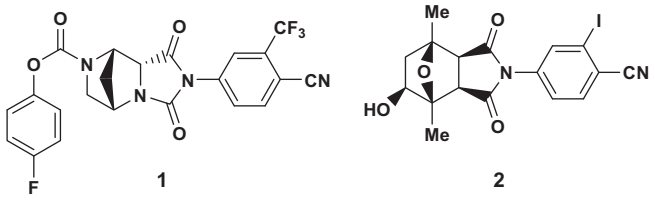


Figure 1. Our lead antiandrogens.

* Corresponding author. Tel.: +1 609 252 6469; fax: +1 609 252 6804.
E-mail address: haiyun.xiao@bms.com (H.-Y. Xiao).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.06.034

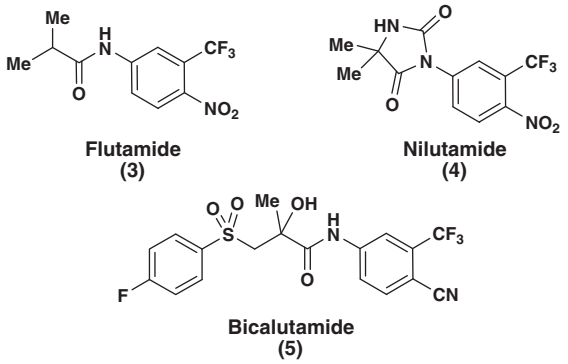


Figure 2. Clinically used antiandrogens.

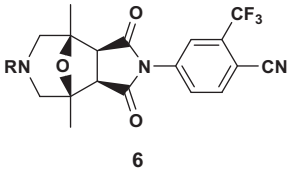


Figure 3. Proposed diazatricyclic antiandrogens.

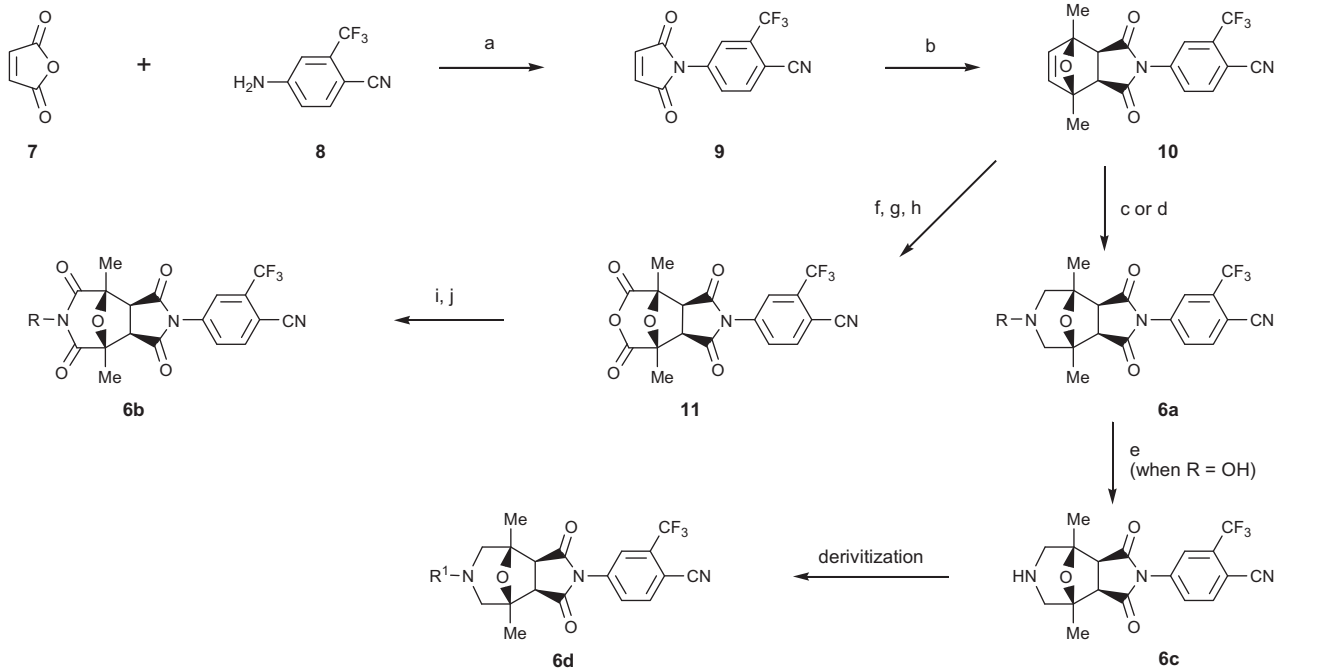
Figure 3, would allow us to rapidly explore the SAR in a novel series of compounds.

