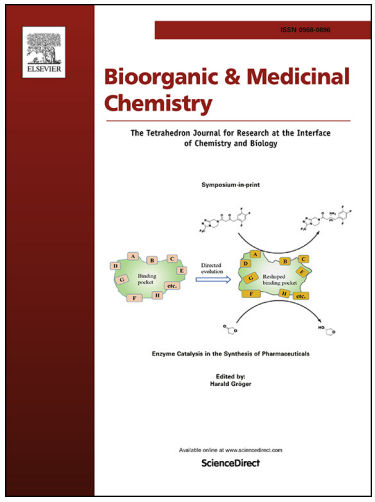

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Development of novel silanol-based human pregnane X receptor (PXR) agonists with improved receptor selectivity

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Keywords: Pregnane X receptor; Nuclear receptor; Silanol; Sila-substitution; C/Si-Exchange; Alcohol/silanol-exchange; T0901317

Abstract

Pregnane X receptor (PXR) is a ligand-dependent transcription factor that is considered to be a potential therapeutic target for multiple diseases. Herein, we report the development and structure-activity relationship studies of a new series of hPXR agonists. Focusing on our recently developed silanol-sulfonamide scaffold, we developed the potent hPXR agonist **28**, which shows good selectivity over hLXRα and β, hFXR, and hRORα and γ. Examination of the structure-activity relationship suggested a possible strategy to manipulate the selectivity. Docking simulation indicated the presence of an additional binding cavity and polar contacts in the ligand-binding pocket of hPXR. This information should be helpful for the future development of more potent and selective hPXR ligands.

1. Introduction

Nuclear receptors (NRs) are ligand-dependent transcription factors that regulate the expression of their target genes.[1,2] They play roles in many essential physiological systems, including the decision of cell fate, and thus are attractive targets for drug discovery. For example, retinoic acid receptors (RARs),[3,4] steroid hormone receptors such as estrogen receptors (ERs),[5,6] and androgen receptor (AR)[7–9] are promising therapeutic targets for multiple diseases, including cancer, and a number of drugs have entered clinical use. In addition to these classical NRs, liver X receptor (LXR) α and β, which are sensors of oxysterols, may be therapeutic targets for metabolic syndrome, including atherosclerosis and diabetes.[9–11] Farnesoid X receptor (FXR) functions as sensor of bile acids in the intestine and liver, and is also a potential target for metabolic syndrome.[12] Further, various ligands of retinoic acid receptor-related orphan receptor γ (RORγ) have been developed for treatment of inflammatory diseases.[13,14] Thus, development of modulators of so-called orphan NRs is considered a promising approach for drug discovery.

Human pregnane X receptor (hPXR), also known as SXR (steroid and xenobiotic receptor) and PAR

(pregnane activated receptor), is a nuclear receptor identified in 1998 as a human orthologue of murine PXR.[15-17] hPXR is involved in physiological processes such as absorption, distribution, metabolism and elimination of xenobiotics and endobiotics. It is expressed in kidney and intestine, and representative target genes of hPXR include drug-metabolizing enzyme *CYP3A4* (cytochrome P450) and multidrug resistance transporter *MDR1*.[18,19] hPXR also plays important roles in bone homeostasis[20] and inflammation.[21] Therefore, modulation of hPXR could have potential therapeutic applications. Various hPXR ligands, including natural hormones, vitamins and therapeutic agents, are known. The antibiotic rifampicin (**1**) is a representative hPXR agonist, and steroid hormones and lipophilic vitamins such as progesterone (**2**) and menaquinone-4 (vitamin K_2: **3**) are natural PXR agonists.[20,22] The antifungal agent ketoconazole (**4**) is a hPXR antagonist.[23] However, most of these compounds have other primary targets, and hPXR is an off-target. Also, though a few structure-activity relationship (SAR) studies have been reported,[24] the SAR of hPXR ligands is largely obscure at present. Thus, investigation of the SAR of hPXR ligands and development of more potent and selective hPXR ligands would be helpful to clarify the therapeutic potential of hPXR.

Recently, we developed **6** (sila-T) as a silanol analog (sila-substitution) of the multi-target nuclear receptor modulator T0901317 (**5**).[25] Benzenesulfonamide derivative **5** was originally developed as an agonist for hLXRα and hLXRβ,[26] but subsequent studies revealed that **5** exhibits agonistic activity toward multiple nuclear receptors including hFXR and hPXR, as well as hLXRs,[27,28] and is also an inverse agonist of hRORs.[29] In the field of medicinal chemistry, several series of silanol derivatives, including silanediols, have been developed.[30] We previously examined the similarities and differences among silanols, alcohols and perfluoroalcohols from the viewpoint of physicochemical properties. We found that conversion of the perfluoroalcohol functionality of **5** into a silanol group altered the selectivity profile, and silanol **6** exhibited agonistic activity toward hPXR, partial agonistic activity toward hFXR, inverse agonistic activity toward hRORs, and no activity toward hLXRs. Based on these findings, we aimed to develop novel PXR-selective agonists using silanol **6** as a lead compound.

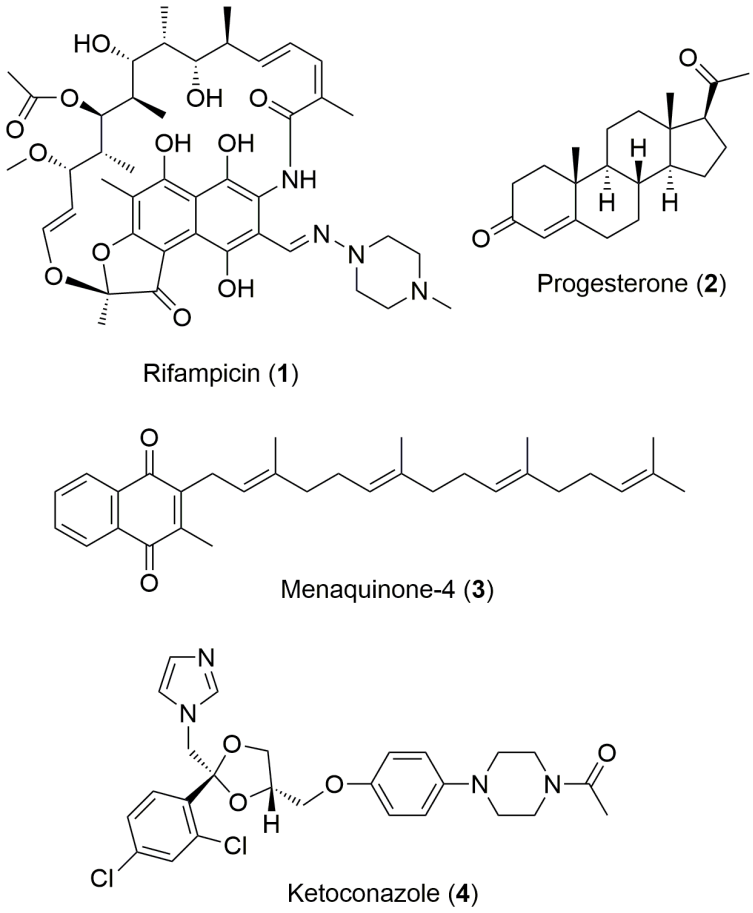


Fig.1. Examples of reported natural and synthesized PXR ligands.

