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Effects of Isosteric Pyridone Replacements in Androgen Receptor Antagonists Based on 1,2-Dihydro- and 1,2,3,4-Tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinolines

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Abstract—A series of nonsteroidal human androgen receptor (hAR) antagonists based on 8-substituted 1,2-dihydro- and 1,2,3,4-tetrahydro-2,2-dimethyl-6-trifluoromethylpyrido[3,2-*g*]quinolines was synthesized. Compounds in this series were tested for the ability to bind to hAR and inhibit hAR-dependent transcription in a mammalian cellular background.

Introduction

Nonsteroidal human androgen receptor (hAR) antagonists such as flutamide (**1a**)[1] and bicalutamide (**2**)[2] are currently used in combination with leutinizing-hormone-releasing hormone agonists for the treatment of prostate cancer.[3] Additionally, AR antagonists may have clinical utility in indications such as benign prostatic hyperplasia, alopecia, acne, and hirsutism.[4–7] We recently reported the discovery of a novel template for AR modulators, and our preliminary findings with respect to the pharmacologic profile of these agents based on 8-pyridono[5,6-*g*]quinolines such as **3** (Fig. 1).[8–13]

Subsequent efforts attempting to investigate the contribution of the hydroxypyridine tautomer[14] and nature of the small molecule contribution to hydrogen-bonding in the ligand-binding domain of hAR in these antagonists led us to explore compounds with isosteric replacements for the pyridone moiety of the parent molecules. The current series of analogues examines the effects of various 8-position substituents on antiandrogenic activity, as measured in cell-based gene transcription and hormone binding assays.

Chemistry

All 8-substituted pyrido[3,2-*g*]quinolines were derived from the corresponding 8-pyridono[5,6-*g*]quinolines **4**, with the exception of the 8-trifluoromethyl compound **20**, which was derived from 7-amino-1,2,3,4-tetrahydro-2,2-dimethylquinoline **19**.[14] Chloro- and bromo- substituents were introduced at the 8-position by heating pyridonoquinolines **4** with the appropriate phosphorous oxyhalide.[15] The 8-chloro compounds were then converted to the corresponding 8-fluoro compounds by treatment with potassium fluoride[16] in sulfolane at elevated temperatures. The 8-bromo-substituted pyridines were reductively dehalogenated under free radical conditions,[17] and subsequently converted to the 8-cyano analogues **9** via a Reissert intermediate using potassium cyanide and tosyl chloride[18,19] (Scheme 1).[20]

The 8-sulfonyl and 8-sulfinyl-analogues were accessed through selective *S*-alkylation[21] of the thioquinolones **10** (prepared by reacting **4** with Lawesson's reagent[22]) followed by oxidation of the resultant sulfide with *m*CPBA or magnesium monoperoxyphthalate respectively[23] (Scheme 2). Heating quinolone **3** with *p*-methoxybenzylamine, *p*-toluenesulfonic acid, and hexamethyldisilazane afforded the PMB-protected aminopyridine **14**.[24] Deprotection of the amine with trifluoroacetic acid,[25] either preceded by alkylation or followed by mesylation, yielded the appropriately *N*-substituted analogues **16a**, **16b** and **18** (Scheme 3). The 8-trifluoromethyl-substituted analogue **20** was prepared

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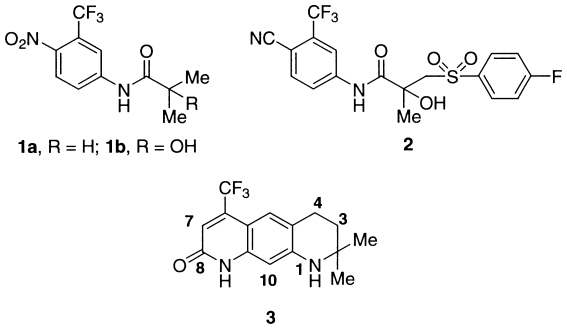
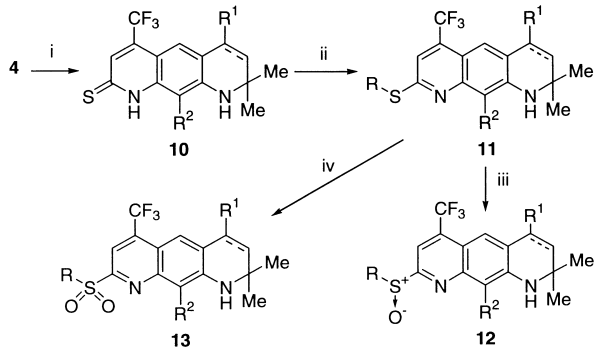
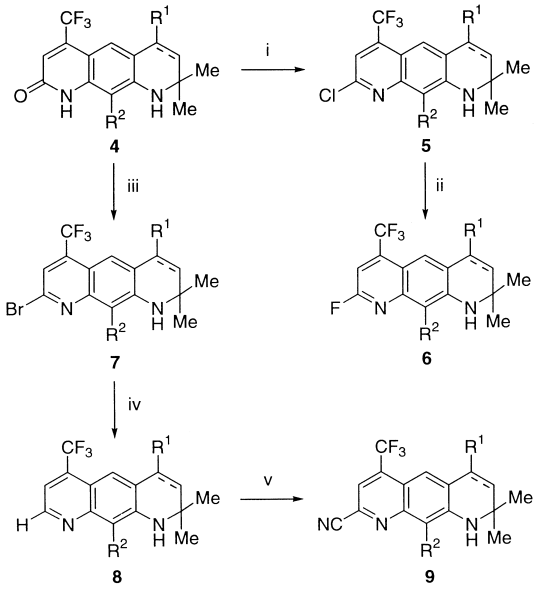


