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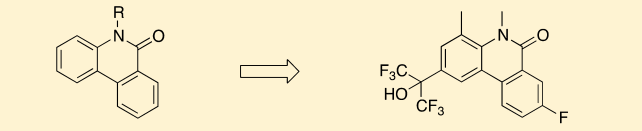
Novel Nonsteroidal Progesterone Receptor (PR) Antagonists with a Phenanthridinone Skeleton

Yuko Nishiyama,[†] Shuichi Mori,[‡] Makoto Makishima,[§] Shinya Fujii,[†] Hiroyuki Kagechika,[‡] Yuichi Hashimoto,[†] and Minoru Ishikawa*[,†]

[†]Institute of Molecular and Cellular Biosciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan
[‡]Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan
[§]Nihon University School of Medicine, 30-1 Oyaguchi-kamicho, Itabashi-ku, Tokyo 173-8610, Japan

Supporting Information

ABSTRACT: The progesterone receptor (PR) plays an important role in various physiological systems, including female reproduction and the central nervous system, and PR antagonists are thought to be effective not only as contraceptive agents and abortifacients but also in the treatment of various diseases, including hormone-dependent cancers and endometriosis. Here, we identified phenanthridin-6(5*H*)-one derivatives as a new class of PR antagonists and investigated their structure−activity relationships. Among the synthesized compounds, **37**, **40**, and **46** exhibited very potent PR antagonistic activity with high selectivity for PR over other nuclear receptors. These compounds are structurally distinct from other nonsteroidal PR antagonists, including cyanoaryl derivatives, and should be useful for further studies of the clinical utility of PR antagonists.



phenanthridinone scaffold steroid surrogate

progesterone receptor antagonist potent and new chemical class

KEYWORDS: *Progesterone receptor, antagonist, nonsteroid, phenanthridinone*

Progesterone receptor (PR) is a member of the nuclear receptor superfamily of ligand-dependent transcription factors[1] and is expressed in female tissues including uterus, ovary, vagina, fallopian tubes and breast, and brain. It plays an important role in female reproduction, being associated with the establishment and maintenance of pregnancy and with alveolar development in the breast. Recently, there is increasing evidence suggesting that PR has a role in the central nervous system.[2,3] PR agonists, including the endogenous agonist progesterone (**1**, Figure 1), have been used extensively to treat gynecological disorders, as well as in female contraception and hormone replacement therapy. However, their steroidal skeleton brings with it the potential to cross-react with other steroid receptors, which can result in unwanted side effects, potentially limiting the benefits of these agents. To overcome these issues, nonsteroidal PR agonists such as tanaproget (**2**) have been developed[4]

PR antagonists may be potentially useful for the treatment of various diseases including hormone-dependent cancers,[5] uterine fibroids,[6] endometriosis,[7] and abortifacient. However, the steroidal PR antagonist mifepristone (**3**) is in only limited clinical use as an abortifacient at present. It is known that **3** demonstrates potent activities against other steroid receptors such as glucocorticoid receptor (GR). Therefore, development of selective nonsteroidal PR antagonists is necessary for the estimation of their clinical utility. Indeed, various nonsteroidal PR antagonists, including **4**,[8] **5**,[9] and **6**,[6] have been synthesized based on the structure of **2**, with the aim of improving the selectivity for PR over other steroid receptors. Some of the present authors also developed **7**−**9**.[10−13] PR antagonists containing a cyanoaryl moiety, a common pharmacophore motif, found that quite small structural modifications cause agonist/antagonist activity switching.[10,8,9] A concern about such activity switching is that metabolites of an antagonist act as agonists. Although we recently reported nonsteroidal PR antagonist **10**, which does not have a cyanoaryl moiety,[14] there is still a need for a new, more robust pharmacophore motif of PR antagonists to avoid such activity switching.

Here, to obtain nonsteroidal PR antagonists without a cyanoaryl moiety, we focused on our previously developed liver X receptor (LXR) and retinoic acid receptor-related orphan receptor (ROR) ligands **12** and **13**, which contain a phenanthridin-6(5*H*)-one skeleton as a cyclized carba-analog of T0901317 (**11**) (Figure S1).[15,16] Because hydroxycholesterols are endogenous ligands for both LXR and ROR, we hypothesized that if the phenanthridin-6(5*H*)-one scaffold acts as a steroid surrogate, phenanthridinone derivatives would also bind to other nuclear receptors that recognize endogenous steroidal ligands. Based on this idea, we successfully identified phenanthridinone derivatives with PR-antagonistic activity and examined their structure−activity relationships (SAR) and selectivity.

