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A bioisosteric approach to the discovery of indole carbinol androgen receptor ligands

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Abstract—Two potential bioisosteres of the nonsteroidal antiandrogen bicalutamide, an imidazolidinone and an indole, were synthesized and tested for their androgen receptor binding. Indole was discovered to be a suitable bioisostere for the acyl anilide moiety in the parent compound. Several analogs in the indole series were found to be 10-fold better than bicalutamide in binding to the recombinant androgen receptor binding domain.

The androgen receptor (AR) belongs to the nuclear hormone receptor superfamily and is responsible for a range of biological functions including sexual differentiation and function as well as various anabolic effects.[1] These effects are mediated[2] by the action of the natural ligand testosterone (T) and its more potent tissue metabolite dihydrotestosterone (DHT). The SAR of steroidal[3] analogs of these natural ligands has been extensively studied. Recently, there has been a surge in interest in both agonist and antagonist structures of a nonsteroidal[4] nature. As part of our interest[5] in the field, we looked into bioisosteric[6] replacement of portions of the nonsteroidal antiandrogen bicalutamide (Fig. 1). Replacement of the β-hydroxy aryl sulfone portion with a heterocycle incorporating both a hydrogen bond donating NH group and a pendant aromatic ring (pathway a) led to a series of imidazolidinones **2**. Alternatively, tying the amide carbonyl back onto the anilide aromatic ring (pathway b) resulted in the indole carbinol scaffold **3** with a variety of linking groups (Z) for the aryl ring.

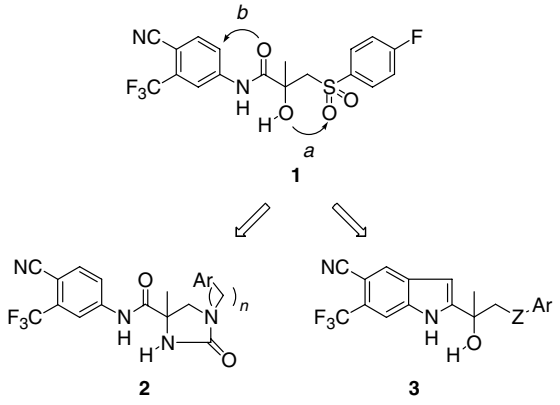

Figure 1. Bicalutamide bioisosteres.

To prepare the imidazolidinone, we started with the known[7] serine-derived aldehyde **4** (Scheme 1). Stepwise reductive amination of the aldehyde with the appropriate amine followed by Boc deprotection and triphosgene cyclization provided key intermediate imidazolidinone **5**. Ester hydrolysis, acid chloride generation, and coupling to the appropriate aniline afforded the target structures **2**.

The synthesis of the indole isosteres started with commercially available anilines that are transformed via acid catalyzed iodination,[8] bis-sulfonylation, and hydrolysis to the corresponding *ortho* iodo sulfonamides **6** (Scheme 2). These key intermediates were then reacted under Sonogashira[9a] coupling-cyclization[9b] conditions with propargyl alcohols **7** or **11** to afford the β-siloxy (**8**) or β-chloro (**12**) indolyl carbinols, respectively. To avoid cleavage of the ester linkage, elaboration of **8** required

