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Design and Synthesis of 4-(4-Benzoylaminophenoxy)phenol Derivatives As Androgen Receptor Antagonists

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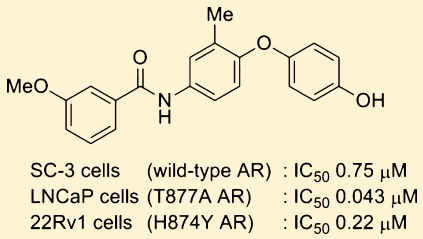
Supporting Information

ABSTRACT: We report the design and synthesis of novel 4-(4-benzoylaminophenoxy)phenol derivatives that bind to the androgen receptor (AR) ligand-binding domain and exhibit potent androgen-antagonistic activity. Compound **22** is one of the most potent of these derivatives, inhibiting the dihydrotestosterone-promoted growth of SC-3 cell line bearing wild-type AR (IC_{50} 0.75 μM), LNCaP cell line bearing T877A-mutated AR (IC_{50} 0.043 μM), and 22Rv1 cell line bearing H874Y-mutated AR (IC_{50} 0.22 μM). Structure−activity relationship studies confirmed that the pharmacophore of these novel AR antagonists is distinct from the nitro- or cyano-substituted anilide substructure of other nonsteroidal AR antagonists. This novel pharmacophore is expected to provide a basis for designing new antiprostate cancer agents.



KEYWORDS: *Androgen receptor (AR), AR antagonist, prostate cancer, pharmacophore, 4-(4-benzoylaminophenoxy)phenol*

Androgen receptor (AR) is a member of the nuclear receptor superfamily of ligand-dependent transcriptional factors.[1,2] AR is activated by binding of endogenous androgens, such as testosterone and its activated form, dihydrotestosterone (DHT), and regulates numerous physiological processes, including growth, maintenance of the male reproductive system, and homeostasis of bone and muscle.[3,4] Because AR plays an important role in progression of prostate cancer, AR antagonists are used clinically for treatment of prostate cancer. However, chronic administration of AR antagonists often leads to development of resistance, so-called castration-resistant prostate cancer (CRPC),[5,6] and mutation of AR is thought to be the main cause.[7−9] For example, a representative nonsteroidal AR antagonist, flutamide (**1**), and its activated metabolite, hydroxylflutamide (**2**), act as agonists of AR bearing T877A, the most common mutation of AR in CRPC and consequently exacerbate the cancer.[10]

All the nonsteroidal AR antagonists currently in clinical use are derivatives of flutamide bearing a nitrophenyl or a cyanophenyl group as the pharmacophore (Figure 1),[11] and these antagonists are often ineffective for mutated ARs.[12] Intensive studies based on flutamide derivatives have been investigated, and recently, novel flutamide derivative MDV3100 (**5**) was developed as a potent AR antagonist effective for CRPC.[13] Another possible approach to overcome CRPC would be to develop AR antagonists bearing a novel pharmacophore, different from those of flutamide analogues. For example, nicotinamide derivative DIMN (**6**) was developed as novel type of nonsteroidal AR antagonists.[14]

With the aim of developing novel AR antagonists, we focused on the structure of the natural pigment curcumin (**7**, Figure 2). Several curcumin analogues possess antiandrogenic activity,[15,16] and **7** does not possess the cyanophenyl or nitrophenyl group

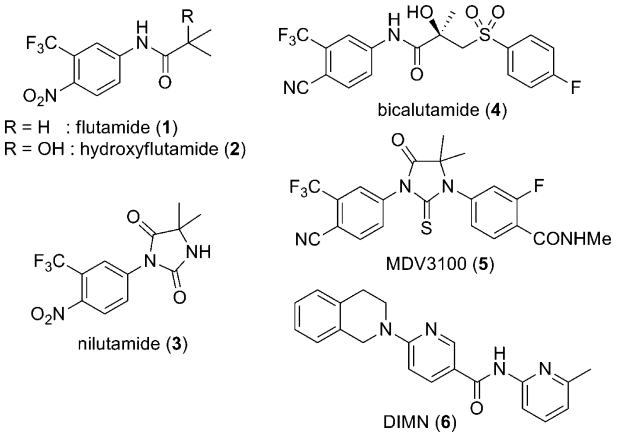


Figure 1. Structures of nonsteroidal AR antagonists.