2. Results and discussion

2.1. Molecular design

Our previous results indicated that the silanol moiety, which was introduced as an alternative to the perfluoroalcohol moiety of **5**, functions as the polar pharmacophore of hPXR, hFXR and hRORs ligands. On the other hand, carbinol derivative **7** exhibited no significant activity toward any of these receptors. We hypothesized that the relatively high acidity of the silanol moiety in comparison to carbinol is important for the activities. Therefore, we initially set out to investigate the utility of the acidic carboxy group as a polar functionality for PXR agonists. Then, we planned structural development of the silanol derivatives to improve the PXR selectivity, with the aid of the reported X-ray co-crystal structures of hPXR, hFXR, and hRORγ. It is suggested that the hPXR cavity is larger than those of hFXR and hRORs.[31] The X-ray structure of hPXR bound to **5** and a docking simulation of **6** bound to hPXR also indicated that multiple hydrophobic amino acid residues surround the 2,2,2-trifluoroethyl moiety of **5** and **6**. Based on these considerations, we designed silanol derivatives bearing various substituents, including bulky hydrophobic groups, on the nitrogen atom of sulfonamide as candidate PXR-selective ligands.

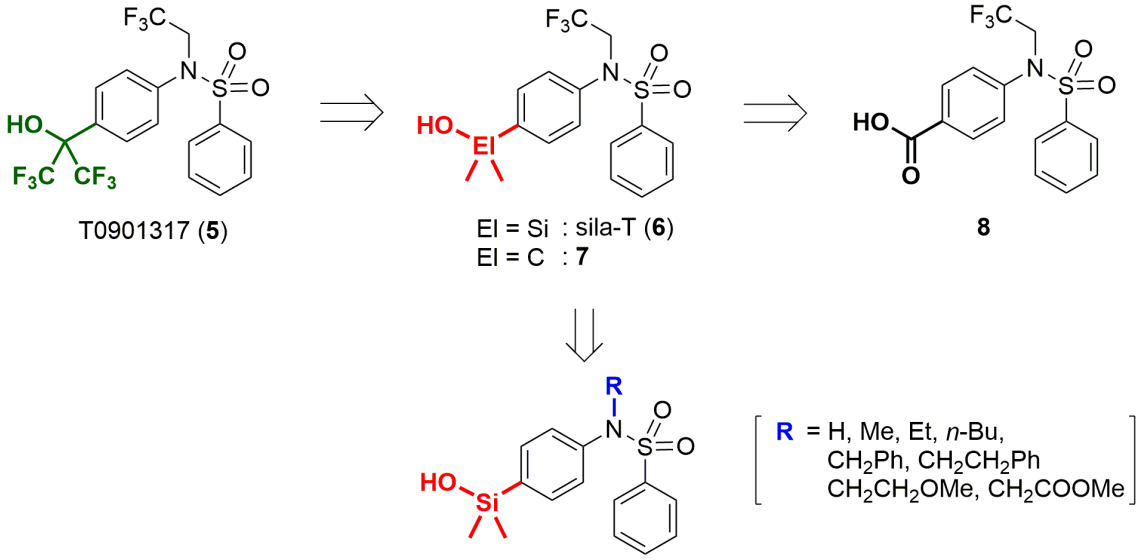
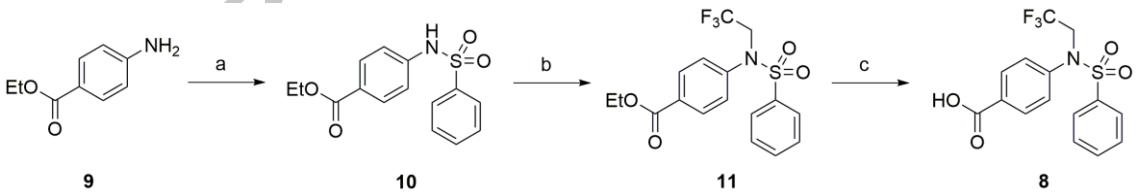


Fig.2. Design scheme of selective hPXR ligands.

2.2 Synthesis

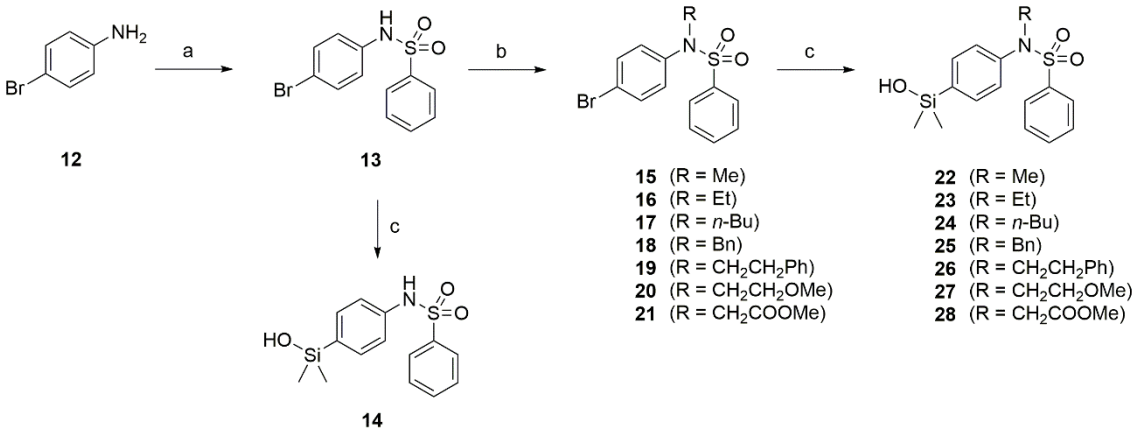
Scheme 1 illustrates the synthesis of carboxy derivative **8**. Reaction between ethyl 4-aminobenzoate (**9**) and benzenesulfonyl chloride gave sulfonamide **10**, and then alkylation of the nitrogen atom with 1-bromo-2,2,2-trifluoroethane afforded **11**. Hydrolysis of the ethyl ester group under basic conditions gave the desired carboxylic acid **8** (Scheme 1).