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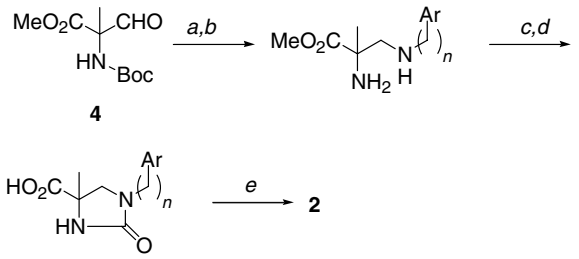
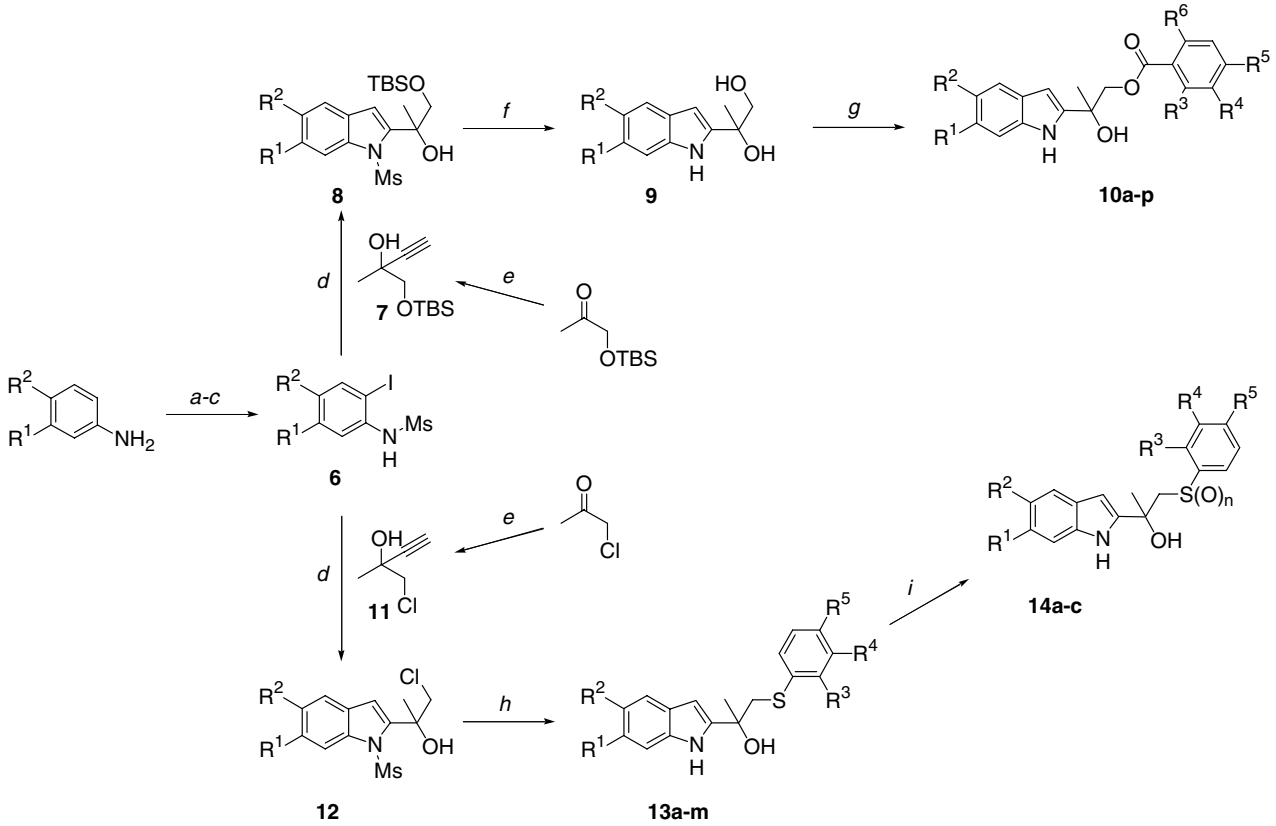


Scheme 1. Synthesis of imidazolidinone isosteres. Reagents: (a) $Ar(CH_2)_nNH_2$, pTsOH (cat)/toluene, Dean–Stark; (b) $NaBH_4$/MeOH then HCl/dioxane; (c) $(Cl_3CO)_2CO$, Et_3N/THF; (d) NaOH/MeOH—H_2O; (e) $(COCl)_2$, DMF (cat)/CH_2Cl_2, then 4-amino-2-(trifluoromethyl)benzonitrile, Et_3N/THF.

concurrent cleavage of the sulfonamide and the silyl groups followed by mono-acylation of the resulting diol **9** with a single equivalent of the corresponding acid chloride to afford the target benzoates **10** as racemic mixtures. Treatment of **12** with two equivalents of the appropriate phenyl thiol in the presence of sodium methoxide effected the displacement and indole deprotection in one step to yield the targets **13** also as racemic mixtures. These β-arylthio carbinols could be oxidized to sulfoxides or sulfones **14** by treatment with 1–3 equivalents of Oxone® in a bisphasic mixture of ethyl acetate and water assisted by phase transfer catalysis.

With the chemical synthesis worked out and our compounds in hand, we examined the SAR of all three series. To evaluate the binding affinity of the compounds, we selected a commercially recombinant AR ligand binding domain kit.[10] The use of this kit, in contrast to isolation of AR from rat prostate cytosol, had two key advantages. First, the ease of use and ready availability of a validated receptor allowed this assay to be utilized in a high throughput screening program that was run in parallel with our directed synthesis efforts. Second, the higher concentration of the AR leads to a more robust response and a lower signal-to-noise ratio. One caveat to bear in mind when using this system is that, in general, non-steroidal AR ligands tended to show a lower AR binding affinity than that reported using prostate cytosol-derived receptor. To compensate for this discrepancy, we used bicalutamide as a comparator in this screening protocol.