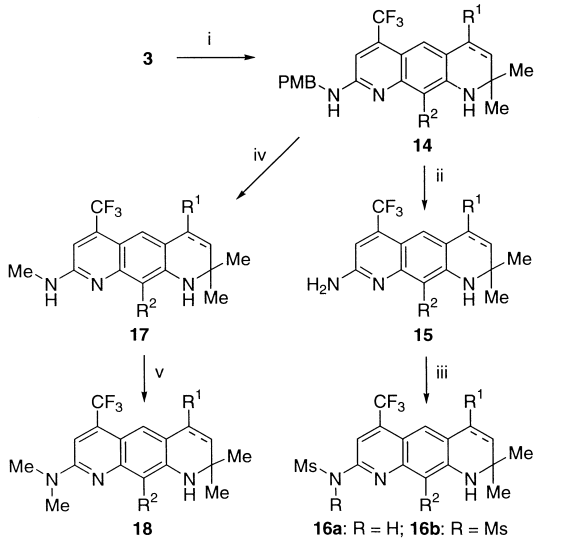
Figure 1. Flutamide (**1a**) and 2-hydroxyflutamide (**1b**); bicalutamide (**2**); 1,2,3,4-tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono-[5,6*g*]quinoline (**3**).



Scheme 2. (i) Lawesson's reagent, THF, rt; (ii) R-X, DMF; (iii) MMPP, EtOH, reflux, 1 h; (iv) *m*CPBA, CH_2Cl_2, −78 °C, 20 min.

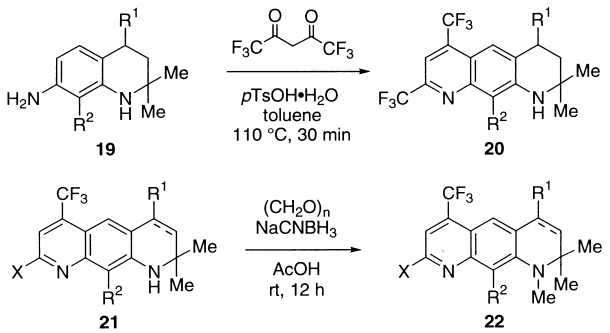


Scheme 1. (i) $POCl_3$, 80 °C, 3 h; (ii) KF, sulpholane, 200–210 °C, 18 h; (iii) $POBr_3$, 70 °C, 4 h; (iv) *n*-Bu_3SnH, AlBN, toluene, reflux, 20 h; (v) KCN, TsCl, CH_2Cl_2, H_2O, rt, 5d.



Scheme 3. (i) PMB-NH_2, *p*TsOH·H_2O, HMDS, 140 °C, 2 h; (ii) CH_3CO_2H, 60–70 °C, 3 h; (iii) MsCl, NEt_3, CH_2Cl_2, 0 °C, 30 min; (iv) 1. NaH, MeI, DMF; 2. CF_3CO_2H, 60–70 °C; (v) NaH, MeI, DMF, 0 °C, rt.

by condensing aminotetrahydroquinoline **19** with 1,1,1,5,5,5-hexafluoropentane-2,4-dione using catalytic *p*-toluenesulfonic acid in toluene. Methylation of compounds **5a**, **5c**, **6c**, **7b**, **8b** and **9** at N1 was achieved under standard reductive amination conditions to yield compounds **22**.[26]



