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Bioorganic & Medicinal Chemistry Letters 17 (2007) 2545–2548
Bioorganic & Medicinal Chemistry Letters

β-Alkylthio indolyl carbinols: Potent nonsteroidal antiandrogens with oral efficacy in a prostate cancer model

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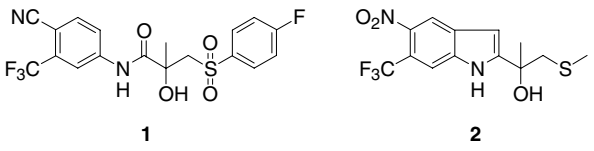
Received 26 November 2006; revised 21 January 2007; accepted 6 February 2007
Available online 8 February 2007

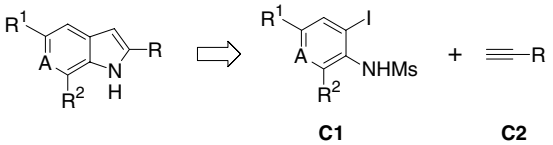
Abstract—Through an in vivo screening model, we developed the in vivo SAR of β-alkylthio indolyl carbinols. Through these efforts we identified a compound with potent oral in vivo efficacy in both immature and mature rat prostate weight reduction models and in a murine xenograft prostate cancer model.

The androgen receptor[1] (AR), a member of the nuclear hormone receptor superfamily, is responsible for a variety of developmental and myotropic events through modulation by its principal circulating ligand testosterone (T) and its more potent tissue metabolite 5α-dihydrotestosterone (DHT).[2] Although these anabolic processes are critical to the development of male sexual and physiologic characteristics, the stimulatory effects of T and DHT are also key contributors to proliferative disease states such as benign prostatic hyperplasia (BPH) and prostate carcinoma (PC). The side effects associated with the clinical use of steroidal antiandrogens[3] prompted research[4] into nonsteroidal scaffolds as a means of mitigating the potential for crosstalk within the endocrine system. The culmination of these efforts, bicalutamide (Casodex®, **1**), has been the gold standard for antiandrogen treatment for the past decade (Fig. 1). This success along with a suboptimal side effect profile has prompted further research[5] in the field though, to date, no third generation compounds have been commercialized. As part of our interest[6] in the field we pursued bioisosteric replacement[7] of the anilide portion of **1**, establishing the indole carbinol moiety as a potent androgen receptor ligand.[8] Through our in vivo screening model,[9] we found that compound **2** was orally efficacious; the novelty of the structure coupled with its synthetic tractability prompted further investigation. Retrosynthetically, these compounds can be prepared by Sonogashira coupling–cyclization[10] of the appropriate iodosulfonamide **C1** and propargyl alcohol **C2** (Scheme 1). The iodosulfonamides were prepared by the iodination of commercially available anilines using Boger's conditions[11] followed by mono-mesylation with KO^{t}Bu and mesyl chloride. Preparation of the other coupling partner was achieved by Grignard addition to the appropriate α-thio ketone. The ketones were either purchased or prepared in one step by condensation[12] of the corresponding sulfide and α-halo ketone.



1 **2**

Figure 1. Bicalutamide and our lead compound.



C1 **C2**

Scheme 1. Retrosynthetic analysis of the target molecules.

Keywords: Androgen receptor; Bioisostere.
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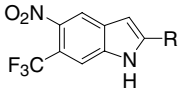
doi:10.1016/j.bmcl.2007.02.014