Scheme 1. Synthesis of carboxylic acid **8**. Reagents and conditions: (a) Benzenesulfonyl chloride, pyridine, THF, rt, quant; (b) NaH, CF_3CH_2Br, DMF, 80℃, 33%; (c) LiOH, H_2O-EtOH, 80℃, quant.

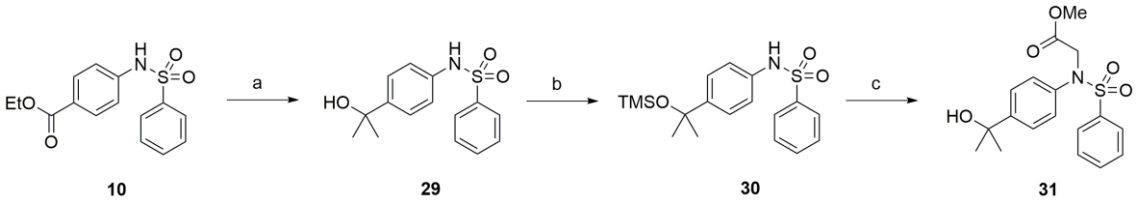
The synthesis of the designed silanol derivatives **22-28** is illustrated in Scheme 2. Sulfonamide formation using 4-bromoaniline (**12**) and benzenesulfonyl chloride gave sulfonamide **13**, which was converted to dimethylsilanol **14** under Denmark's conditions.[32] Namely, in the presence of $PdCl_2$ and 2-(di-*tert*-butylphosphino)biphenyl (BPTBP), the bromide reacted with 1,2-diethoxy-1,1,2,2-tetramethyldisilane to afford a ethoxydimethylsilyl intermediate, and then removal of the ethyl group gave the desired silanol **14**. Sulfonamide **13** was also alkylated with alkyl halides or alkyl triflates to afford compounds **15-21**. The bromines of compounds **15-21** were converted to

dimethylsilanol under the same conditions as used for **14**. In some cases the yield was not sufficient, since the conversion of starting material was low and formation of siloxane was also observed.



Scheme 2. Synthesis of the designed silanol derivatives **22**-**28**. Reagents and conditions: (a) Benzenesulfonyl chloride, pyridine, THF, rt, 93%; (b) NaH, R-X, DMF, 80°C, 3-92%; (c) i, $PdCl_2$, BPTBP, *i*-Pr_2EtN, NMP, $(Me_2EtOSi)_2$, 60°C; ii, AcOH, $Me_2NCH_2CH_2SH$, MeCH; 3-26%.

We also designed and synthesized alcohol **31**, which is the carbinol derivative corresponding to silanol **28**. Treatment of ester **10** with methylmagnesium bromide gave alcohol **29**. Protection of the hydroxyl group of **29** using trimethylsilyl chloride gave compound **30**, and then alkylation with methyl bromoacetate under basic conditions afforded the desired carbinol **31** (Scheme 3).



Scheme 3. Synthesis of carbinol derivative **31**. Reagents and conditions: (a) MeMgBr, THF, 0°C, 28% yield; (b) TMSCl, imidazole, DMF, 0°C to rt, quant; (c) NaH, $BrCH_2COOMe$, DMF, 80°C, 86% yield.

2.3. Determination of log$P_{o/w}$ values

We firstly determined the hydrophobicity of the synthesized silanol and carbinol derivatives in terms of the octanol–water partition coefficient ($P_{o/w}$), using an HPLC method.[33] The determined log$P_{o/w}$ values are listed in Table 1. In this study, silanol **28** exhibited a log$P_{o/w}$ value of 2.79, which is 0.44 larger than that of the corresponding carbinol **31** (log$P_{o/w}$: 2.35). We recently reported that sila-T (**6**) exhibited a log$P_{o/w}$ value of 4.23, which is 0.53 larger than that of the corresponding carbinol **7** (log$P_{o/w}$: 3.70). We also showed that C/Si-exchange of the tertiary butyl group to a trimethylsilyl group increased the log$P_{o/w}$ value by 0.6.[34] These results suggest that the increase of hydrophobicity in silanol/carbinol exchange is

smaller than that in C/Si exchange of the tertiary alkyl group. The differences can be attributed to the differences of hydrophobic surface area, namely, three methyl groups in *t*-butyl/TMS alcohol or two methyl groups in silanol/alcohol.

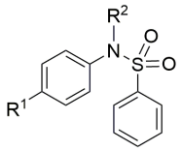
2.4. Biological evaluation

We next evaluated the potencies of the compounds toward hPXR by means of luciferase reporter gene assay in HEK293 cells. The carboxy derivative **8** exhibited no activity toward hPXR. This result suggests that the acidity of the hydroxyl group is not sufficient, and that suitable hydrophobicity around the acidic hydroxyl group is important. In contrast to the carboxy (**8**) or carbinol (**7**) derivatives, all the synthesized silanol derivatives exhibited significant hPXR-agonistic activity. Among the silanol derivatives, trifluoroethyl derivative **6** (sila-T) exhibited the most potent activity, and methoxycarbonylmethyl derivative **28** was the second most potent compound, with an EC_{50} value of 1.4 μM. Compounds bearing comparatively small substituents such as **14**, **22** and **23** also exhibited potent activity. On the other hand, introduction of bulky substituents such as an *n*-butyl group (**24**) or a phenethyl group (**26**) reduced the activity. Significant correlation between hydrophobicity (LogP value) and PXR agonistic activity was not observed. We initially considered that introduction of a bulky and hydrophobic functionality on the nitrogen might improve the PXR activity and selectivity, but the hydrophobic cavity in this region seems to be restricted. It is interesting that compounds **27** and **28** with hydrogen-bonding capability exhibited potent hPXR activity. Alcohol **31**, which is the carbinol derivative corresponding to the potent silanol derivative **28**, did not exhibit PXR agonistic activity, suggesting that the silanol moiety is important for PXR activity.