Biological Results and Discussion

Inhibition of hAR-dependent transcriptional activity was measured using a cotransfection assay in mammalian (CV-1) cells,[27,28] and hAR binding was measured in a whole cell assay using mammalian (COS-1) cells (Table 1). The effects of 8-position substitution on bioactivity varied dramatically with steric and electronic parameters. Although the relative activities of amino compounds **15** and **17**, most closely isosteric with the hydroxypyridine tautomer of the parent **3** ($IC_{50} = 27 \pm 5$ nM, efficacy = 74 ± 2%), were greatly diminished, as were activities of 8-alkoxy analogues,[8] compounds with less electron-rich N-based functional groups at the 8-position, as in sulfonamides **16a** and **16b**, regained partial activity. Electron-withdrawing substitutions at the 8-position were therefore generally pursued, and as a general trend, conferred activities similar to those of the parent pyridones. Somewhat narrow steric restrictions

Table 1. hAR antagonist activity in cotransfected CV-1 cells and binding affinities for hAR transfected into COS-1 cells

Ligand	R^1	R^2	3,4-[a]	8-position (X)	Cotransfection assay IC_{50}[b,c] (nM)	Cotransfection assay Efficacy[c,d] (%)	Binding K_i[c] (nM)
1b			2-Hydroxyflutamide		43 ± 4	97 ± 0	34 ± 8
2			Bicalutamide		338 ± 28	98 ± 0	117 ± 35
3[8]	H	H	2*H*	(OH)	27 ± 5	74 ± 2	26 ± 5
5a	Me	H	Δ	Cl	30 ± 9	70 ± 3	320 ± 67
5b	Me	Me	2*H*	Cl	675 ± 114	60 ± 6	>1000
5c	H	H	2*H*	Cl	30 ± 12	75 ± 3	84 ± 22
6a	Me	H	Δ	F	31 ± 9	56 ± 11	57
6b	Me	Me	2*H*	F	1448	68	>1000
6c	H	H	2*H*	F	22 ± 10	66 ± 1	11
7a	Me	Me	2*H*	Br	785	82	>1000
7b	H	H	2*H*	Br	72	83	159
8a	Me	Me	2*H*	H	244	99	>1000
8b	H	H	2*H*	H	212	95	5
9	H	H	2*H*	CN	9 ± 2	83 ± 3	22
11a	H	H	2*H*	MeS	751	95	>1000
11b	H	H	2*H*	*n*-BuS	1866	75	>1000
11c	H	H	2*H*	CF_3CH_2S	889	80	>1000
12a	H	H	2*H*	MeSO	63 ± 23	98 ± 2	20
12b	H	H	2*H*	*n*-BuSO	335 ± 145	96 ± 0	96
13	H	H	2*H*	$MeSO_2$	479	94	>1000
14	H	H	2*H*	PMB-NH[e]	3217	57	>1000
15	H	H	2*H*	NH_2	1159 ± 280	70 ± 5	>1000
16a	H	H	2*H*	MsNH[f]	503	80	572
16b	H	H	2*H*	Ms_2N[f]	636	84	>1000
17	H	H	2*H*	MeNH	>10000	< 20	>1000
18	H	H	2*H*	Me_2N	>10000	< 20	>1000
20	H	H	2*H*	CF_3	467 ± 11	95 ± 1	>1000
22a	Me	H	Δ	Cl	336 ± 90	86 ± 2	>1000
22b	H	H	2*H*	Cl	251 ± 81	87 ± 2	294 ± 89
22c	H	H	2*H*	F	172 ± 52	86 ± 9	96
22d	H	H	2*H*	Br	72	93	426
22e	H	H	2*H*	H	725 ± 330	83 ± 5	>1000
22f	H	H	2*H*	CN	45 ± 8	94 ± 3	86 ± 30

[a]Δrepresents unsaturation and 2*H* represents saturation between C_3 and C_4.
[b]IC_{50} values represent the concentration of ligand required for half maximal inhibition in the presence of dihydrotestosterone at its EC_{50}.
[c]Values represent mean ± SEM; values without SEM are single determinations.
[d]Efficacies are determined as% maximal inhibition.
[e]PMB = *p*-methoxybenzyl.
[f]Ms = methanesulfonyl.

were observed, as activity rapidly dropped off with increasing substituent size, though this trend was obfuscated in *N*-methylated analogues **22**. Substituents with the optimal combination of small size, electronegative character, and hydrogen bond accepting ability were found in compounds such as **6c** (8-F), and particularly **9** (8-CN), which actually showed improved activity over the parent. Elsewhere in the molecule, methyl substitution at N1 (**22a–f**) or at the 10-position (**5b**, **6b**, **7a**, **8a**) both significantly lowered activity compared to the unmethylated versions, while substitution at the 4-position and/or presence of C3,4 unsaturation had relatively little effect. As previously reported for compounds with geminal alkyl substitution at the 2-position, no androgen agonist activity was observed in the present series of analogues. The present results together with SAR gleaned from our previous efforts around this pharmacophore[8–13] strongly support an emphasis on a strong H-bond acceptor near the 8-position, consistent with the pyridone tautomer.

