Development of *N*-(4-Phenoxyphenyl)benzenesulfonamide Derivatives as Novel Nonsteroidal Progesterone Receptor Antagonists

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S Supporting Information

ABSTRACT: We report here development of *N*-(4-phenoxyphenyl)benzenesulfonamide derivatives as a novel class of nonsteroidal progesterone receptor (PR) antagonists. PR plays key roles in various physiological systems, including the female reproductive system, and PR antagonists are candidates for clinical treatment of multiple diseases, including uterine leiomyoma, endometriosis, breast cancer, and some psychiatric disorders. We found that the benzenesulfonanilide skeleton functions as a novel scaffold for PR antagonists, and we adopted 3-chlorobenzenesulfonyl derivative **20a** as a lead compound for structural development. Among the synthesized compounds, 3-trifluoromethyl derivative **32** exhibited the most potent PR-antagonistic activity, with high binding affinity for PR and selectivity over androgen receptor (AR). It is structurally distinct from other nonsteroidal PR antagonists, including cyanopyrrole derivatives, and further modification is expected to afford novel selective PR modulators.

KEYWORDS: Progesterone, nuclear receptor, antagonist, *N*-(4-phenoxyphenyl)benzenesulfonamide

Progesterone receptor (PR) is a member of the nuclear receptor superfamily of ligand-dependent transcriptional factors.¹ It is regulated by its endogenous agonist progesterone (P4, **1**, Figure 1) and plays key roles in multiple physiological systems, including the female reproductive system in which it influences uterine cell proliferation and differentiation, the ovulation cycle, and mammary gland growth and differentiation.^{2–6} Thus, synthetic PR modulators have potential clinical value. For instance, various synthetic P4 derivatives have been developed as PR agonists and are used for clinically for treatment of gynecological disorders, contraception, and hormone replacement therapy.^{7–9} However, steroidal compounds may have side effects, and therefore, development of nonsteroidal PR agonists such as tanaproget (**3**)^{10,11} has been investigated.¹² However, the pharmaceutical potential of PR antagonists has been little explored. Though a steroidal PR antagonist mifepristone (**2**) and related PR antagonists are used as contraceptive agents in some countries,¹³ it is suggested that PR antagonists might be effective not only as contraceptive agents but also in the treatment of uterine leiomyoma, endometriosis breast cancer, and some psychiatric disorders.¹⁴ Therefore, development of potent nonsteroidal PR antagonists is desired for detailed investigation of the clinical potential of PR modulation. Based on the structure of nonsteroidal PR

agonist **3**, several nonsteroidal PR antagonists such as **4** and **5** have been developed.^{15–18} We also developed cyanophenyl derivatives bearing a spherical hydrophobic skeleton, such as a boron cluster derivative **6**, as nonsteroidal PR antagonists.^{19,20} However, these PR antagonists contain a cyanoaryl moiety or related substructure as a common pharmacophore motif. In addition, quite small structural modifications of tanaproget-based PR ligands such as **4** can cause agonist/antagonist activity switching.^{16,21} Based on these considerations, we wished to develop PR antagonists bearing a novel nonsteroidal scaffold.

To develop novel nonsteroidal PR antagonists, we focused on a series of compounds that we had synthesized previously as candidate androgen receptor (AR) antagonists. AR is also a member of the family of steroid hormone nuclear receptors, and the AR ligand-binding domain (LBD) shows high homology with the PR LBD: there is 55% sequence identity and 87% sequence similarity between them.²² We have developed some novel nonsteroidal AR antagonists^{23–25} and recently reported the development of potent AR antagonists

Received: May 2, 2016

Accepted: September 15, 2016

Published: September 15, 2016

Figure 1. Structures of progesterone (1) and some synthetic PR ligands. In the structure of 6, closed circles indicate carbon atoms, and other vertices of the icosahedra are B–H.

bearing a benzanilide scaffold, such as 7.²⁶ Initially, we investigated the PR-antagonistic activity of these benzanilide derivatives and related sulfonamide derivatives by means of PR-dependent alkaline phosphatase activity assay using human breast cancer cell line T47D.²⁷ The benzanilide derivatives including 7 exhibited moderate PR-antagonistic activity. However, interestingly, sulfonamide derivatives exhibited more potent PR-antagonistic activity than did the corresponding benzanilide derivatives, and the sulfonamide derivatives 10 and 12 exhibited PR-antagonistic activity with submicromolar IC₅₀ values. These results suggested that the benzenesulfonanilide skeleton is a promising scaffold for nonsteroidal PR antagonists. Therefore, in this work we investigated the structure–activity relationship of PR antagonists bearing the benzenesulfonanilide scaffold (Figure 2).

Figure 2. Structure of our previously developed AR antagonist 7 and PR-antagonistic activity of benzanilide and benzenesulfonamide derivatives 7–12. ^aPR-antagonistic activity was evaluated in the presence of 1 nM P4.