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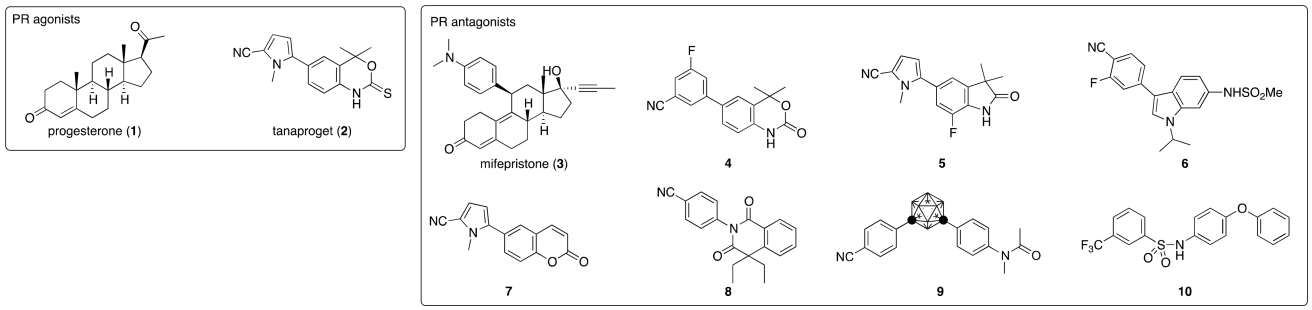


Figure 1. Chemical structures of PR agonists **1**−**2** and antagonists **3**−**10**.

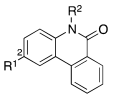
Compounds **12**−**24** were prepared as described in refs 15 and 16. PR-antagonistic activity was evaluated by assay of PR-regulated alkaline phosphatase activity in human breast cancer cell line T47D.[17] Under our assay conditions, mifepristone (**3**) showed subnanomolar IC_{50} value with a reproducibility (Table 1). We found that compound **14**, a phenanthridin-6(5*H*)-one bearing an *n*-butyl group on the nitrogen atom, showed PR-antagonistic activity with the IC_{50} value of 7.1 μM. Although the activity was not potent, we considered it promising, as this compound belongs to a different chemical class from other known PR antagonists. Thus, we focused on **14** as a lead compound and investigated the SAR of analogs we had previously synthesized.[16] First, we examined SARs at the 2-position (Table 1). Introduction of alkyl groups (**15**−**17**) or a hydroxymethyl group (**18**) retained the PR-antagonistic activity. On the other hand, compound **19** bearing a hexafluoropropanol moiety showed the strongest activity, suggesting that trifluoromethyl groups at this position are favorable for potent activity.

Next, we evaluated substituent effects on the nitrogen atom. Hydrogen analog **12** and methyl analog **20** increased PR-antagonistic activity, affording submicromolar IC_{50} (Table 1). Introduction of a longer alkyl group (**22**−**24**) resulted in a decrease of antagonistic activity. Thus, we concluded that hydrogen or a methyl group is a suitable substituent on the nitrogen atom.

Next, the effect of introduction of a methoxy group at every position (methoxy scanning) was investigated (**25**−**31**; Table 2) because many types of nuclear receptor ligands possess a methoxy group(s).[18] 3-Methoxy and 4-methoxy analogs **26** and **27** showed more than 3-fold and 2-fold enhanced activity compared with the unsubstituted analog **19**, respectively. In contrast, 9-methoxy analog **30** showed 5-fold weaker activity. We believe that introduction of a substituent into every position is favorable in order to investigate substituent effects. It is important to note that phenanthridin-6(5*H*)-one analogs bearing substituent(s) at any position can be quite easily synthesized, and this represents a considerable advantage compared to the steroid skeleton. Based on the SARs shown in Tables 1−3, we proceeded to synthesize new compounds, aiming to obtain more potent antagonists.