that is the key structure of potent nonsteroidal AR antagonists so far developed. Structurally, curcumin (**7**) consists of two phenolic groups linked by an unsaturated 1,3-diketone (or its enol form), which would be chemically and metabolically reactive.[17] Therefore, we assumed that at least one phenolic group of **7** was essential for the AR antagonistic activity and that the overall structural framework of **7** could be replaced by stable, drug-like structures. Our previous studies on retinoids suggested that benzanilide is a versatile structure for replacing conjugated polyene substructure.[18,19] Recent studies by us and others also suggested that a Ph−X−Ph skeleton, such as diphenylmethane (X = carbon),[20] diphenyl ether (X =

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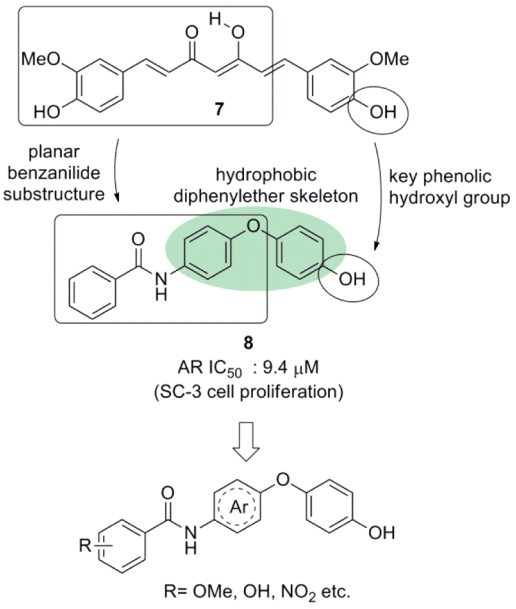


Figure 2. Design of novel AR antagonists bearing phenol substructure.

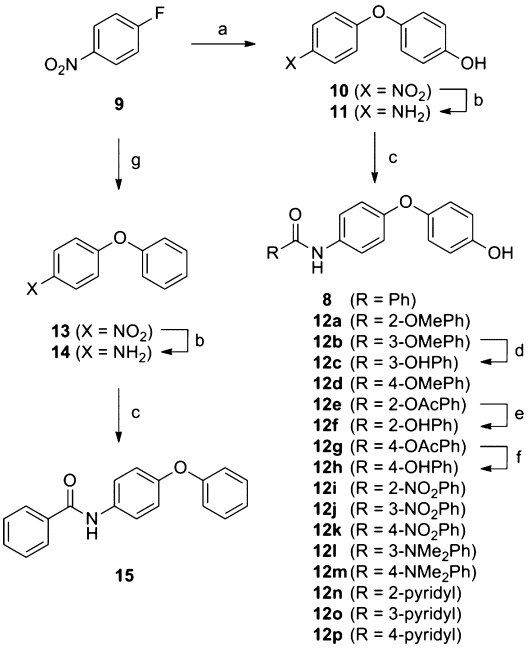
oxygen),[21] diphenylamine (X = nitrogen),[22] or diphenylsilane (X = silane),[23] is a suitable hydrophobic substructure for nuclear receptor ligands.

On the basis of those findings, we designed the phenoxybenzanilide core structure as a candidate scaffold of AR antagonists, and we initially synthesized the parent compound **8** (Figure 2). Biological evaluation revealed that **8** exhibited significant AR antagonistic activity, being a potent inhibitor of androgen-dependent SC-3 cell[24] proliferation (IC_{50} = 9.4 μM). Here, we report the synthesis and biological activity of **8** and its derivatives (general formula shown in Figure 2) as candidate new-generation AR antagonists bearing a novel pharmacophore distinct from those of conventional flutamide analogues.

Compound **8** and 4-phenoxyphenols **12a**–**p** were synthesized as shown in Scheme 1.[25] S_NAr reaction using 4-fluoronitrobenzene (**9**) and hydroquinone gave diphenyl ether **10**, and then reduction of the nitro group afforded primary amine **11**. Amide bond formation of **11** with benzoic acid or benzoyl chloride derivatives gave compounds **8** and **12a**–**p**. Compounds **12c**, **12f**, and **12h** were synthesized from the corresponding *O*-monomethyl (for **12c**) or *O*-monoacetyl (for **12f** and **12h**) derivatives by removal of the *O*-substituent. Diphenyl ether **15** without a phenolic hydroxyl group was also prepared for investigation of the significance of the phenolic hydroxyl group. S_NAr reaction using **7** and phenol gave diphenyl ether **13**, and then reduction of the nitro group afforded primary amine **14**. Amide bond formation of **14** using benzoyl chloride gave compound **15** (Scheme 1).