The SAR of the indole 2-substituent represented our first point of exploration (Table 1). While transposition of the methylthio and hydroxy moieties (**3**) reduced activity, extension of the sulfur alkyl chain by one carbon (**4**) brought the efficacy to the same level as bicalutamide. Extending the angular methyl group by one carbon atom (**5**) maintained the level of potency while substitution with an additional thiomethyl group (**6**) or replacement with a hydrogen atom (**7**) led to a substantial loss in activity. Trifluorination (**8**) of the sulfur chain of **4** as well as chain lengthening to the S-propyl (**9**) and S-butyl (**10**) analogs reduced potency. Although branching next to the sulfur atom (**11**) of **4** greatly reduced potency, intercalation of a methylene group (**12**) returned it, indicating the need for some flexibility in the sulfur side chain. This was supported by the observation that tying the sulfur chain terminus of **4** into a five-membered ring with the angular methyl group (**13**) also resulted in a loss of potency. While some flexibility on the sulfur substituent improved potency, loosening the connection either to the sulfur atom (**14**) of the indole moiety (**15**) led to a substantial loss of activity. Aryl (**16**) and heteroaryl (**17** and **18**) substitution of the thiomethyl group in 2 also resulted in a loss of efficacy. Finally O-methylation of **4** was well tolerated (**19**).

With these results in hand we turned our attention to the SAR of the indole ring using **4** as our comparator molecule (Table 2). Changing the indole nitrogen to an oxygen (**20**) resulted in a substantial loss of efficacy while moving the trifluoromethyl group from the 6 to the 7 position (**21**) had a minimal effect. Removal of the trifluoromethyl substituent reduced or abolished activity over a range of 5-substitutions (**22**–**25**). Replacement of the nitro group with fluorine (**26**), chlorine (**28**), and methyl (**31**) groups reduced efficacy to varying degrees while reduction (**30**) abolished activity. Exchanging the nitro group with a nitrile (**32**) provided better efficacy than bicalutamide. Replacement of the trifluoromethyl group of **32** with a chlorine atom (**33**) was tolerated while introduction of a methoxy (**34**), methyl (**35**) or nitrogen (**36**) at this position was not.

We then focused our efforts on optimizing the substituents on **32**. In order to make some of the desired substitution patterns, we needed to modify our synthesis (Scheme 2). Introduction of a methyl group to the indole

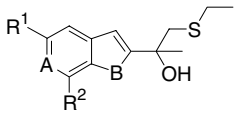
Table 1. Carbinol SAR



Compound	R	% Redn[a] Pros Wt.
2	$CMe(OH)CH_2SCH_2H$	66
3	$CMe(SCH_2H)CH_2OH$	49
4	$CMe(OH)CH_2SCH_2Me$	75
5	$CEt(OH)CH_2SCH_2Me$	73
6	$C(OH)(CH_2SCH_2Me)_2$	32
7	$CH(OH)CH_2SCH_2Me$	30
8	$CMe(OH)CH_2SCH_2CF_3$	46
9	$CMe(OH)CH_2SCH_2Et$	40
10	$CMe(OH)CH_2SCH_2{}^nPr$	40
11	$CMe(OH)CH_2SCHMe_2$	42
12	$CMe(OH)CH_2SCH_2CHMe_2$	75
13	3-(3-OH)-Tetrahydrothiophene	49
14	$CMe(OH)CH_2CH_2SMe$	44
15	$CH_2CMe(OH)CH_2SCH_2Me$	na
16	$CMe(OH)CH_2SCH_2Ph$	54
17	$CMe(OH)CH_2SCH_2$(2-furyl)	46
18	$CMe(OH)CH_2SCH_2$(2-thiophenyl)	28
19	$CMe(OMe)CH_2SCH_2Me$	76
Bical.	—	75

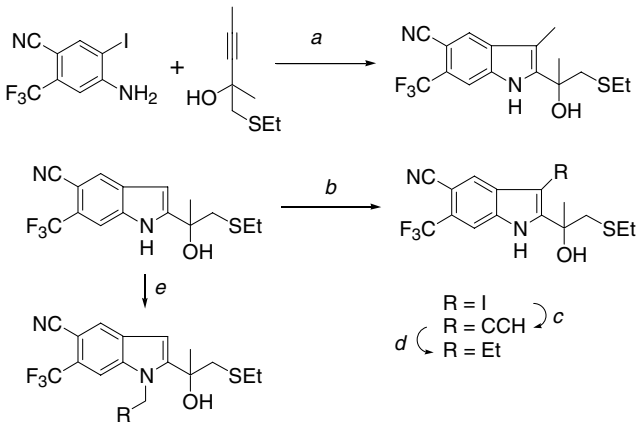
[a] Values are means of three experiments (na, not active).