Using this assay, we first examined the SAR of the imidazolidinone series to determine how well it mimicked the β-hydroxy arylsulfone segment of bicalutamide. The closest analog we prepared (Compound **2**, Fig. 1; Ar = 4-fluorophenyl, $n = 0$) had an IC_{50} of only 30 μM in the binding assay. Inserting a methylene spacer between the aryl ring and the imidazolinone (Ar = 4-fluorophenyl, $n = 1$) nitrogen atom led to further erosion in binding affinity (<50% inhibition at 30 μM concentration). We explored a range of substituents on both aromatic rings but unfortunately none these analogs improved on the potency of the initial compounds. We speculate that the rigidity of the imidazolidinone ring



Scheme 2. Synthesis of indole sulfide, sulfone and benzoate isosteres. Reagents and condition: (a) NIS, pTsOH (cat)/MeOH–THF; (b) excess MsCl/pyridine, heat; (c) NaOH/MeOH–H_2O; (d) $(PPh_3)_2PdCl_2$ (cat), CuI (cat), Et_3N/THF; (e) HCCMgBr/THF; (f) NaOH/THF–H_2O; (g) ArCOCl, Et_3N/THF; (h) NaOMe, ArSH/THF; (i) oxone®, TBAHS (cat), EtOAc–H_2O.

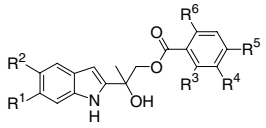
may prevent these structures from fitting into the binding pocket normally accommodating the more flexible aryl methylenesulfonyl moiety of bicalutamide.[11] We did not further investigate this scaffold in vitro, turning our attention instead to the indole bioisosteres.

In the benzoate series we first synthesized the exact analog (**10a**) of bicalutamide and were pleased to note that its binding affinity was roughly equivalent (Table 1). Removal of the 4-fluoro substituent (**10b**) led to an increase in binding affinity; replacement of the nitrile in this analog with chlorine (**10c**) maintained the potency and replacement with a nitro group (**10d**) marginally decreased potency. We further explored the SAR of **10d**, substituting the *para* position of benzoate ring with strongly electron withdrawing (**10e**) and donating (**10f** and **10g**) substituents but these led to a decrease in activity. Substitution of that position with alkyl groups (**10h** and **10i**) also decreased activity, while introduction of both phenyl (**10j**) and chloro (**10k**) moieties maintained the potency. Moving the chlorine atom from the *para* to the *meta* (**10l**) or *ortho* (**10m**) positions led to an increase in potency. Replacement of the chlorine atom in **10m** by the isosteric trifluoromethyl group (**10n**) produced a compound that was 10-fold more potent than bicalutamide. Reduction of the nitro group (**10o**) caused a significant loss in activity much of which was recovered by capping of the aniline with trifluoroacetyl group (**10p**).

We then turned our attention to the SAR of the β-arylthio carbinol substituted indoles (Table 2). As with the benzoate series we first prepared the exact analogs of bicalutamide. Although the sulfide linked carbinol (**13a**) was only 2-fold less potent than bicalutamide, the sulfone linked structure (**14a**) was significantly less active. Removal of the fluorine atom on the sulfide (**13b**) or replacement with a chlorine atom (**13c**) did not lead to any improvement in activity so we examined the indole ring. Removal of all indole substituents (**13d**) from **13c** as well as introduction of a carboxymethyl group at the 5-position (**13e**) led to inactive compounds, while introduction of a chlorine at the same position (**13f**) increased potency. Addition of a trifluoromethyl group (**13g**) to the indole 6-position of **13f** further increased potency. Returning to investigate the sulfide ring SAR, we found that a fluorine replacement (**13h**) of the chlorine atom of **13g** was well tolerated. We oxidized the sulfur atom to two epimeric sulfoxides (**14b** and **epi-14b**) that were both substantially less potent than the parent structure. Further oxidation of the linker to the sulfone oxidation state (**14c**) led to a 10-fold recovery of the activity. Introduction of a strongly electron donating group (**13i**) in place of the chlorine atom in **13g** diminished activity somewhat, while replacement with a hydrogen atom (**13j**) was well tolerated. Moving the chlorine atom from the *para* position (**13g**) to the *ortho* position (**13k**) was also well tolerated, while the addition of a second chlorine to the 3-position (**13l**) provided a compound that was more than 10-fold more potent than bicalutamide. Comparison of this structure with the **13m** indicated that, of the compounds surveyed, the 5-chloro-6-trifluoromethyl indole substitution pattern provided the best activity.

