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Letter

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Development of *N*-(4-phenoxyphenyl)benzenesulfonamide derivatives as novel nonsteroidal progesterone receptor antagonists

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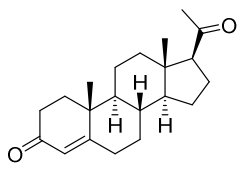
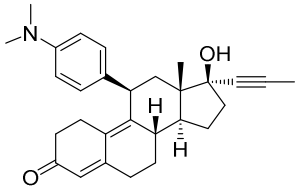
KEYWORDS: Progesterone, Nuclear receptor, Antagonist, N-(4-Phenoxyphenyl)benzenesulfonamide,

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.

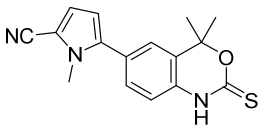
Progesterone receptor (PR) is a member of the nuclear receptor superfamily of ligand-dependent transcriptional factors.[1] It is regulated by its endogenous agonist progesterone (P4, **1**), and plays key roles in multiple physiological systems, including the female reproductive system, in which it influences 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] On the other hand, 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.



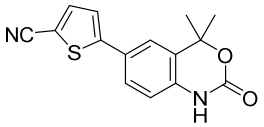
Progesterone (P4: **1**)



Mifepristone (RU486: **2**)



Tanaproget (**3**)



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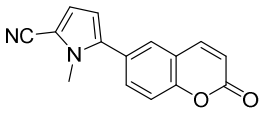

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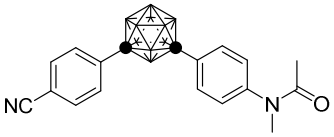
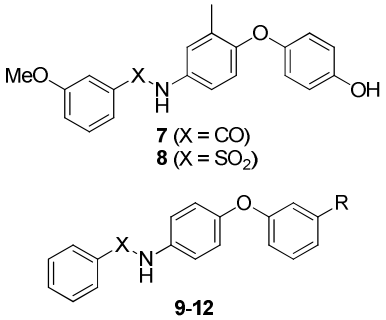


6

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

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 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. On the other hand, 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 IC_{50} 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).

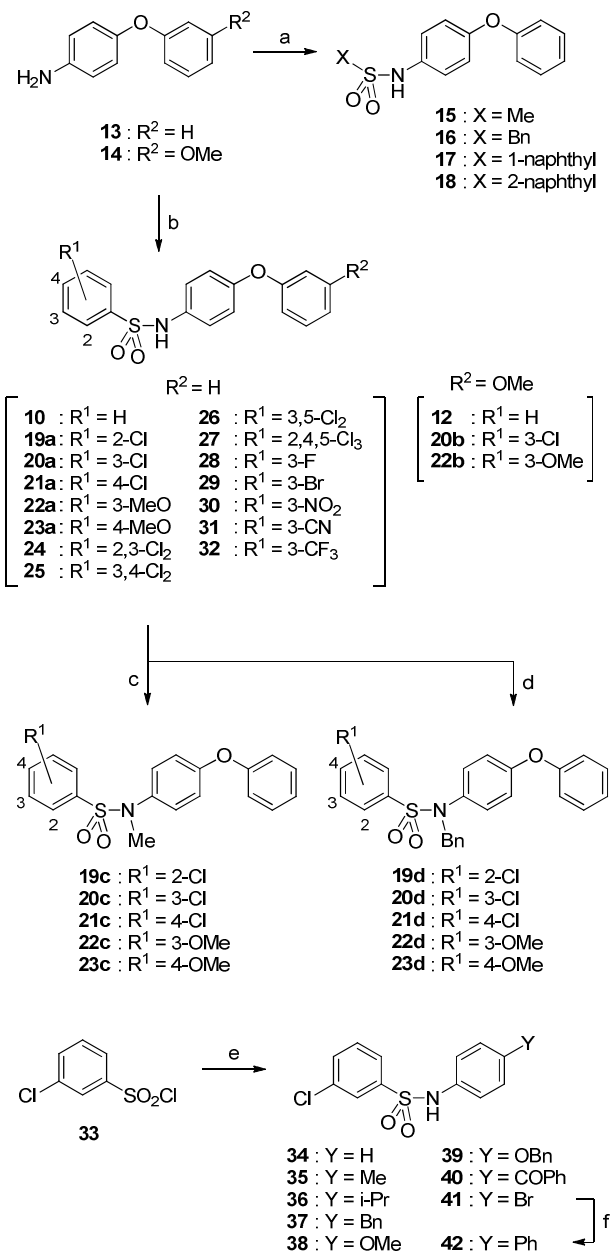


compound	X	R	PR IC_{50} [μM] (T-47D)[a]
7	CO	-	5.0
8	SO_2	-	2.0
9	CO	H	2.8
10	SO_2	H	0.52
11	CO	OMe	3.8
12	SO_2	OMe	0.48

Figure 2. Structure of our previously developed AR antagonist **7** and PR-antagonistic activity of benzanilide and benzenesulfonamide derivatives **7-12**. [a] PR-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 **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.