At this stage, the substituent on the nitrogen atom was fixed to hydrogen, and we focused on fluoro derivatives to

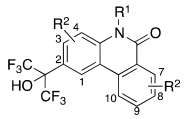
Table 1. SAR at the 2-Position and the Nitrogen Atom[a]



compounds	R^1	R^2	PR IC_{50} (nM)
Mifepristone (**3**)			0.073 ± 0.0047 (*N* = 19)
7			123
9			95.3
10			107
14	H	*n*-Bu	7100
15	Me	*n*-Bu	7900
16	Et	*n*-Bu	7800
17	*t*-Bu	*n*-Bu	8300
18	CH_2OH	*n*-Bu	8600
19	$(CF_3)_2COH$	*n*-Bu	1200
12	$(CF_3)_2COH$	H	780
20	$(CF_3)_2COH$	Me	340
21	$(CF_3)_2COH$	Et	1400
22	$(CF_3)_2COH$	*n*-Pr	3800
23	$(CF_3)_2COH$	*n*-Hex	2500
24	$(CF_3)_2COH$	*n*-C_9H_{19}	10000

[a]Alkaline phosphatase assay. Mean IC_{50} values with standard error of mean (SEM) from 1 or *N* times independent experiments.

Table 2. SAR at the 4-Position and Other Substitution Effects[a]



compounds	R^1	R^2	PR IC_{50} (nM)
25	*n*-Bu	1-MeO	4000
26	*n*-Bu	3-MeO	410
27	*n*-Bu	4-MeO	560
28	*n*-Bu	7-MeO	12000
29	*n*-Bu	8-MeO	1100
30	*n*-Bu	9-MeO	5800
31	*n*-Bu	10-MeO	2700
32	H	4-F	130
33	H	7-F	730
34	H	8-F	310
35	H	9-F	1000
36	H	4-MeO	270 ± 20 (*N* = 2)
37	H	4-Me	150 ± 17 (*N* = 5)
38	H	4-Et	210 ± 3.7 (*N* = 2)
39	H	4-*n*-Pr	360 ± 15 (*N* = 2)
40	H	4-Me, 8-F	46 ± 4.4 (*N* = 4)
45	Me	4-Me	180 ± 8.9 (*N* = 3)
46	Me	4-Me, 8-F	27 ± 16 (*N* = 2)

[a]Alkaline phosphatase assay. Mean IC_{50} values with standard error of mean (SEM) from 1 or *N* times independent experiments.

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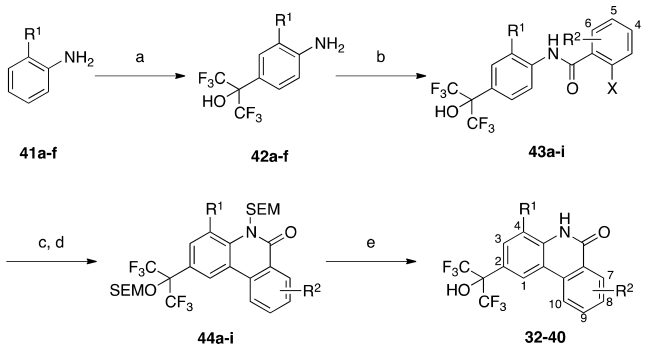
Table 3. Binding Affinity of Representative PR Antagonists[a]

compounds	PR IC_{50} (nM)
Mifepristone	5.2 ± 0.53
37	1500 ± 540
40	340 ± 150
46	150 ± 110

[a]4 nM [1,2,6,7-^{3}H]progesterone was used.

investigate the effect of the electron withdrawing substituent. Synthesis of the novel analogs **32**−**40** is illustrated in Scheme 1. Briefly, *ortho*-substituted anilines **41** were treated with

Scheme 1. Synthesis of the Novel Analogs 32−**40**[a]



[a]Reagents and conditions: (a) $CF_3COCF_3 \cdot 1.5H_2O$, *p*-TsOH·H_2O, toluene, reflux, 8−49%; (b) 2-iodobenzoic acids or 2-bromobenzoic acids, EDC, DMAP, DMF, 100 °C, 19−91%; (c) SEMCl, NaH, DMF, 0 °C to rt; (d) $Pd(OAc)_2$, $PCy_3 \cdot HBF_4$, Cs_2CO_3, DMA, 130 °C, 9−44% in 2 steps; (e) TBAF, THF, reflux, 30−80%.

hexafluoroacetone trihydrate to give 1,1,1,3,3,3-hexafluoro-2-hydroxypropyl derivatives **42**. Anilines **42** were condensed with *o*-bromo-/iodobenzoic acids to give amides **43**. After protection of the amide and hydroxyl group with SEM, palladium-catalyzed intramolecular cyclization afforded **44**. Compounds **32**−**40** were obtained by deprotection of the SEM groups. The 4-fluoro analog **32** and 8-fluoro analog **34** were 6-fold and 3-fold more potent than the unsubstituted analog **12**, respectively (Table 2). These preferences of fluorine-substitution position are roughly consistent with the results of the methoxy scanning, that is, 4- and 8-substituted analogs showed enhanced activity whereas 9-substituted analogs showed weaker activity.