Table 2. Indole ring SAR



Compound	A	R^1	R^2	B	% Redn[a] Pros Wt
4	CCF_3	NO_2	H	NH	75
20	CCF_3	NO_2	H	O	38
21	CH	NO_2	CF_3	NH	66
22	CH	NO_2	H	NH	34
23	CH	CN	H	NH	na
24	CH	Cl	H	NH	na
25	CH	H	H	NH	26
26	CCF_3	F	H	NH	58
27	CCl	F	H	NH	60
28	CCF_3	Cl	H	NH	54
29	CCl	Cl	H	NH	na
30	CCF_3	NH_2	H	NH	na
31	CCF_3	CH_3	H	NH	22
32	CCF_3	CN	H	NH	100
33	CCl	CN	H	NH	83
34	$COCH_3$	CN	H	NH	na
35	CCH_3	CN	H	NH	na
36	N	CN	H	NH	na
Bical.	—	—	—	—	75

[a] Values are means of three experiments (na, not active).



Scheme 2. Preparation/derivatization of analogs of **32**. Reagents and conditions: (a) 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, KOAc, LiCl/DMF; (b) NaOMe, NIS/MeOH; (c) 5 mol% $PdCl_2(PPh_3)_2$, 10 mol% CuI, TMSA, Et_3N/THF, then TBAF/THF; (d) 10 mol% Pd/C, H_2/MeOH; NaH/DMF, then XCH_2R.

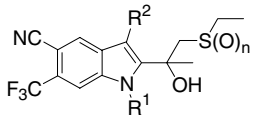
C3 position required Larock's indole annulation methodology.[13] Coupling of the iodo aniline and 1-ethylsulfanyl-2-methyl-pent-3-yn-2-ol in the presence of palladium delivered the target molecule in good yield. Introduction of an ethyl group at the same position could be achieved through direct derivatization of **32**. An iodine atom was introduced at C3 by deprotonation of the indole in the presence of NIS. Sonogashira coupling of this compound with TMS–acetylene followed by TBAF deprotection afforded the 3-ethynyl compound which was hydrogenated to provide the sulfide. Sulfide oxidation of this and all other compounds was achieved using Oxone® under phase-transfer conditions.[14] Alkylation of the indole nitrogen was effected by treatment with sodium hydride in anhydrous DMF followed by introduction of the appropriate electrophile. Key compounds were resolved into their constituent enantiomers by chiral chromatography. The absolute configuration of **44** was determined by X-ray crystallography and used as a point of reference for related analogs.

Alkylation of the indole nitrogen of **32** with a range of substituted methylenes (**38**–**42**) decreased or abolished activity (Table 3). Of the two enantiomers of **32**, the (*R*) antipode had all the activity while the (*S*) enantiomer was inactive. Oxidation of the sulfur to the sulfoxide (**43**) reduced potency while further oxidation to the sulfone (**44**) restored it. In a six week intact mature rat (2-month-old) model for prostate weight reduction, compounds ***R*-32** and **44** displayed the same potency. We examined the pharmacology of (*R*)-**32** and found that it was consumed after only 30 min in vivo, metabolizing to a mixture of **43** and **44**. Within 24 h, only **44** was observable; further studies on this sulfone indicated that it had high oral bioavailability (68%) and a 52-h half-life. This long half-life was maintained over a variety of species (dog, guinea pig, and monkey). Given the target indication, we felt that **44** represented an excellent molecule for further characterization. In vitro studies indicated that it was as potent in a COS AR whole cell binding assay as bicalutamide and nearly as potent in an L929 cell-based antagonist functional assay. It did not have any binding to other nuclear steroid hormone receptors (estrogen, progestin, mineralocorticoid or glucocorticoid). Compound **44** did not have any in vivo prostate agonist activity in castrated mature rats when dosed orally.