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]

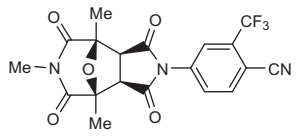
Modification of the tricyclic core has dramatic effect on the activities. The data in Table 1 clearly shows that although the binding potency is maintained with the imides (**12, 13**), the functional potency in the MDA-453 assay is significantly reduced compared to bicalutamide (**5**). However, the 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

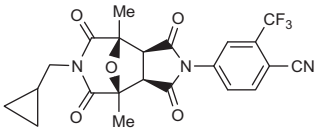


Scheme 1. Synthesis of compound **6**. Reagents and conditions: (a) AcOH, 120 °C; (b) 2,5-dimethylfuran, PhMe, 60 °C, 3 h, 90%; (c) O_3, MeOH, CH_2Cl_2, −78 °C, then $NaBH_3CN$, $ArNH_2$, HOAc, 20–50%; (d) O_3, CH_2Cl_2, −78 °C, then SMe_2, then RNH_2, $NaBH_3CN$, TEA, DMF, 20–40%; (e) $TiCl_3$, MeOH, 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.

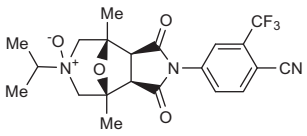
Table 1
SAR around the tricyclic core



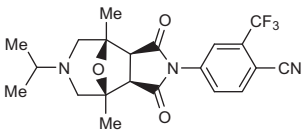
12



13



14



15

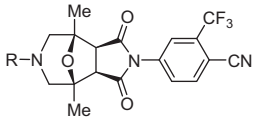
Compd No.	K_i[a], nM	MDA-453 IC_{50}[b], nM (%Inh)[c]	LNCaP IC_{50}[b] nM, (%Inh)[c]
5 Bicalutamide	64	173	400
12	20	2144	>5000
13	50	873	3329
14	3600	3900 (58)	>5000
15	14	32 (99)	125 (99)

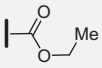
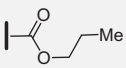
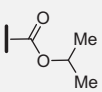
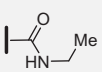
[a] Binding determined through direct displacement of ligand with [^{3}H]-DHT in the MDA-453 cell line (K_i).[10]
[b] Functional antagonist activity determined through a transiently transfected reporter system utilizing a secreted alkaline phosphatase (SEAP) reporter construct and a PSA AR promoter domain.[10]
[c] Percent inhibition of DHT(1 nM)-induced increase of cell growth at 5 μM.

urea and amides in terms of binding activity. However, in terms of the LNCaP functional assays, the differences were not significant. (**23**, **31** vs **19**, **26**). The tertiary aliphatic amines (**15, 18**) were among the most active compounds in the series and superior to bicalutamide (**5**). They were potent not only in binding and WT functional assays but also in MT functional assay. Unfortunately, their in vitro microsomal instabilities across species (data not shown) prevented the compounds from further development. The substituted aromatic amines (**37**, **38**), however, showed excellent activities in the MDA-453 and LNCaP functional assays and good in vitro microsomal stability.[12]

Compounds that had good in vitro functional activity and microsomal stability proceeded into a PK/PD study. In the model, immature rats were treated with compound and testosterone

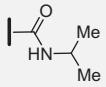
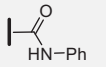
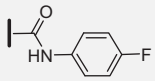
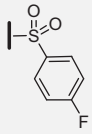
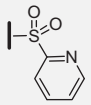
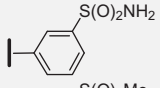
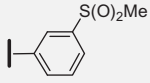
Table 2
SAR of N-substituted analogs