The synthesis of sulfonamide derivatives is illustrated in Scheme 1. Diphenyl ether derivatives 10, 15–18, 19a–23a, and

Scheme 1. Synthesis of Sulfonamide Derivatives^a

^aReagents and conditions: (a) RSO₂Cl, THF, pyridine, rt, 80–87%; (b) R¹C₆H₄SO₂Cl, THF, pyridine, rt, 67–93%; (c) NaH, iodo-methane, DMF, rt, 71–88%; (d) NaH, *n*-Bu₄NI, benzyl bromide, DMF, rt, 64%–quant; (e) *p*-Y-C₆H₄NH₂, pyridine, THF, rt, 76–89%; (f) PhBpin, Pd(PPh₃)₄, Na₂CO₃, dioxane–H₂O, 110 °C, 30%.

24–32 were prepared from 4-phenoxyaniline 13 by reaction with corresponding sulfonyl chlorides. Compounds 12, 20b, and 22b bearing a methoxy group on the phenoxy moiety were similarly synthesized from 4-(3-methoxyphenoxy)aniline 14 as a starting material. Compounds bearing an *N*-methyl group 19c–23c or *N*-benzyl group 19d–23d were prepared by methylation or benzylation of the sulfonamide moiety of the corresponding benzenesulfonanilides 19a–23a. Compounds 34–41 without a diphenyl ether skeleton were prepared from sulfonyl chloride 33 and corresponding anilines, and biphenyl

42 was synthesized from bromide 41 by Suzuki–Miyaura cross coupling.

PR-agonistic and -antagonistic activities of synthesized sulfonamide derivatives were evaluated by means of alkaline phosphatase assay using T47D human breast carcinoma cell line.²⁷ None of the sulfonamide derivatives examined exhibited activity alone, i.e., they did not act as PR agonists. PR-antagonistic activity of the sulfonamide derivatives was examined in the presence of 1 nM progesterone, as shown in Table 1. As described above, compounds 10 and 12 exhibited

Table 1. PR-Antagonistic Activity of Sulfonanilide Derivatives

compd	R ¹	R ²	IC ₅₀ (μM) ^a
10	Ph	PhO	0.52 ± 0.028
12	Ph	3-MeO-PhO	0.49 ± 0.041
15	Me	PhO	2.2 ± 0.042
16	Bn	PhO	1.6 ± 0.12
17	1-naphthyl	PhO	0.19 ± 0.013
18	2-naphthyl	PhO	1.7 ± 0.36
19a	2-Cl-Ph	PhO	0.74 ± 0.057
20a	3-Cl-Ph	PhO	0.17 ± 0.038
20b	3-Cl-Ph	3-MeO-PhO	0.27 ± 0.033
21a	4-Cl-Ph	PhO	0.67 ± 0.020
22a	3-MeO-Ph	PhO	0.25 ± 0.017
22b	3-MeO-Ph	3-MeO-PhO	0.37 ± 0.030
23a	4-MeO-Ph	PhO	0.50 ± 0.17
34	3-Cl-Ph	H	1.5 ± 0.045
35	3-Cl-Ph	Me	1.3 ± 0.22
36	3-Cl-Ph	<i>i</i> -Pr	0.51 ± 0.011
37	3-Cl-Ph	Bn	0.45 ± 0.043
38	3-Cl-Ph	MeO	0.82 ± 0.047
39	3-Cl-Ph	BnO	0.81 ± 0.073
40	3-Cl-Ph	PhCO	6.0 ± 0.54
41	3-Cl-Ph	Br	1.3 ± 0.22
42	3-Cl-Ph	Ph	0.33 ± 0.022

^aExpression of alkaline phosphatase was induced with 1 nM progesterone.

PR-antagonistic activity with IC₅₀ values of ca. 0.5 μM. Methanesulfonamide 15 and benzyisulfonamide 16 exhibited potency significantly lower than that of 10, suggesting that the benzenesulfonyl moiety is important for the PR-antagonistic activity. Arylsulfonyl derivatives 17–23a bearing a diphenyl ether moiety exhibited significant activity, except for 2-naphthyl derivative 18. Substitution at the 3-position of the benzenesulfonyl moiety enhanced the antagonistic activity (20a, 22a), and compounds 20b and 22b with a 3-methoxy group as R² exhibited lower potency than parent compounds 20a and 22a. Among the arylsulfonyl derivatives, 3-chlorobenzenesulfonanilide 20a exhibited the most potent activity with an IC₅₀ value of 0.17 μM. Next, we investigated the importance of the phenoxyphenyl moiety based on the structure of 20a. Isopropyl, benzyl, and phenyl derivatives 36, 37, and 42 exhibited significant activity, whereas methoxy derivative 38 and benzyloxy derivative 39 exhibited moderate activity. Simple aniline and toluidine derivatives 34 and 35 exhibited low activity. By comparison with compound 20a, it is suggested that

N-(4-phenoxyphenyl)benzenesulfonamide structure is favorable for PR-antagonistic activity (Table 1).