In order to verify the hPXR-selectivity of the silanol derivatives, we also investigated their activities toward other nuclear receptors, hLXRα and β, hFXR, and hRORα and γ. None of the synthesized silanol derivatives, as well as sila-T (**6**), showed significant agonistic activity toward hLXRα and β. This result suggests that the hLXRs agonistic activity is extinguished by conversion of the hexafluoropropanol moiety of **5** to a silanol group, and increased hydrophobicity does not compensate for this. Concerning the T0901317 (**5**) derivatives, the hexafluoropropanol moiety seems to be indispensable for hLXR activity, and therefore the silanol-sulfonamide scaffold we developed is a promising core structure for the development of hPXR agonists without hLXR activity. The silanols **14** and **22-28** synthesized in this study did not exhibit hFXR activity, while sila-T (**6**) exhibited partial hFXR-agonistic activity.[25] The hFXR activity may depend upon the presence of the 2,2,2-trifluoroethyl moiety. Regarding hRORα and γ, silanol derivatives bearing ethyl (**23**), *n*-butyl (**24**), benzyl (**25**) and 2-methoxyethyl groups (**27**), as well as sila-T (**6**), exhibited moderate or weak agonistic activities toward RORα and γ, whereas compounds bearing a hydrogen atom (**14**) or a bulky substituent such as **26** did not exhibit activity toward hRORα and γ. Compound **24** bearing methyl group exhibited agonistic activity toward hRORα and γ. The structure-activity relationship data for hRORα and γ indicate that there is a "window" of bulkiness or hydrophobicity for hRORα and γ modulators. These findings support the idea that the silanol-sulfonamide scaffold we focused on in this study is a versatile core structure for development of hPXR agonists, and

that proper selection of the substituent on the nitrogen atom can improve the selectivity toward hPXR.

Table 1. Hydrophobicity parameters and biological activities of synthesized compounds.



Compd	R^1	R^2	$logP_{o/w}$	hPXR	hLXRα	hLXRβ	hFXR	hRORα[a]	hRORγ[a]
				EC_{50} (μM)				IC_{50} (μM)	
1	-	-	-	2.0	-	-	-	-	-
5	$-C(CF_3)_2OH$	$-CH_2CF_3$	5.38	0.12	0.40 [b]	0.23 [b]	3.4 [b]	11	4.4
6	$-SiMe_2OH$	$-CH_2CF_3$	4.23	0.63	n.a. [b]	n.a. [b]	11 [b]	>30	11
7	$-CMe_2OH$	$-CH_2CF_3$	3.70	n.a.	n.a.	n.a.	n.a.	n.a.	>30
8	-COOH	$-CH_2CF_3$	n.d.[c]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
14	$-SiMe_2OH$	-H	2.22	2.4	n.a.	n.a.	n.a.	n.a.	n.a.
22	$-SiMe_2OH$	-Me	2.90	3.4	n.a.	n.a.	n.a.	(+53%)[d]	(+54%)[d]
23	$-SiMe_2OH$	-Et	3.20	1.9	n.a.	n.a.	n.a.	>30	>30
24	$-SiMe_2OH$	-*n*-Bu	4.05	6.5	n.a.	n.a.	n.a.	>30	>30
25	$-SiMe_2OH$	-Bn	3.92	3.2	n.a.	n.a.	n.a.	>30	>30
26	$-SiMe_2OH$	$-(CH_2)_2Ph$	4.32	14	n.a.	n.a.	n.a.	>30	>30
27	$-SiMe_2OH$	$-(CH_2)_2OMe$	2.81	4.2	n.a.	n.a.	n.a.	n.a.	n.a.
28	$-SiMe_2OH$	$-CH_2CO_2Me$	2.79	1.4	n.a.	n.a.	n.a.	n.a.	n.a.
31	$-CMe_2OH$	$-CH_2CO_2Me$	2.35	n.a.	n.a.	n.a.	n.a.	n.a.	>30

[a] IC_{50} values were calculated with respect to the activity of **5** (30 μM) as the maximum response. [b] Reported values in reference 25. [c] Not determined. [d] Agonistic activity (% activation with respect to the basal luciferase activity). n.a.: Activation or inhibition in the concentration of 30 μM was less than 11%.

2.5. Docking simulation

In order to estimate the binding mode of the developed silanol derivatives and to investigate the structure-activity relationships, we conducted docking simulation of the co-crystal structure of the hPXR LBD with T0901317 (**5**) (PDB ID: 2O9I).[35] We first investigated docking of the methoxycarbonyl derivative **28**, which exhibited potent and selective PXR-agonistic activity. We obtained two distinct

binding forms. The first (form A) is similar to that of **5** in the co-crystal. In this calculated structure, the silanol moiety of **28** forms a polar contact with His 407, with which the hexafluoropropanol of **5** forms a polar contact in the crystal structure. The sulfonyl group also forms a polar contact with Gln285. The methoxycarbonyl moiety is located the hydrophobic cavity, surrounded by several hydrophobic amino acid residues, including Leu209, Val211, Trp299, Leu308 and Leu324, where the trifluoroethyl moiety of **5** is located in the crystal structure (Fig. 3, top). On the one hand, the second binding form (form B) is quite different. In this calculated structure, the phenylsilanol moiety, instead of the methoxycarbonyl moiety in form A, is located in the hydrophobic cavity, and the hydroxyl group of silanol forms a polar contact with amide groups of the protein backbone. The sulfonyl group forms a polar contact with Gln285, similarly to form A, and interestingly, in addition to the sulfonyl group, the ester group also forms a polar contact with Gln285 (Fig. 3, middle). Although we could not establish which conformation is close to the actual binding form of compound **28**, the additional polar contact at the methoxycarbonyl moiety in form B could be a possible reason for the high potency of **28**.

We also conducted docking simulations of compounds **14** and **22**. These compounds have a relatively small substituent at the nitrogen atom, and exhibited potent PXR-agonistic activity. Generally, both of secondary and tertiary aromatic sulfonamides have a synclinal structure,[37-39] different from the case of aromatic carboxamides.[40] The calculations on these compounds indicated binding forms fairly different from both form A and form B. In these calculated structures, similarly to the co-crystal of **5** and form A of **28**, the hydroxyl group of the silanol moiety is located near His407 and forms a polar contact with it. However, the benzenesulfonyl group is located in a hydrophobic cavity surrounded by amino acid residues, including Leu206, Lys210, Leu239 and Leu240, and this is distinct from the cavity occupied by **5** or **28**. The relatively small substituents on the nitrogen atom of **14** and **22** could allow these compounds to access this cavity (Fig. 3, bottom).