While modification to the C3 position of **44** from a hydrogen to a methyl (**46**) and ethyl (**47**) improved potency up to 10-fold in vitro, the modification led to a slight erosion in the immature rat screening assay, an observation which was even more pronounced in the mature rat model. Investigation of the pharmacokinetic parameters of **46** and **47** in mature rats revealed that the half-life of these analogs dropped to 2 h and 0.9 h, respectively. This implies that metabolism occurs on the C3 position of the analogs and suggests a possible reason for their lower efficacy in spite of their superior in vitro activity.

To evaluate the potential of **44** to treat prostate cancer, we utilized a mouse xenograft of the LNCaP cell line. It was effective in slowing tumor growth in and prolonging the survival of three out of ten mice through 51 days after tumor inoculation, while all of the vehicle-treated mice died by Day 44. Bicalutamide had identical activity to **44** (Fig. 2). The compound was also found to be as efficacious or more so than bicalutamide in two other prostate tumor models—Dunning and CWR-22. Those data as well as the beneficial effects of **44** in bone are dis-

Table 3. Lead compound fine tuning



Compound	R^1	R^2	*n*	% Redn[a] Pros. Wt.	ID_{50}[b] Pros.	ID_{50}[c] Pros.
32	NH	H	0	100	—	—
38	NCH_2H	H	0	43	—	—
39	NCH_2CH_3	H	0	55	—	—
40	NCH_2CF_3	H	0	53	—	—
41	NCH_2OCH_3	H	0	37	—	—
42	NCH_2CN	H	0	na	—	—
S-**32**	NH	H	0	na	—	—
R-**32**	NH	H	0	100	0.44	22
43[d,e]	NH	H	1	62	—	—
44[d]	NH	H	2	100	0.89	22
45[d]	NH	Me	0	61	0.82	>60
46[d]	NH	Me	2	—	2.40	>30
47[d]	NH	Et	2	—	1.40	—
Bical.	—	—	—	75	0.44	44

[a] For immature rats; values are means of three experiments (na, not active).
[b] For immature rats in mg/d.
[c] For mature rats in mg/kg.
[d] (*R*)-absolute configuration at the tertiary carbinol center.
[e] A mixture (ca. 1:1) of diastereomers at the sulfur atom.

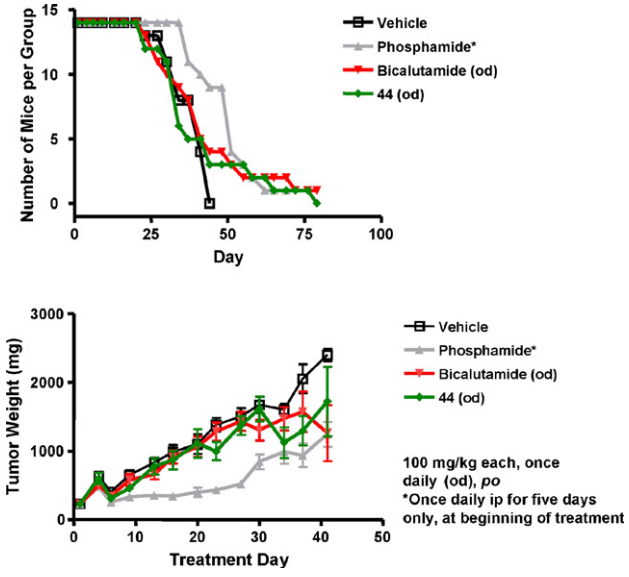


Figure 2. The effect of **44** in a LnCAP tumor model.

cussed in a separate publication.[15] On the basis of these data, compound **44** was selected as a development candidate.

In summary, through an in vivo screening approach, we have discovered a potent novel antiandrogen. This compound was evaluated in mature male rats and found to shrink the prostate with greater potency than bicalutamide. Further testing of this compound indicated that it had efficacy equal to or greater than the market leader in three prostate cancer models. Preliminary data from other in vivo models suggest that this molecule has beneficial effects in both bone and muscle tissue.

Acknowledgments

The authors thank Professor Dale Boger for his suggestions regarding the iodination of electron deficient anilines and the Biosciences Team for pharmacology support.

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