Next we focused on the structure–activity relationship of the sulfonamide moiety. Table 2 shows the PR-antagonistic activity

Table 2. PR-Antagonistic Activity of *N*-Substituted Sulfonanilide Derivatives

compd	R ¹	R ²	IC ₅₀ (μM) ^a
19a	2-Cl	H	0.74 ± 0.057
19c		Me	0.39 ± 0.039
19d		Bn	2.2 ± 0.28
20a	3-Cl	H	0.17 ± 0.038
20c		Me	0.65 ± 0.029
20d		Bn	2.2 ± 0.12
21a	4-Cl	H	0.67 ± 0.020
21c		Me	0.96 ± 0.11
21d		Bn	3.0 ± 0.25
22a	3-OMe	H	0.25 ± 0.017
22c		Me	0.47 ± 0.027
22d		Bn	2.6 ± 0.35
23a	4-OMe	H	0.50 ± 0.17
23c		Me	0.99 ± 0.13
23d		Bn	3.5 ± 0.22

^aExpression of alkaline phosphatase was induced with 1 nM progesterone.

of *N*-H, *N*-methyl, and *N*-benzyl sulfonamide derivatives. Introduction of a methyl group at the nitrogen atom of sulfonamide resulted in modest loss of potency, except in the case of 2-chlorobenzenesulfonyl derivatives 19a and 19c. Introduction of a benzyl group caused significant loss of the activity. These results suggest that a bulky substituent is unsuitable for the activity, and the secondary sulfonamide appears to be the optimal substructure (Table 2).

Then we investigated optimization of the substituent at the benzenesulfonyl group, as shown in Table 3. Introduction of an

Table 3. PR-Antagonistic Activity of Benzenesulfonanilide Derivatives 20a and 24–32

compd	R ¹	IC ₅₀ (μM) ^a
20a	3-Cl	0.17 ± 0.038
24	2,3-Cl ₂	0.64 ± 0.72
25	3,4-Cl ₂	0.41 ± 0.015
26	3,5-Cl ₂	0.32 ± 0.052
27	2,4,5-Cl ₃	1.6 ± 0.051
28	3-F	0.22 ± 0.014
29	3-Br	0.11 ± 0.025
30	3-NO ₂	0.14 ± 0.035
31	3-CN	0.30 ± 0.018
32	3-CF ₃	0.033 ± 0.003

^aExpression of alkaline phosphatase was induced with 1 nM progesterone.

additional chlorine atom reduced the potency (24–27). 3-Fluoro (28), 3-bromo (29), and 3-nitro (30) derivatives exhibited potent activity, comparable to that of 3-chlorobenzenesulfonanilide 20a, whereas compound 31 bearing a cyanophenyl group, which is a common pharmacophore motif of developed nonsteroidal PR antagonists, exhibited slightly lower activity. Introduction of a trifluoromethyl group significantly enhanced the PR-antagonistic activity, and compound 32 exhibited the most potent activity among the examined compounds, with an IC_{50} value of 33 nM (Table 3).

We also examined the binding affinity of the selected compounds with PR. The binding affinities were evaluated using hPR LBD and ^3H -labeled P4 (Table 4). Compounds that

Table 4. Binding Affinities of Selected Compounds toward PR

compd	binding IC_{50} (μM) ^a
20a	0.062
28	0.31
29	0.047
30	0.14
32	0.040
40	>10
42	0.11

^aThe concentration of [^3H]progesterone was 4 nM.

exhibited potent antagonistic activity in T47D alkaline phosphatase assay also exhibited high binding affinity, whereas less potent compound 40 did not exhibit binding affinity to PR. Compound 32, the most potent compound in T47D assay, also exhibited the highest binding affinity among the tested compounds. This result suggests that the PR-antagonistic activity of these compounds in T47D alkaline phosphatase assay was indeed mediated by binding of the compounds with PR (Table 4).

In order to confirm the PR antagonistic activity of compound 32, we investigated the effect on the protein expression of PR-regulated genes. The $\beta 1$ subunit of Na/K-ATPase is one of PR-regulated genes,²⁸ and we examined the amount of Na/K-ATPase- $\beta 1$ subunit by Western blotting. Treatment of compound 32 as well as mifepristone decreased the P4-promoted protein expression of Na/K-ATPase- $\beta 1$ in T47D cell. These results confirmed that compound 32 inhibits expression of PR-regulated genes and functions as a PR antagonist (Figure S1 in Supporting Information).