In summary, of the two bicalutamide bioisosteres we investigated, the indole series showed great promise, while the imidazolidinone series did not warrant further investigation. Within the indolyl carbinol scaffold, both β-benzoyloxy and thioaryl groups yielded compounds

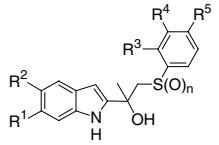
Table 1. Androgen receptor binding for benzoates **10**



Compound	R^1	R^2	R^3	R^4	R^5	R^6	AR binding[a] (IC_{50}, nM)
Bical	—	—	—	—	—	—	1300 (±106)
10a	CF_3	CN	H	H	F	H	1200 (±450)
10b	CF_3	CN	H	H	H	H	480 (±115)
10c	CF_3	Cl	H	H	H	H	440 (±49)
10d	CF_3	NO_2	H	H	H	H	820 (±110)
10e	CF_3	NO_2	H	H	NO_2	H	1600 (±289)
10f	CF_3	NO_2	H	H	OMe	H	6400 (±572)
10g	CF_3	NO_2	H	H	NMe_2	H	2600 (±572)
10h	CF_3	NO_2	H	H	Me	H	3000 (±491)
10i	CF_3	NO_2	H	H	^{t}Bu	H	3600 (±1386)
10j	CF_3	NO_2	H	H	Ph	H	940 (±127)
10k	CF_3	NO_2	H	H	Cl	H	720 (±225)
10l	CF_3	NO_2	H	Cl	H	H	460[b]
10m	CF_3	NO_2	Cl	H	H	H	460 (±37)
10n	CF_3	NO_2	CF_3	H	H	H	140[b]
10o	CF_3	NH_2	CF_3	H	H	H	4100[b]
10p	CF_3	$NHCOCF_3$	CF_3	H	H	H	150[b]

[a] Values are means of three experiments, standard error of measurement (SEM) is given in parentheses (na, not active: <50% inhibition at 30 μM).
[b] Values are means of two experiments.

Table 2. Androgen receptor binding for β-thiocarbinols **13** and **14**



Compound	R^1	R^2	R^3	R^4	R^5	*n*	AR binding[a] (IC_{50}, nM)
Bical	—	—	—	—	—		1300 (±106)
13a	CF_3	CN	H	H	F	0	2600 (±288)
14a	CF_3	CN	H	H	F	2	> 6900 (± >1559)
13b	CF_3	CN	H	H	H	0	3000 (±329)
13c	CF_3	CN	H	H	Cl	0	1700 (±866)
13d	H	H	H	H	Cl	0	na
13e	H	CO_2Me	H	H	Cl	0	na
13f	H	Cl	H	H	Cl	0	660 (±41)
13g	CF_3	Cl	H	H	Cl	0	180 (±41)
13h	CF_3	Cl	H	H	F	0	160 (±21)
14b	CF_3	Cl	H	H	F	1	5100 (±1328)
epi-14b	CF_3	Cl	H	H	F	1	4900[b]
14c	CF_3	Cl	H	H	F	2	460[b]
13i	CF_3	Cl	H	H	NH_2	0	930 (±139)
13j	CF_3	Cl	H	H	H	0	220 (±37)
13k	CF_3	Cl	Cl	H	H	0	180[b]
13l	CF_3	Cl	H	Cl	Cl	0	100 (±20)
13m	CF_3	NO_2	H	Cl	Cl	0	1000 (±508)

[a] Values are means of three experiments, standard error of measurement (SEM) is given in parentheses (na, not active: <50% inhibition at 30 μM).
[b] Values are means of two experiments.

with 10-fold better binding affinity than the parent structure. These results provided an impetus for further evaluation of this novel series and will be discussed in due course.

Acknowledgment

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10. A typical procedure: five picomoles of the rat androgen receptor ligand binding domain (Invitrogen, Carlsbad, CA) was incubated with test compound (dissolved in DMSO) and 0.5 nM tritium-labeled R1881(Perkin-Elmer, Boston, MA) in 10 mM Tris–HCl, pH 7.4, 1.5 mM EDTA, 1 mM dithiothreitol and 10% (v/v) glycerol. Incubation was performed in a 0.15 mL volume in a 96-well plate at 4 °C overnight. The next day, 20 μL of 25 mg/mL human γ-globulin (MP Biomedicals, Irvine, CA) and 55 μL of 40% (w/v) polyethylene glycol (PEG) 8000 (JT Baker, Phillipsburg, NJ) were added to each well. After one more hour at 4 °C, the binding reaction mixtures were filtered through a FilterMate 196 (Perkin-Elmer) onto a GF/C UniFilter-96, using 10% (w/v) PEG for filtration and washing. The filter was dried, sealed on one side, and 25 μL of MicroScint-20 (Perkin-Elmer) was added to each well. The other side was sealed and the plate was read on a TopCount (Perkin-Elmer). Counts per minute from each well were converted to percentage of inhibition using compound-free and 1 μM R1881-containing wells as zero and 100% inhibition controls, respectively.
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