The docking simulation suggested the existence of multiple binding forms, depending on the substructure of the compounds. It is possible that the comparatively large binding pocket of hPXR allows the compounds to bind in multiple binding modes. Although the stability of the methoxycarbonyl group in the biological system can be problematic for in vivo application, the additional binding cavity and polar contacts suggested by the docking simulations might provide useful clues for the development of potent and selective hPXR ligands.

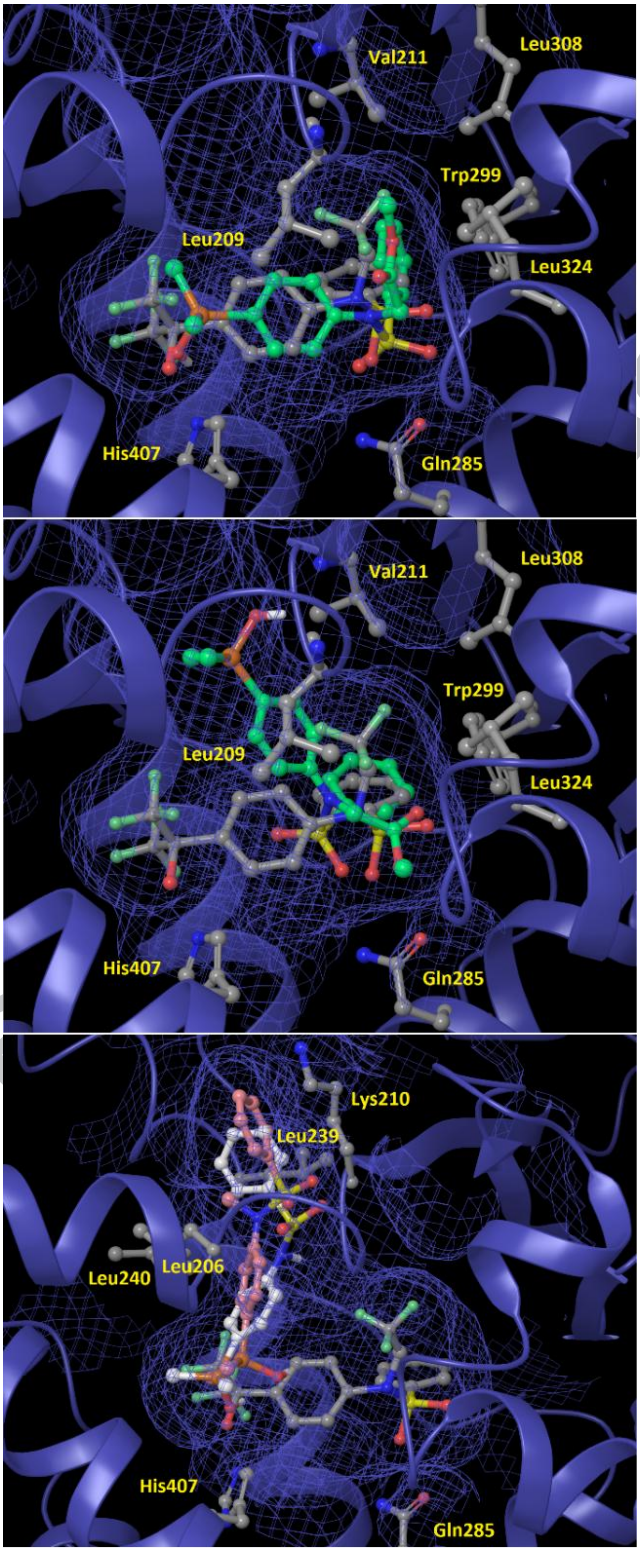


Fig. 3. Docking models of silanol derivatives with hPXR LBD (PDB ID: 2O9I) obtained with AutoDock.[36] (Top and middle) Superimposition of the hPXR LBD complex with **5** (gray) and docking models of **28** (green) (top: form A, middle: form B). (Bottom) Superimposition of the hPXR LBD complex with **5** (gray) and docking models of **14** (white) and **22** (pink).

3. Conclusion

In this study, we developed a new series of selective hPXR agonists based on our previously developed silanol-sulfonamide scaffold. Structure-activity relationship studies of the sulfonamide derivatives toward hPXR, hLXRα and β, hFXR, and hRORα and γ suggested a possible strategy to manipulate the selectivity of the compounds. The hexafluoropropanol moiety of **5** is indispensable for hLXRs activity, whereas the silanol group is acceptable in hPXR ligands. In addition, carbinol and carboxylic acid resulted in loss of activity as a hPXR ligand. Therefore, the silanol-sulfonamide scaffold we developed seems to be a promising core structure for hPXR ligands with selectivity over hLXRs. As regards hFXR and hRORs, there seems to be a "window" of acceptable bulkiness or hydrophobicity for these receptors. Based on these findings, we developed compound **28** as a potent and selective hPXR agonist. Though the PXR potency of compound **28** was not potent than the lead compound **5**, we succeeded in reducing the potency toward other NRs to improve the PXR selectivity. Docking simulation suggested multiple binding modes of the compounds, including an additional binding cavity and polar contacts. The potent and selective hPXR agonist **28** and the structure–activity relationship data obtained in this study should be useful to expand the pharmaceutical potential of hPXR modulation and to assist the development of more potent and selective hPXR modulators.

4. Experimental

4.1. Chemistry

General remarks. All reagents were purchased from SigmaAldrich Chemical Co., Tokyo Kasei Kogyo Co., Wako Pure Chemical Industries, or Kanto Kagaku Co., Inc. Silica gel for column chromatography was purchased from Kanto Kagaku Co., Inc. Melting points were taken on a Yanagimoto micro melting point apparatus. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL JNM-GX500 (500 MHz and 125 MHz, respectively) spectrometer. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane (TMS) as an internal reference. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Electrospray ionization mass spectra (ESI-MS) and high-resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF spectrometer with Low Concentration Tuning mix (G1969-85000).