Since the initial lead compounds 7 and the sulfonamide derivatives 10 and 12 were originally designed as AR antagonists, we examined the AR-antagonistic activity of the novel sulfonamide derivatives. AR-antagonistic activity was evaluated by means of cell growth inhibitory activity toward androgen-dependent SC-3 cell line.²⁹ Table 5 shows the results of SC-3 assays. The AR antagonist 7 potently inhibited dihydrotestosterone (DHT)-promoted SC-3 cell proliferation. However, sulfonanilide derivatives had almost no effect on SC-3 cell proliferation, indicating that these compounds have no antagonistic activity toward AR. This result suggested that the sulfonanilide derivatives have selectivity for PR over AR.

In order to investigate the selectivity profile of compound 32, we performed reporter gene assay using hAR, hGR α , hER α , and hER β . Compound 32 exhibited only modest antagonistic activities toward AR (IC_{50} = 5.3 μM), glucocorticoid receptor- α (GR α) (IC_{50} = 12 μM), estrogen receptor- α (ER α) (IC_{50} > 30

Table 5. Inhibitory Activity toward DHT-Promoted SC-3 Cell Proliferation

compd	inhibition at 1 μM (%) ^a
7	66 $\pm$ 2.1
20a	8.4 $\pm$ 23
29	N.D. ^b
30	N.D. ^b
32	N.D. ^b

^aCell proliferation was promoted by 1 nM DHT. ^bNo inhibition was observed.

μM), and ER β (IC_{50} = 23 μM) in the reporter gene assay (Table S1 in Supporting Information).

Thus, we found that *N*-(*p*-aryloxyphenyl)benzene-sulfonamides exhibit PR-antagonistic activity, while the *N*-(*p*-aryloxyphenyl)benzamides were selective AR antagonists. Generally, aromatic sulfonamides have a synclinal structure,^{30,31}

different from the planar *trans* conformation of aromatic secondary amides.³² The folded synclinal structure of the sulfonamide skeleton appears to fit well into the ligand-binding pocket of PR, but not into that of AR, while the latter can accommodate the planar *trans* structure of the secondary amide skeleton. Next, we conducted a docking simulation of the X-ray crystal structure of the hPR LBD complex with 2 (PDB ID: 2W8Y),³³ using AutoDock 4.2.³⁴ Figure 3 shows the docking

Figure 3. Docking model of trifluoromethylbenzenesulfonanilide 32 and hPR-LBD. The docking model of 32 (carbon in green) is superimposed on the hPR LBD bound to mifepristone (2: gray). The protein surface is indicated as a brown mesh.

model of the developed PR antagonist 32 in the PR LBD. In the docked structure, compound 32 occupies the ligand-binding pocket, adopting the synclinal conformation of the sulfonamide moiety, and the benzenesulfonyl group occupies the space that would be occupied by the dimethylaminophenyl group of 2. Thus, the dimethylaminophenyl group of 2 functions as a pharmacophore for inhibiting active folding of PR. In addition, in the calculated structure, the 3-trifluoromethyl group of 32 is located at the hydrophobic cavity adjacent to H12 of PR. The docking simulation suggests that the developed sulfonanilides could act as PR antagonists by inhibiting formation of the active conformation of PR (Figure 3).

In summary, we set out to develop nonsteroidal PR antagonists bearing a novel pharmacophore by focusing on the similarity of the PR and AR LBD structures. We found that

benzenesulfonamide derivatives exhibit PR antagonistic activity, and structure–activity relationship studies revealed that the *N*-(4-phenoxyphenyl)benzenesulfonamide structure is a promising scaffold for PR antagonists. Structural development afforded the potent nonsteroidal PR antagonist **32**. Development of novel class of PR antagonists should open up new possibilities for exploitation of the pharmaceutical potential of PR modulation. Compound **32** developed in this study is a potent nonsteroidal PR antagonist with a structure–activity relationship distinct from those of other nonsteroidal PR antagonists and should expand the pharmaceutical potential of PR modulation and development of novel PR modulators.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmchemlett.6b00184.

Experimental procedures and analytical data of compounds (PDF)

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Author Contributions

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

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partly supported by JSPS KAKENHI Grant Nos. 25460146 (to S.F.), 22136013 (to H.K.), and 24590137 (to A.T.), JSPS Core-to-Core Program, A. Advanced Research Networks, and Platform Project for Supporting in Drug Discovery and Life Science Research (Platform for Drug Discovery, Informatics, and Structural Life Science) from Japan Agency for Medical Research and Development (AMED). A.T. thanks The Naito Foundation for financial support. We thank Dr. Minoru Ishikawa (The University of Tokyo) for helpful discussions.

■ ABBREVIATIONS

AR, androgen receptor; DHT, dihydrotestosterone; LBD, ligand-binding domain; PR, progesterone receptor; GR, glucocorticoid receptor; ER, estrogen receptor

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