We next focused on the 4-position because 4-fluoro analog **32** showed the most potent activity among the methoxy- and fluorine-substituted compounds, and 4-substituted analogs are easier to synthesize than 3-substituted analogs; in the course of synthesis of the 3-substitued analog, the 1-substitued analog is also obtained. 4-Methoxy analog **36** was more potent than the unsubstituted analog **12**, in accordance with the results for the *n*-butyl analog **19** and **27** (Table 1). 4-Alkyl analogs **37**−**39** showed greater activity than the unsubstituted analog **12**. In particular, 4-methyl analog **37** had around 0.1 μM IC_{50} value (Table 2).

Next, we planned to introduce a fluorine atom at the 8-position of **37**, because the 8-fluoro analog **34** showed enhanced antagonistic activity. Indeed, the 4-methyl and 8-fluoro-substituted analog **40** showed even more potent activity than **37**. Finally, based on the SARs shown in Table 2, we investigated *N*-methyl analogs **45**−**46** (Scheme S1). The antagonistic activity of 4-methyl analog **45** was stronger than that of unsubstituted **20** as expected but weaker than that of N−H analog **37**. On the other hand, the N,4-dimethyl and 8-fluoro analog **46** showed very potent antagonistic activity (Table 2), being more potent than the cyanoaryl,[10−13] and noncyanoaryl[14] chemical classes of nonsteroidal PR antagonists in alkaline phosphatase assay (Table S1). In addition, these representative compounds did not show PR agonistic activity at 10 μM. This result suggests that the phenanthridinone skeleton might be a more robust pharmacophore motif of PR antagonists to avoid such activity switching. Therefore, we selected **37**, **40**, and **46** as representative compounds and investigated their biological activities in more detail.

The alkaline phosphatase inhibitory activity assay utilized for SAR analyses may be affected not only by inhibition of PR-mediated transcription (antagonistic activity) but also by direct inhibition of the enzymatic activity. Therefore, to validate the PR-antagonistic activity of representative compounds, we measured the expression of another PR-regulated protein, the β1 subunit of Na/K-ATPase,[19] in T47D cells by means of Western blotting. Potent PR antagonists **37**, **40**, and **46** decreased progesterone-induced β1-Na/K ATPase expression, whereas the weak antagonist **24** had little effect on the β1-Na/K ATPase level at the evaluated concentration (Figure 2). The

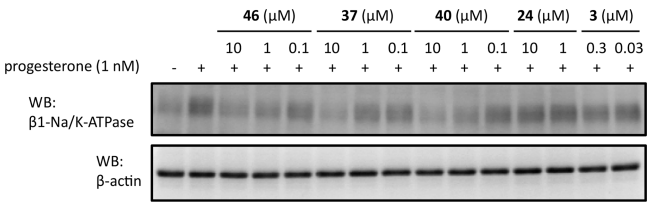


Figure 2. Western blot analysis of β1-Na/K-ATPase in T47D cells in the presence of test compounds.

activity of 1 μM **40** and **46** was equal to or greater than 0.3 μM mifepristone, indicating that these nonsteroidal antagonists are very potent, at least under these assay conditions.

We next investigated whether the representative compounds bind directly to PR, using human PR ligand-binding domain (LBD) and ^{3}H-labeled progesterone (**1**) (Table 3). Compounds **37**, **40**, and **46** all exhibited strong binding affinity. These results, together with the results of alkaline phosphatase assay, Western blotting of β1-Na/K ATPase, and PR binding assay, indicate that compounds **37**, **40**, and **46** bind directly to the progesterone-binding pocket of PR and inhibit expression of PR-regulated genes; thus, they function as PR antagonists.