Scheme 1. Synthesis of sulfonamide derivatives[a]

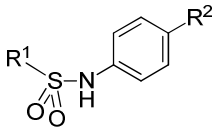


[a]Reagents and conditions: (a) RSO_2Cl, THF, pyridine, rt, 80-87%; (b) $R^1C_6H_4SO_2Cl$, THF, pyridine, rt, 67-93%; (c) NaH, iodomethane, DMF, rt, 71-88%; (d) NaH, *n*-Bu_4NI, benzyl bromide, DMF, rt, 64%-quant; (e) *p*-Y-$C_6H_4NH_2$, pyridine, THF, rt, 76-89%; (f) PhBpin, $Pd(PPh_3)_4$, Na_2CO_3, dioxane-H_2O, 110°C, 30%.

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 exhibit-

ed 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 PR-antagonistic activity with IC_{50} values of ca. 0.5 μM. Methanesulfonamide **15** and benzylsulfonamide **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 R^2 exhibited lower potency than parent compounds **20a** and **22a**. Among the arylsulfonyl derivatives, 3-chlorobenzenesulfonanilide **20a** exhibited the most potent activity with an IC_{50} 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).

Table 1. PR-antagonistic activity of sulfonanilide derivatives.

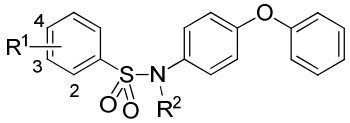


compound	R^1	R^2	IC_{50} (μM)[a]
10	Ph	PhO	0.52 ± 0.028
12	Ph	3-MeO−PhO	0.49 ± 0.041
15	Me	PhO	2.2 ± 0.042
16	Bn	PhO	1.6 ± 0.12
17	1-naphthyl	PhO	0.19 ± 0.013
18	2-naphthyl	PhO	1.7 ± 0.36
19a	2-Cl−Ph	PhO	0.74 ± 0.057
20a	3-Cl−Ph	PhO	0.17 ± 0.038
20b	3-Cl−Ph	3-MeO−PhO	0.27 ± 0.033
21a	4-Cl−Ph	PhO	0.67 ± 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*-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

[a] Expression of alkaline phosphatase was induced with 1 nM progesterone.

Next we focused on the structure-activity relationship of the sulfonamide moiety. Table 2 shows the PR-antagonistic activity 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 **19b**. 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).

Table 2. PR-antagonistic activity of *N*-substituted sulfonanilide derivatives.



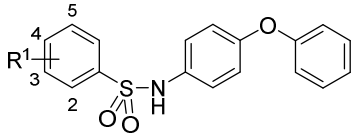
compound	R^1	R^2	IC_{50} (μM)[a]
19a	2-Cl	H	0.74 ± 0.057
19c		Me	0.39 ± 0.039
19d		Bn	2.2 ± 0.28
20a	3-Cl	H	0.17 ± 0.038
20c		Me	0.65 ± 0.029
20d		Bn	2.2 ± 0.12
21a	4-Cl	H	0.67 ± 0.020
21c		Me	0.96 ± 0.11
21d		Bn	3.0 ± 0.25
22a	3-OMe	H	0.25 ± 0.017
22c		Me	0.47 ± 0.027
22d		Bn	2.6 ± 0.35
23a	4-OMe	H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

[a] Expression of alkaline phosphatase was induced with 1 nM progesterone.

Then we investigated optimization of the substituent at the benzenesulfonyl group, as shown in Table 3. Introduction of an 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 ^{3}H-labelled P4 (Table 4). Compounds that 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).

Table 3. PR-antagonistic activity of benzenesulfonanilide derivatives 20a and 24-32.



compound	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

[a] Expression of alkaline phosphatase was induced with 1 nM progesterone.

Table 4. Binding affinities of selected compounds toward PR.

compound	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

[a] The concentration of [^{3}H]progesterone was 4 nM.