4.1.1. Ethyl 4-(phenylsulfonamido)benzoate (10). To a solution of **9** (2.00 g, 12.1 mmol) in THF (121 mL) were added benzenesulfonyl chloride (4.65 mL, 36.3 mmol) and pyridine (9.76 mL, 121 mmol), and the mixture was stirred room temperature for 1.5 h. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 3:1) to give **10** as a white solid. This material was used in the next step without further purification. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.92 (td, 2H, *J* = 5.6, 3.2 Hz), 7.84-7.82 (m, 2H), 7.56 (tt, 1H, *J* = 7.4, 1.3 Hz), 7.46 (td, 2H, *J* = 7.7, 3.1 Hz), 7.13 (dt, 2H, *J* = 9.0, 2.3 Hz), 7.08 (1H, s), 4.33 (q,

2H, *J* = 7.3 Hz), 1.36 (t, 3H, *J* = 7.2); MS (ESI+) *m/z* 328 [for $(M+Na)^+$].

4.1.2. Ethyl 4-(*N*-(2,2,2-trifluoroethyl)phenylsulfonamido)benzoate (11). To a solution of **10** (1.20 g, 3.92 mmol) in DMF (18.0 mL) was added sodium hydride (188 mg, 7.84 mmol), and the mixture was stirred room temperature for 30 min. 2,2,2-Trifluoroethyl triflate (1.70 mL, 11.8 mmol) was added, and the mixture was refluxed for 1 h. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 5:1) to give **11** as a yellow solid (767 mg, 33% (2 steps)). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.00 (dt, 2H, *J* = 9.0, 2.3 Hz), 7.63-7.58 (m, 3H), 7.48 (dt, 2H, *J* = 12.2, 2.9 Hz), 7.13 (dt, 2H, *J* = 9.0, 2.0 Hz), 4.38 (q, 2H, *J* = 7.3 Hz), 4.25 (q, 2H, *J* = 8.2 Hz), 1.39 (t, 3H, *J* = 7.2 Hz); MS (ESI+) *m/z* 410 (for $[M+Na]^+$).

4.1.3. 4-(*N*-(2,2,2-Trifluoroethyl)phenylsulfonamido)benzoic acid (8). To a solution of **11** (213 mg, 0.550 mmol) in H_2O-EtOH (H_2O:EtOH = 1:3, 45.5 mL) was added $LiOH \cdot H_2O$ (34.6 mg, 0.825 mmol), and the mixture was stirred at 80℃ for 4 h. The reaction was then quenched with HCl, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated to give **8** as a white solid (529 mg, quant.). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.06 (dt, 2H, *J* = 9.0, 2.0 Hz), 7.64-7.59 (m, 3H), 7.49 (t, 2H, *J* = 8.0 Hz), 7.19 (dt, 2H, *J* = 9.0, 2.3 Hz), 4.27 (q, 2H, *J* = 8.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 169.86, 143.90, 137.91, 133.72, 131.50, 129.42, 129.31, 129.14, 127.76, 124.73, 122.51, 52.30, 52.02, 51.74, 51.46. HRMS (ESI-) *m/z* 358.0374 [$(M-H)^-$:calcd for $C_{15}H_{11}F_3O_4NS$, 358.0355].

4.1.4. *N*-(4-Bromophenyl)benzenesulfonamide (13). To a solution of **12** (1.00 g, 5.81 mmol) in THF (58.1 mL) were added benzenesulfonyl chloride (1.49 mL, 11.6 mmol) and pyridine (4.68 mL, 58.1 mmol), and the mixture was stirred at room temperature for 1.5 h. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 3:1) to give **13** as a white solid (1.53 g, 84%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.79-7.77 (m, 2H), 7.56 (tt, 1H, *J* = 7.4, 1.3 Hz), 7.46 (t, 2H, *J* = 8.0 Hz), 7.35 (dt, 2H, *J* = 9.4, 2.3 Hz), 6.98-6.94 (m, 3H); MS (ESI-), *m/z* 311, 309 [$(M-H)^-$].

4.1.5. *N*-(4-(Hydroxydimethylsilyl)phenyl)benzenesulfonamide (14). To a solution of $PdCl_2$ (7.1 mg, 40.1 μmol), 2-(di-*t*-butylphosphino)biphenyl (23.9 mg, 80.2 μmol) and **13** (250 mg, 0.801 mmol) in 1-methyl-2-pyrrolidinone (8.00 mL) was added diisopropylethylamine (411 μL), and the mixture was stirred at 60 °C under an argon atmosphere. 1,2-Diethoxy-1,1,2,2-tetramethyldisilane (238 μL, 0.961 mmol) was added, and the mixture was stirred at 60 °C for 4 h, then cooled to rt. CH_3CN (17.7 mL), 2-(dimethylamino)ethanethiol hydrochloride (28.4 mg, 0.200 mmol) and 0.1 M acetic acid (23.1 mL) were added to it, and the resulting mixture was stirred at rt for 2 h. The reaction was then quenched with

H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2:1) to give **14** as a colorless oil (14.2 mg, 6%). ^{1}H-NMR (500 MHz, DMSO-*d*6) δ 10.38 (s, 1H), 7.79-7.77 (m, 2H), 7.62-7.58 (m, 1H), 7.57-7.53 (m, 2H), 7.37 (2H, d, *J* = 8.6 Hz), 7.08 (2H, d, *J* = 8.6 Hz), 5.76 (s, 1H), 0.16 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 139.20, 137.31, 136.24, 134.12, 133.08, 129.07, 127.19, 120.19, 0.62; HRMS (ESI-) *m/z* 306.0642 [$(M-H)^-$: calcd for $C_{14}H_{16}NO_3SSi$, 306.0615].

4.1.6. *N*-(4-Bromophenyl)-*N*-methylbenzenesulfonamide (15). To a solution of **13** (302 mg, 0.966 mmol) in DMF (9.66 mL) was added sodium hydride (27.8 mg, 1.16 mmol), and the mixture was stirred at room temperature for 30 min. Iodomethane (72.2 μL, 1.16 mmol) was added, and stirring was continued at 80 °C. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 5:1) to give **15** as a pale-yellow oil (267 mg, 85%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.59 (dq, 1H, *J* = 11.5, 2.6 Hz), 7.54 (dd, 2H, *J* = 8.6, 1.1 Hz), 7.49-7.45 (m, 2H), 7.42 (td, 2H, *J* = 6.0, 3.4 Hz), 6.97 (td, 2H, *J* = 5.9, 3.6 Hz), 3.15 (s, 3H); MS (ESI+) *m/z* 348, 350 [$(M+Na)^+$].