Scheme 2 shows the synthesis of compounds **22** and **23** bearing methyl group(s) at the central benzene ring and the synthesis of heterocyclic analogues **30** and **31**. S_NAr reaction using hydroquinone and fluoronitrobenzene **16** or **17** gave diphenyl ethers **18** and **19**, respectively. Reduction of the nitro group gave amine **20** and **21**, and following amide formation afforded the target compounds **22** and **23**. Compounds bearing pyridine or pyrimidine as the central aromatic ring were also similarly synthesized. Reaction of 2-chloro-5-nitropyridine **24** or 2-chloro-5-nitropyrimidine **25** with 4-benzyloxyphenol gave diaryl ethers **26** and **27**, respectively. Reduction of the nitro

Scheme 1. Synthesis of 8, 12a–p, and 15[a]



[a]Reagents and conditions: (a) hydroquinone, NaOH, DMSO–H_2O, 50 °C, 56%; (b) Pd–C, H_2, MeOH, rt, 92–98%; (c) method A, aroyl chloride, THF, rt, 55–86%; method B, aroyl chloride, pyridine, rt, 50–60%; method C, (i) $(COCl)_2$, DMF, CH_2Cl_2, rt; (ii) **11**, THF, rt, 39–84%; method D, (i) $(COCl)_2$, DMF, CH_2Cl_2, rt; (ii) **11**, pyridine, THF, rt, 46%; (d) BBr_3, CH_2Cl_2, 40 °C, 50%; (e) K_2CO_3, MeOH–H_2O, rt, 95%; (f) NaOEt, EtOH, rt, 30%; (g) phenol, K_2CO_3, DMF, 40 °C, 90%.

group and deprotection of the benzyl group by catalytic hydrogenation afforded amines **28** and **29**, and then, amide condensation gave the target compounds **30** and **31**.

The antiandrogenic activity of the synthesized compounds was initially evaluated by assay of growth-inhibitory activity toward SC-3.[24] SC-3 cells have wild-type AR and proliferate androgen-dependently. None of the synthesized compounds promoted growth of SC-3 cells. Table 1 shows the inhibitory potency of the test compounds toward DHT-promoted cell growth of SC-3. Compound **12b** exhibited the most potent antiandrogenic activity among the synthesized compounds, and **12l** also exhibited potent antiandrogenic activity exceeding that of the lead compound **8**. Deletion of the phenolic hydroxyl group (compound **15**) resulted in significant loss of potency (20% inhibition at the concentration of 10 μM). Ohtsu et al. reported that the phenolic hydroxyl group was not essential for its AR antagonistic activity,[15] and therefore, the importance of this hydroxyl group is intriguing. Interestingly, compounds **12i**, **12j**, and **12k** bearing a nitrophenyl group did not exhibit significant antiandrogen activity. The nitrophenyl group is a common pharmacophore of conventional nonsteroidal AR antagonists, and this result suggested that the 4-(4-benzoylaminophenoxy)phenol derivatives are a novel class of AR antagonists bearing a unique pharmacophore, different from those of AR antagonists so far known. Bisphenol compound **12f** and compounds bearing a pyridine ring **12n** and **12o** exhibited moderate activity similar to that of **8**. These results indicate that the 3-methoxybenzoyl group of **12b** was the most suitable as the terminal functionality.