Some of the analogs shown in Tables 1 and 2 were identified as RORs inverse agonists or LXRs antagonists. And PR, GR, and androgen receptor (AR) all belong to the class I steroid receptor family. Thus, selectivity of PR antagonists toward AR and GR is an important concern, and selectivity of PR antagonists over AR and GR has been investigated[8] (**3**: PR IC_{50}: 0.3 nM, AR IC_{50}: 5 nM, GR IC_{50}: 0.8 nM; **4**: PR IC_{50}: 16 nM, AR IC_{50}: 1300 nM, GR IC_{50}: 1800 nM). Here, the activities of the representative PR antagonists toward other nuclear receptors, including RORα/β/γ inverse agonistic activities, and LXRα/β, GR and AR antagonistic activities, were evaluated by means of reporter gene assays.[20] Among these compounds, **37** showed more than 100-fold selectivity for PR over all the NRs evaluated (Table 4). Compounds **40** and **46** also showed more than 300-fold selectivity over these

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Table 4. Selectivity of Representative Compounds for PR over other NRs

compounds	PR[a,b]	RORα[a,c]	RORβ[a,c]	RORγ[a,c]	LXRα[a,c]	LXRβ[a,c]	AR[a,c]	GRα[a,c]
37	0.15	NA[d]	>20	>20	>20	>20	>20	>20
40	0.046	NA[d]	>20	NA[d]	>20	NA[d]	1.8	>20
46	0.027	NA[d]	>20	NA[d]	>20	>20	0.3	>20

[a]IC_{50} (μM). [b]Alkaline phosphatase assay. [c]Reporter gene assay. [d]No activity at 20 μM. T0901317 (0.3 μM), T0901317 (0.1 μM), dihydrotestosterone (0.3 nM), and dexamethasone (1 nM) were used as agonists for LXRα, LXRβ, AR, and GR, respectively.

NRs except for AR. For AR, **40** and **46** showed over 30- and 10-fold selectivity, respectively. Compounds **37** demonstrated medium Caco-2 permeability, sufficient human liver microsomal stability, and acceptable Log*P* value (Table S2).

In summary, we have identified a series of PR antagonists with a phenanthridin-6(5*H*)-one skeleton and investigated their SARs by means of alkaline phosphatase assay using T47D cells. Among them, **37** exhibited potent PR-antagonistic activity with the IC_{50} value of around 0.1 μM and showed more than 100-fold selectivity over other NRs examined. Compounds **46** and **40** showed very potent PR-antagonistic activity, with IC_{50} values of 0.01 μM order. These compounds showed over 100-fold selectivity for PR over RORs, LXRs, and GR and about more than 10-fold selectivity over AR. The PR-antagonistic activity of these representative compounds was validated by means of Western blot analysis of a PR-regulated protein (β1-Na/K-ATPase) and PR-binding assay. Compounds **37**, **40**, and **46** are PR antagonists belonging to a novel chemical class distinct from other PR antagonists, and their activity is similar to or stronger than those of reported PR antagonists, including cyanoaryl compounds. The phenanthridinone skeleton might be a more robust pharmacophore motif of PR antagonists to avoid activity switching. Thus, these compounds should open up new possibilities for exploitation of the pharmaceutical potential of PR antagonists.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.8b00058.

Structures of phenanthridinones and their lead compound, synthesis of **45** and **46**, tables of PR antagonistic activity and physicochemical and pharmaceutical potential of PR antagonists, experimental section, and purity of the synthesized compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: m-ishikawa@iam.u-tokyo.ac.jp.

ORCID

Makoto Makishima: 0000-0002-4630-905X
Hiroyuki Kagechika: 0000-0002-6747-1013
Minoru Ishikawa: 0000-0002-3937-2261

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

PR, progesterone receptor; GR, glucocorticoid receptor; AR, androgen receptor; LXR, liver X receptor; ROR, retinoic acid receptor-related orphan receptor; Ts, *p*-toluenesulfonyl; EDC, *N*-ethyl-*N*′-(3-(dimethylamino)propyl)carbodiimide; DMAP, 4-(*N*,*N*-dimethylamino)pyridine; DMF, dimethylformamide; SEM, 2-(trimethylsilyl)ethoxymethyl; Cy, cyclohexyl; DMA, dimethylacetamide; TBAF, tetrabutylammonium fluoride; THF, tetrahydrofuran.

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