In order to confirm the PR antagonistic activity of compound **32**, we investigated the effect on the protein expression of PR-regulated genes. The β1 subunit of Na/K-ATPase is one of PR-regulated genes,[28] and we examined the amount of Na/K-ATPase-β1 subunit by western blotting. Treatment of compound **32** as well as mifepristone decreased the P4-promoted protein expression of Na/K-ATPase-β1 in T47D cell. These results confirmed that compound **32** inhibits expression of PR-regulated genes and functions as a PR antagonists (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. On the other hand, 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.

Table 5. Inhibitory activity toward DHT-promoted SC-3 cell proliferation.

compound	Inhibition at 1 μM (%)[a]
7	66 ± 2.1
20a	8.4 ± 23
29	N.D.[b]
30	N.D.[b]
32	N.D.[b]

[a] Cell proliferation was promoted by 1 nM DHT. [b] No inhibition was observed.

In order to investigate the selectivity profile of compound **32**, we performed reporter gene assay using hAR, hGRα, hERα and hERβ. Compound **32** exhibited only modest antagonistic activities toward AR (IC_{50} = 5.3 μM), glucocorticoid receptor-α (GRα) (IC_{50} = 12 μM), estrogen receptor-α (ERα) (IC_{50} > 30 μM), and ERβ (IC_{50} = 23 μM) in the reporter gene assay. (Table S1 in Supporting Information).

Thus, we found that *N*-(*p*-aryloxyphenyl)benzenesulfonamides 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 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.

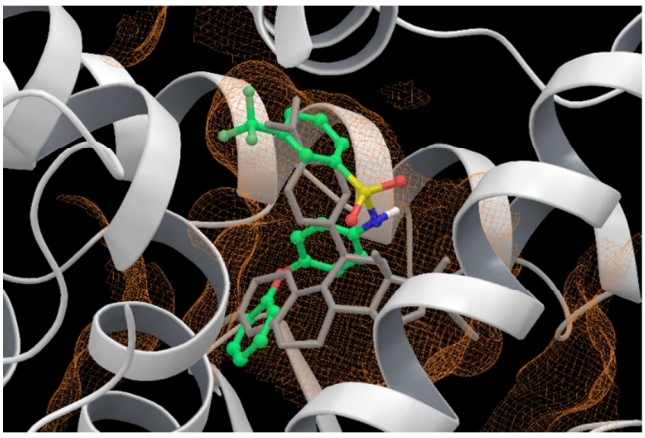


Figure 3. Docking model of trifluoromethylbenzenesulfonanilide **32** and hPR-LBD. The docking model of **32** (carbon in green) is superimposed on the hPR LBD bound to mifepristone (**2**: gray). The protein surface is indicated as a brown mesh.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
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.

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ABBREVIATIONS

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

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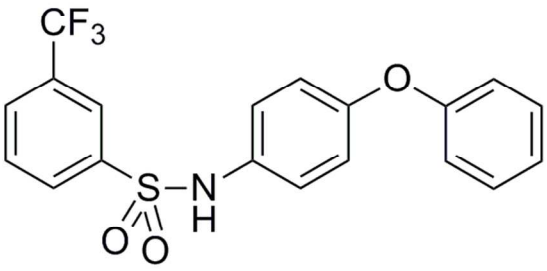
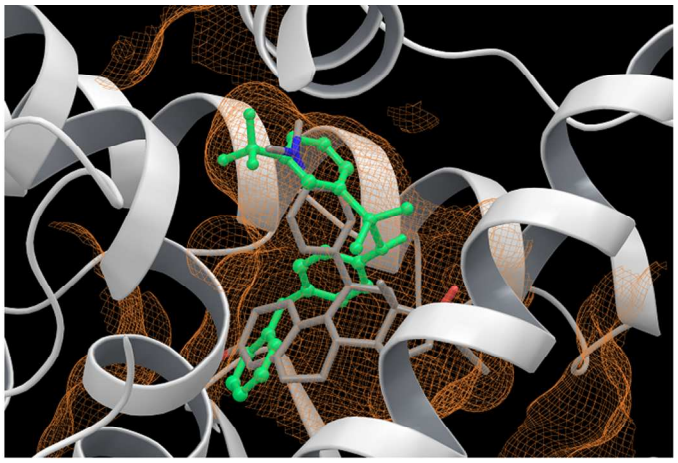


32

PR: IC_{50} = 0.033 μM (T47D)
AR: inactive (SC-3)



green ; compound **32**
gray ; mifepristone