Compd No.	R	K_i[a], nM	MDA-453 IC_{50}[b], nM (%Inh)[c]	LNCaP IC_{50}[b], nM (%Inh)[c]	In vivo IRPW[d]
5	Bicalutamide	64	173	400	41
6c	H	21	128 (98)	>5000 (20)	
16	OH	37	182 (97)	1280 (79)	
17	OMe	3.7	24 (99)	179 (72)	
18	*n*-Propyl	14	14 (99)	25 (98)	
19		84	129 (95)	549 (91)	
20		39	215 (98)	1610 (72)	
21		36	69 (99)	404 (95)	
22		23	54 (99)	177 (98)	94
23		5.7	65 (99)	590 (93)	
24		6.6	9.3 (99)	54 (99)	
25		11	12 (99)	69 (99)	50
26		176	313 (97)	1456 (76)	

(*continued on next page*)

Table 2 (*continued*)

Compd No.	R	K_i[a], nM	MDA-453 IC_{50}[b], nM (%Inh)[c]	LNCaP IC_{50}[b], nM (%Inh)[c]	In vivo IRPW[d]
27		98	876 (88)	4600 (52)	
28		40	16 (99)	123 (98)	64
29		29	39 (99)	104 (98)	52
30		56	205 (99)	3511 (61)	
31		16	85 (99)	600 (90)	
32		12	99 (99)	979 (91)	
33		32	54 (100)	685 (95)	61
34		93	170 (98)	1241 (80)	
35		9.0	7.4 (98)	127 (99)	
36		22	37 (99)	337 (94)	
37		9.4	7.4 (96)	150 (98)	36
38		3.5	11 (98)	104 (100)	37
39		6.1	31 (99)	377 (97)	

[a,b,c] See Table 1.

[d] Immature rat prostate weight assay: QD × 3 days PO dosing at 10 mpk of drug with testosterone propionate (1 mpk). Weight of seminal vesicles (SV) and full body weight (FB) were measured. The number is reported as percentage of SV/FB relative to those of the control group where animals were treated only with testosterone propionate (1 mpk).

propionate. The stronger antagonism of the compound will give a smaller ratio of seminal vesicles weight (SV) to full body weight (FB) (i.e., SV/FB) than those of the control group where animals were treated with testosterone propionate only. It is clear, from Table 2, that the in vivo activity roughly followed the functional activity in the MDA-453 cell line. This is reasonable since the growth of the prostate is dominated by WT androgen receptor activation. The IRPW data showed that some of the compounds (**37**, **38**) were very efficacious and the effect was dose-dependent (e.g., compound **37** had SV/FB of 36% at 10 mpk and 28% at 30 mpk; compound **38** had SV/FB of 59% at 1 mpk and 37% at 10 mpk).

In summary, we have developed an efficient synthesis of a novel series of androgen receptor antagonists. These diazatricyclic compounds were proposed based on the common structure of the existing AR antagonists. Most of the new compounds demonstrated potent binding to the WT AR and the full functional antagonism in the cell lines expressing the WT and especially the MT AR. Modification of the cyclic core and optimizing the substitution on the nitrogen atom led to the identification of compounds (**37**, **38**) that were very efficacious in our PK/PD model.

Acknowledgment

The authors thank Dr. Murali Dhar for his helpful suggestions.

References and notes

1. Jemal, A.; Thomas, H.; Murray, T.; Thun, M. *CA Cancer J. Clin.* **2002**, *52*, 23.
2. (a) Gao, K. L. *Drugs* **1991**, *43*, 254; (b) Motta, M.; Serio, M. *Hormonal Therapy of Prostatic Diseases: Basic and Clinical Aspects*; Medicom Europe: Amsterdam, 1998; (c) Crawford, E. D.; DeAntonio, E. P.; Labrie, F.; Schroder, F. H.; Geller, J. *J. Clin. Endocrinol. Metab.* **1995**, *80*, 1062.
3. (a) Blackledge, G. *Cancer* **1993**, 3830; (b) Maucher, A.; von Angerer, E. *J. Cancer Res. Clin. Oncol.* **1993**, *119*, 669; (c) Sufrin, G.; Coffey, D. S. *Invest. Urol.* **1976**, *13*, 429; (d) Narayana, A. S.; Loening, S. A.; Culp, D. A. *Br. J. Urol.* **1981**, *53*, 152.
4. (a) Huggins, C.; Stevens, R.; Hodges, C. V. *Arch. Surg.* **1947**, *43*, 209; (b) Westin, P.; Stattin, P.; Damber, J.-E.; Bergh, A. *Am. J. Pathol.* **1995**, *146*, 1368.