4.1.7. *N*-(4-Bromophenyl)-*N*-ethylbenzenesulfonamide (16). To a solution of **13** (312 mg, 1.00 mmol) in DMF (9.90 mL) was added sodium hydride (28.8 mg, 1.20 mmol), and the mixture was stirred at room temperature for 30 min. Iodoethane (124 μL, 1.20 mmol) was added, and stirring was continued at 80 °C. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 5:1) to give **16** as a pale-yellow oil (312 mg, 92%); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, 3H, *J* = 9.2, 7.4 Hz), 7.48-7.43 (m, 4H), 6.91 (td, 2H, *J* = 5.9, 3.6 Hz), 3.58 (q, 2H, *J* = 7.1 Hz), 1.07 (t, 3H, *J* = 7.2 Hz). MS (ESI+) *m/z* 362, 364 [$(M+Na)^+$].

4.1.8. *N*-(4-Bromophenyl)-*N*-butylbenzenesulfonamide (17). To a solution of **13** (367 mg, 1.18 mmol) in DMF (11.8 mL) was added sodium hydride (33.9 mg, 1.41 mmol), and the mixture was stirred room temperature for 30 min. 1-Iodobutane (162 μL, 1.41 mmol) was added, and stirring was continued at 80 °C. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 5:1) to give **17** as a pale-yellow oil (273 mg, 63%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.60-7.56 (m, 3H), 7.48-7.42 (m, 4H), 6.91 (dt, 2H, *J* = 5.9, 3.6 Hz), 3.50 (t, 2H, *J* = 6.9 Hz), 1.41-1.25 (m, 4H), 0.86 (3H, t, *J* = 7.2 Hz); MS (ESI+) *m/z* 390, 392 [$(M+Na)^+$].

4.1.9. *N*-Benzyl-*N*-(4-bromophenyl)benzenesulfonamide (18). To a solution of **13** (429 mg, 1.37 mmol)

in DMF (13.7 mL) was added sodium hydride (39.5 mg, 1.65 mmol), and the mixture was stirred room temperature for 30 min. Benzyl bromide (189 μL, 1.65 mmol) was added, and stirring was continued at 80 °C. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 5:1) to give **18** as a pale-yellow oil (465 mg, 84%); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.66 (td, 2H, *J* = 4.3, 1.3 Hz), 7.62 (tt, 1H, *J* = 7.7, 1.7 Hz), 7.51 (t, 2H, *J* = 7.7 Hz), 7.32 (dt, 2H, *J* = 9.2, 2.4 Hz), 7.21 (dt, 5H, *J* =9.4, 4.4 Hz), 6.84 (td, 2H, *J* = 6.0, 3.4 Hz), 4.70 (s, 2H); MS (ESI) *m/z* 424, 426 [$(M+Na)^+$].

4.1.10. *N*-(4-Bromophenyl)-*N*-phenethylbenzenesulfonamide (19). To a solution of **13** (327 mg, 1.05 mmol) in DMF (10.5 mL) was added sodium hydride (43.1 mg, 1.26 mmol), and the mixture was stirred room temperature for 30 min. (2-Bromoethyl)benzene (170 μL, 1.26 mmol) was added, and stirring was continued at 80 °C. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 5:1) to give **19** as a pale-yellow oil (265 mg, 61%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.56 (tdd, 3H, *J* = 8.5, 3.8, 2.3 Hz), 7.44 (dq, 4H, *J* = 7.4, 2.4 Hz), 7.26 (dq, 2H, *J* = 11.3, 2.7 Hz), 7.21 (dq, 1H, *J* = 10.0, 2.3 Hz), 7.10 (t, 2H, *J* = 4.3 Hz), 6.89 (td, 2H, *J* = 6.0, 3.4 Hz), 3.76-3.73 (m, 2H), 2.76 (dd, 2H, *J* = 8.9, 7.2 Hz); MS (ESI+) *m/z* 438, 440 [$(M+Na)^+$].

4.1.11. *N*-(4-Bromophenyl)-*N*-(2-methoxyethyl)benzenesulfonamide (20). To a solution of **13** (415 mg, 1.33 mmol) in DMF (13.3 mL) was added sodium hydride (38.3 mg, 1.59 mmol), and the mixture was stirred room temperature for 30 min. 2-Bromoethyl methyl ether (150 μL, 1.59 mmol) was added, and stirring was continued at 80 °C. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 5:1) to give **20** as a crude oil (377 mg, 77%). This material was used in the next step without further purification.

4.1.12. Methyl *N*-(4-bromophenyl)-*N*-(phenylsulfonyl)glycinate (21). To a solution of **13** (304 mg, 0.972 mmol) in DMF (9.72 mL) was added sodium hydride (40.0 mg, 1.17 mmol), and the mixture was stirred room temperature for 30 min. Methyl bromoacetate (108 μL, 1.17 mmol) was added, and the stirring was continued at 80 °C. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 5:1) to give **21** as a crude oil (165 mg, 44%). This material was used in the next step without further purification. MS (ESI+) *m/z* 405, 407 [$(M+Na)^+$].

4.1.13. *N*-(4-(Hydroxydimethylsilyl)phenyl)-*N*-methylbenzenesulfonamide (22). To a solution of

$PdCl_2$ (8.2 mg, 46.2 μmol), 2-(di-*t*-butylphosphino)biphenyl (27.6 mg, 92.4 μmol) and **15** (302 mg, 0.924 mmol) in 1-methyl-2-pyrrolidinone (9.20 mL) was added diisopropylethylamine (474 μL) and the mixture was stirred at 60 °C under an argon atmosphere. 1,2-Diethoxy-1,1,2,2-tetramethyldisilane (274 μL, 1.11 mmol) was added to the mixture and stirring was continued at 60 °C for 4 h. The reaction mixture was cooled to rt and CH_3CN (20.5 mL), 2-(dimethylamino)ethanethiol hydrochloride (32.7 mg, 0.231 mmol) and 0.1 M acetic acid (26.7 mL) were added. The resulting mixture was stirred at rt for 2 h. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2:1) to give **22** as a colorless oil (11.3 mg, 4%). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 7.71 (tt, 1H, *J* = 7.2, 1.6 Hz), 7.59 (dt, 2H, *J* = 12.4, 2.7 Hz), 7.52 (tdd, 4H, *J* = 10.6, 5.3, 3.0 Hz), 7.09 (dt, 2H, *J* = 8.4, 2.0 Hz), 5.93 (1H, s), 3.13 (3H, s), 0.23 (s, 6H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ 142.38, 139.98, 136.78, 134.12, 133.82, 129.82, 127.86, 125.73, 38.35, 1.09; HRMS (ESI+) *m/z* 344.0758 [$(M+Na)^+$: calcd for $C_{15}H_{19}NO_3SSiNa$, 344.0747].