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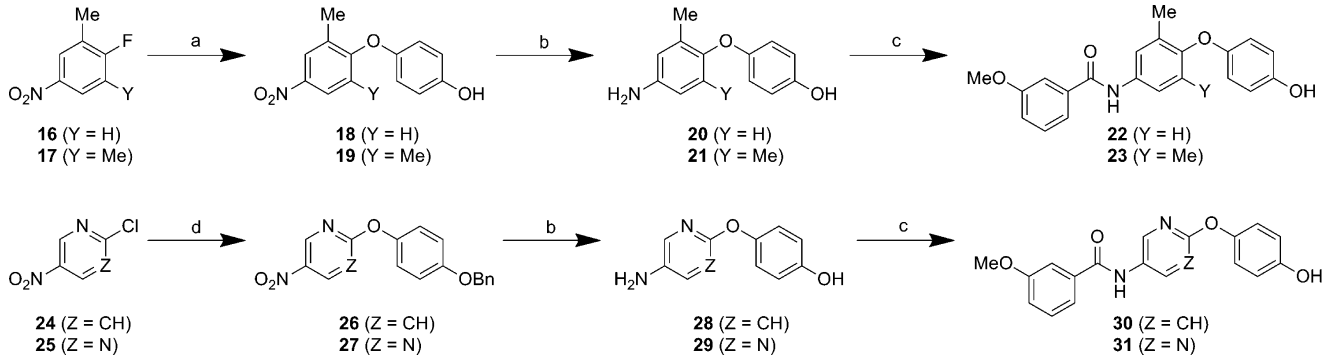
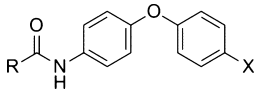
Scheme 2. Synthesis of 22, 23, 30, and 31[a]



[a]Reagents and conditions: (a) hydroquinone, NaOH, DMSO−H_2O, 50 °C to rt, 66% (**18**), 55% (**19**); (b) for **20**, Pd−C, H_2, MeOH, rt, 94%: for **21**, Pd−C, H_2, THF, rt, 90%; (c) for **22**, *m*-anisoyl chloride, THF, rt, 63%; for **23**, *m*-anisoyl chloride, pyridine, THF, rt, 67%; (d) for **26**, 4-benzyloxyphenol, *t*-BuOK, DMF, rt, 46%; for **27**, *p*-benzyloxyphenol, K_2CO_3, DMF, rt, 38%; (e) Pd−C, H_2, THF, rt, quant (**28**), 80% (**29**); (f) *m*-anisoyl chloride, THF, rt, 76% (**30**), 79% (**31**).

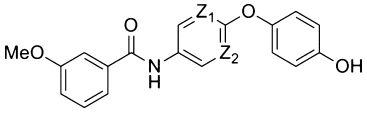
Table 1. AR Antagonistic Activity of Synthesized Compounds by Means of Inhibition of DHT-Promoted SC-3 Cell Proliferation[a]



compd	R	X	IC_{50} (μM)
2			0.37
8	Ph	OH	9.4
12a	2-MeO−Ph	OH	>10
12b	3-MeO−Ph	OH	2.0
12d	4-MeO−Ph	OH	>10
12f	2-HO−Ph	OH	8.8
12c	3-HO−Ph	OH	n.d.[b]
12h	4-HO−Ph	OH	n.d.[b]
12i	2-NO_2−Ph	OH	>10
12j	3-NO_2−Ph	OH	>10
12k	4-NO_2−Ph	OH	>10
12l	3-NMe_2−Ph	OH	3.0
12m	4-NMe_2−Ph	OH	6.7
12n	2-pyridyl	OH	8.7
12o	3-pyridyl	OH	9.7
12p	4-pyridyl	OH	>10
15	Ph	H	>10

[a]SC-3 cell growth was promoted by 1 nM DHT. [b]Inhibition was not detected at the concentration of 10 μM.

Table 2. Androgen Antagonistic Activity of Synthesized Phenol Derivatives by Means of SC-3 Assay, Binding Affinity, and Reporter Assay



			SC-3 assay[a]	binding affinity[b]	luciferase assay[c]
compd	Z_1	Z_2	IC_{50} (μM)	IC_{50} (μM)	% inhibition
2			0.37	7.1	60
12b	CH	CH	2.0	20	6
22	CMe	CH	0.75	9.2	66
23	CMe	CMe	2.9	5.4	69
30	N	CH	7.2	>10	n.d.[d]
31	N	N	5.9	>10	n.d.[d]

[a]Cell growth was promoted by 1 nM DHT. [b]Competitive binding assay using hAR-LBD and ^{3}H-labeled DHT (4 nM). [c]Inhibition (% of control) of luciferase activity by 10 μM test compound using MDA-Kb2 cell line. The concentration of DHT was 0.1 nM. [d]Inhibition was not detected at the concentration of 10 μM.