5. (a) Scher, H.; Sawyers, C. *J. Clin. Oncol.* **2005**, *23*, 8253; (b) Chen, C. D.; Welsbie, D. S.; Tran, C.; Baek, S.-H.; Chen, R.; Vessella, R.; Rosenfeld, M. G.; Sawyers, C. L. *Nat. Med.* **2004**, *10*, 33; (c) Richter, E.; Srivastava, S.; Dobi, A. *Prostate Cancer Prostatic Dis.* **2007**, *10*, 114; (d) Burd, C. J.; Morey, L. M.; Knudsen, K. E. *Endocr. Relat. Cancer* **2006**, *13*, 979; (e) Hendriksen, P. J. M.; Dits, N. F. J.; Kokame, K.; Veldhoven, A.; van Weerden, W. M.; Bangma, C. H.; Trapman, J.; Jenster, G. *Cancer Res.* **2006**, *66*, 5012.
6. (a) Balog, A.; Salvati, M.; Shan, W.; Mathur, A.; Leith, L.; Wei, D.; Attar, R.; Geng, J.; Rizzo, C.; Wang, C.; Krystek, S.; Tokarski, J.; Hunt, J.; Weinmann, R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6107; (b) Salvati, M.; Balog, A.; Shan, W.; Wei, D.; Pickering, D.; Attar, R.; Geng, J.; Rizzo, C.; Gottardis, M.; Weinmann, R.; Krystek, S.; Sack, J.; An, Y.; Kish, K. *Design, Structural Analysis and Biological Profile of a Novel Series of AR Antagonists*, Poster Presentation, American Association of Cancer Research, 95th Annual Meeting, 2004; (c) Salvati, M.; Balog, A.; Shan, W.; Geise, S. U.S. Patent 885,798, 2003.
7. (a) Salvati, M.; Balog, A.; Wei, D.; Pickering, D.; Attar, R.; Geng, J.; Rizzo, C.; Hunt, J.; Weinmann, R.; Martinez, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 289; (b) Salvati, M.; Balog, A.; Shan, W.; Rampulla, R.; Giese, S.; Mitt, T.; Furch, J. A.; Vite, G. D.; Attar, R. M.; Jure-Kunkel, M.; Geng, J.; Rizzo, C. A.; Gottardis, M. M.; Krystek, S. R.; Gougoutas, J.; Galella, M. A.; Obermeier, M.; Aberra Fura, A.; Chandrasena, G. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1910; (c) Salvati, M. E.; Balog, A.; Pickering, D. A.; Giese, S.; Fura, A.; Li, W.; Patel, R.; Hanson, R. L.; Mitt, T.; Roberge, J.; Corte, J. R.; Spergel, S. H.; Rampulla, R. A.; Misra, R.; Xiao, H.-Y. World Patent Application WO 200306224.
8. Balog, A.; Fairfax, D.; Martin, G.; Salvati, M.; Xiao, H.-Y. U.S. 2007088029.
9. Narula, A. S.; Dev, S. *Tetrahedron Lett.* **1969**, *22*, 1733.
10. New analogs were assayed for effect on AR function in MDA-453, a cell line expressing WT AR, and LNCaP, a cell line expressing MT AR. Transactivation assays were done in whole cells and IC_{50}'s were calculated. Both cell lines were obtained from American Type Culture Collection (Rockville, MD). Binding constants (K_i) were determined in whole cells measuring displacement by tritiated DHT in the MDA-453 cell line. See Ref. 11 below for experimental details on assays.
11. Salvati, M.; Gottardis, M.; Krystek, Jr., S.; Attar, R.; Sack, J. U.S. 6,960,474; WO 2002000617.
12. For example, the in vitro metabolic stability of compound **37** was evaluated at 3 μM in the presence of human, rat, and mouse liver microsomes. After a 10 min incubation, the % compound remaining for compound **37** in humans, rats, and mice was 76%, 100%, and 92%, respectively.