Compounds in the present series were generally much more lipophilic than their corresponding parent pyridones. CLogP calculations for typical molecules in the 8-substituted series were on average 1–2 units higher than those of the parent pyridono compounds **3** (ClogP's for compounds **3**, **5c**, **6c** and **9** are 3.4, 5.6, 5.1, and 4.4 respectively),[29] approaching the borderline of the range generally acceptable for orally-administered drugs.[30] As one of the goals of our program is focused on discovery of an AR antagonist for topical administration to address the secondary indications of acne, alopecia, and hirsutism, compounds with physical properties in the range of those exhibited by the present series may have the potential to favorably impact the development of drugs for those indications.

This series of hAR antagonists includes compounds that exhibit in vitro potencies comparable to or better than that of the parent 1,2-dihydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinolines.[8] This series of analogues significantly expands the scope of our AR modulator pharmacophoric template and provides compounds with a wider range of physical properties. This latter aspect may prove beneficial in targeting some of the secondary AR-related clinical indications.

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20. Typical experimental procedures for Scheme 1 are illustrated for compounds **7b**, **8b** and **9**. **Preparation of 7b:** To a flame-dried 25-mL round-bottom (r.b.) flask in a glove bag under N_2 was added phosphorous oxybromide (2.0 g, 7.0 mmol) and quinolone **3** (500 mg, 1.59 mmol). The resultant mixture was heated to 60 °C and allowed to stir for 2.5 h. The reaction was then allowed to cool to rt, and the mixture was then poured into ice and EtOAc and stirred for 10 min. The layers were separated, and the aqueous layer was neutralized with satd $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with water, satd $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated under reduced pressure to yield a dark orange solid. Purification by flash column chromatography (silica gel, hexanes:EtOAc, 2:1) followed by recrystallization of the resultant solid from EtOAc afforded 455 mg (80%) of the bromopyridoquinoline **7b** as yellow needles. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H, 5-H), 7.38 (s, 1H, 7-H), 6.92 (s, 1H, 10-H), 4.43 (br s, 1H, N*H*), 2.99 (t, 2H, J = 6.3 Hz, 4-H), 1.81 (t, 2H, J = 6.7 Hz, 3-H), 1.31 [s, 6H, 2-(CH_3)$_2$]; **Preparation of 8b:** In a flame-dried 100-mL r.b. flask, tributyltin hydride (3.75 mL, 13.9 mmol) in toluene (5 mL) was heated to reflux. To this reaction solution was added a solution of bromoquinoline **7b** (1.25 g, 3.48 mmol) and 2,2′-azobisisobutyronitrile in toluene (20 mL) dropwise over 20 min. The reaction mixture was then refluxed for 20 h. Upon cooling to rt carbon tetrachloride (5 mL) was then added, and the reaction and was stirred for 2.5 h at rt. The solvent was removed under reduced pressure, and the resultant solid was resuspended in hexanes and filtered. Copious washes with hexanes yielded 750 mg (77%) of quinoline **8b** as a bright yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, 1H, J = 4.4 Hz, 8-H), 7.71 (s, 1H, 5-H), 7.29 (d, 1H, J = 4.6 Hz, 7-H), 7.03 (s, 1H, 10-H), 4.35 (br s, 1H, N*H*), 3.05 (t, 2H, J = 6.3 Hz, 4-H), 1.82 (t, 2H, J = 6.7 Hz, 3-H), 1.31 [s, 6H, 2-(CH_3)$_2$]; **Preparation of 9:** To a 10-mL r.b. flask containing quinoline **8b** (500 mg, 1.78 mmol) suspended in CH_2Cl_2 (5 mL) at rt was added potassium cyanide (349 mg, 5.36 mmol) in water (1 mL) in one portion. Then *p*-toluenesulfonyl chloride (713 mg, 3.57 mmol) in CH_2Cl_2 (4 mL) was added to the reaction mixture dropwise over 30 min. The flask was then sealed and stirred for 5 days. The reaction mixture was then filtered through a pad of Celite, washing with CH_2Cl_2. The filtrate was concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexanes:EtOAc, 2:1) followed by recrystallization from MeOH afforded 343 mg (63%) of cyanopyridoquinoline **9** as bright orange needles. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H, 5-H), 7.54 (s, 1H, 7-H), 7.03 (s, 1H, 10-H), 4.59 (br s, 1H, N*H*), 3.06 (t, 2H, J = 6.3 Hz, 4-H), 1.83 (t, 2H, J = 6.7 Hz, 3-H), 1.33 [s, 6H, 2-(CH_3)$_2$].
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