For further structural development of these novel AR antagonists, the structure−activity relationship of the central aromatic ring was investigated. Compounds bearing phenol and methoxybenzoyl groups as terminal aromatic rings and different center rings were synthesized, and their activities were compared by means of antiandrogen activity assay with SC-3 cells, competitive AR binding assay, and luciferase assay (Table 2). Compound **22** bearing a methyl group at the center ring exhibited the most potent activity toward SC-3 cells, and the potency (IC_{50} = 0.75 μM) of this compound was of the same order as that of hydroxyflutamide (**2**). Dimethylated derivative **23** also exhibited similar potency to **12b**, whereas heterocyclic compounds **30** and **31** exhibited lower potency than **12b** in SC-3 assay. Compounds **22** and **23** exhibited strong binding affinity for wild-type AR, whereas heterocyclic derivatives **30** and **31** did not. The results of luciferase assay using MDA-Kb2 cell line[26] also supported the idea that the AR antagonistic activities of compounds **22** and **23** are due to their AR-modulating activity.

Then, we investigated the antiandrogenic activity of the selected compounds toward human prostate cancer cell lines LNCaP and 22Rv1, which have mutation in the AR ligand-binding domain. The LNCaP cell line expresses T877A AR, which is the most frequently detected mutation of AR in castration-resistant prostate cancer.[27,28] Hydroxyflutamide (**2**) and some other AR antagonists act as agonists toward T877A AR,[10] and therefore, we use **4** as positive control of this assay. The 22Rv1 cell line expresses H874Y AR.[29] None of the compounds examined promoted growth of these prostate cancer cell lines, and all of them exhibited significant inhibitory activity toward DHT-induced proliferation of these cell lines (Table 3). Among them, compound **22**, which was the most potent AR antagonist in SC-3 assay, exhibited the most potent antiandrogenic activity toward LNCaP cell line (IC_{50} = 0.043 μM). Compound **22** also exhibited potent antiandrogenic activity toward 22Rv1 cell line (IC_{50} = 0.22 μM). The antiandrogenic activities of compound **22** are more potent than those of bicalutamide (**4**), one of the most effective

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Table 3. Antiandrogenic Activity and Cytotoxicity of Selected Phenol Derivatives toward Three Human Prostate Cancer Cell Lines

	LNCaP (T877A-AR)	22Rv1 (H874Y-AR)	PC-3
compd	IC_{50} (μM)[a]	IC_{50} (μM)[a]	IC_{50} (μM)[b]
4	0.94	4.6	>10
12b	0.29	1.9	5.6
22	0.043	0.22	5.7
23	2.4	1.3	>10

[a]Cell growth was promoted by 10 nM DHT. [b]IC_{50} values for androgen-independent cell proliferation.

nonsteroidal AR antagonists. These results suggest that compound **22** is a potent AR antagonist active toward both wild-type and mutant AR. We also examined the effect of compounds toward androgen-independent prostate cancer cell line PC-3. Compound **12b** and **22** exhibited cell-growth inhibiting potency at micromolar concentrations. This result indicates that these compounds possess anticancer or cytotoxic activity independent to AR antagonistic activity, though the effective concentrations are comparatively higher than that of antiandrogenic activities. It was reported that curcumin and its derivatives have various physiological activities and antiproliferation activity toward prostate cancer by interfering with many transcription pathways.[30−33] The compounds developed in this study certainly bind to AR ligand-binding domain and exhibit AR antagonistic activity; however, these compounds probably possess another biological activity other than AR modulation like curcumin.

In summary, we have developed a new class of nonsteroidal AR antagonists without the nitrophenyl or cyanophenyl substructure of known AR antagonists. We designed and synthesized a series of 4-phenoxyphenol derivatives as AR antagonist candidates. We found that the 4-(4-benzoylaminophenoxy)phenol skeleton serves as a novel core structure of AR antagonists. Compound **22** is one of the most potent of these non-nitrophenyl and non-cyanophenyl type nonsteroidal AR antagonists and exhibited antiandrogenic activity toward several prostate cancer cell lines, including two with mutated ARs. This novel non-flutamide derivative type AR antagonist is a promising candidate for antiandrogen therapy of prostate cancer.

■ ASSOCIATED CONTENT

Supporting Information

Analytical data and experimental procedures for synthetic preparation and biological evaluation of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the manuscript.

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Notes

The authors declare no competing financial interest.

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