4.1.14. *N*-Ethyl-*N*-(4-(hydroxydimethylsilyl)phenyl)benzenesulfonamide (23). To a solution of $PdCl_2$ (8.8 mg, 49.9 μmol), 2-(di-*t*-butylphosphino)biphenyl (29.8 mg, 99.8 μmol) and **16** (340 mg, 1.00 mmol) in 1-methyl-2-pyrrolidinone (9.90 mL) was added diisopropylethylamine (512 μL), and the mixture was stirred at 60 °C under an argon atmosphere. 1,2-diethoxy-1,1,2,2-tetramethyldisilane (296 μL, 1.20 mmol) was added and the mixture was stirred at 60 °C for 4 h. The reaction mixture was cooled to rt and CH_3CN (22.1 mL), 2-(dimethylamino)ethanethiol hydrochloride (35.3 mg, 0.250 mmol) and 0.1 M acetic acid (28.8 mL) were added. The resulting mixture was stirred at rt for 2 h. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2:1) to give **23** as a colorless oil (8.5 mg, 3%). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 7.69 (ddd, 1H, *J* = 12.7, 5.0, 3.9 Hz), 7.35 (d, 4H, *J* = 4.6 Hz), 7.28 (dt, 2H, *J* = 8.2, 1.9 Hz), 6.81-6.78 (m, 2H), 5.70 (1H, s), 3.41-3.32 (m, 2H), 0.77-0.70 (m, 3H), 0.00 (s, 6H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ 140.23, 139.15, 138.12, 133.72, 133.05, 129.29, 127.56, 127.14, 45.06, 13.90, 0.51; HRMS (ESI+) *m/z* 358.0886 [$(M+Na)^+$: calcd for $C_{16}H_{21}NO_3SSiNa$, 358.0904].

4.1.15. *N*-Butyl-*N*-(4-(hydroxydimethylsilyl)phenyl)benzenesulfonamide (24). To a solution of $PdCl_2$ (4.0 mg, 22.5 μmol), 2-(di-*t*-butylphosphino)biphenyl (13.4 mg, 45.0 μmol) and **17** (166 mg, 0.45 mmol) in 1-methyl-2-pyrrolidinone (4.50 mL) was added diisopropylethylamine (231 μL), and the mixture was stirred at 60 °C under an argon atmosphere. 1,2-Diethoxy-1,1,2,2-tetramethyldisilane (133 μL, 0.540 mmol) was added, and the mixture was stirred at 60 °C for 4 h, then cooled to rt. CH_3CN (10.0 mL), 2-(dimethylamino)ethanethiol hydrochloride (16.0 mg, 0.113 mmol) and 0.1 M acetic acid (13.0 mL) were added, and the resulting mixture was stirred at rt for 2 h. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography

(*n*-hexane/EtOAc = 2:1) to give **17** as a colorless oil (15.8 mg, 10%). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 7.71-7.68 (m, 1H), 7.59 (dq, 4H, *J* = 12.3, 2.8 Hz), 7.52 (dt, 2H, *J* = 8.2, 1.9 Hz), 7.04 (dd, 2H, *J* = 10.3, 1.7 Hz), 5.93 (s, 1H), 3.53 (t, 2H, *J* = 6.6 Hz), 1.28-1.25 (m, 4H), 0.81 (t, 3H, *J* = 7.2 Hz), 0.25 (s, 6H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ 140.73, 139.89, 138.48, 134.24, 133.58, 129.82, 128.00, 127.70, 49.94, 30.22, 19.41, 13.91, 1.04; HRMS (ESI+) *m/z* 386.1206 [(M+Na)$^+$: calcd for $C_{18}H_{25}NO_3SSiNa$, 386.1217].

4.1.16. *N*-Benzyl-*N*-(4-(hydroxydimethylsilyl)phenyl)benzenesulfonamide (25). To a solution of $PdCl_2$ (10.3 mg, 57.8 μmol), 2-(di-*t*-butylphosphino)biphenyl (34.5 mg, 116 μmol) and **18** (465 mg, 1.16 mmol) in 1-methyl-2-pyrrolidinone (11.6 mL) was added diisopropylethylamine (593 μL), and the mixture was stirred at 60 °C under an argon atmosphere. 1,2-Diethoxy-1,1,2,2-tetramethyldisilane (342 μL, 1.39 mmol) was added, and the mixture was stirred at 60 °C for 4 h, then cooled to rt. CH_3CN (25.5 mL), 2-(dimethylamino)ethanethiol hydrochloride (40.9 mg, 0.289 mmol) and 0.1 M acetic acid (33.2 mL) were added, and the resulting mixture was stirred at rt for 2 h. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2:1) to give **25** as a colorless oil (84.5 mg, 18%). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 7.75-7.72 (m, 1H), 7.67 (dd, 2H, *J* = 5.4, 3.2 Hz), 7.64-7.61 (m, 2H), 7.42 (dd, 2H, *J* = 6.3, 1.7 Hz), 7.26 (t, 4H, *J* = 2.3 Hz), 7.20-7.17 (m, 1H), 7.07 (d, 2H, *J* = 8.6 Hz), 5.86 (s, 1H), 4.81 (s, 2H), 0.19 (s, 6H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ 140.48, 139.91, 138.58, 136.84, 134.06, 133.78, 130.00, 128.89, 128.41, 127.96, 127.85, 127.79, 53.85, 0.98; HRMS (ESI+) *m/z* 420.1083 [(M+Na)$^+$:calcd for $C_{21}H_{23}NO_3SSiNa$, 420.1060].

4.1.17. *N*-(4-(Hydroxydimethylsilyl)phenyl)-*N*-phenethylbenzenesulfonamide (26). To a solution of $PdCl_2$ (5.6 mg, 31.8 μmol), 2-(di-*t*-butylphosphino)biphenyl (19.0 mg, 63.6 μmol) and **19** (265 mg, 0.636 mmol) in 1-methyl-2-pyrrolidinone (6.36 mL) was added diisopropylethylamine (0.326 mL), and the mixture was stirred at 60 °C under an argon atmosphere. 1,2-Diethoxy-1,1,2,2-tetramethyldisilane (0.188 mL, 0.763 mmol) was added, and the mixture was stirred at 60 °C for 4 h. The reaction mixture was cooled to rt and CH_3CN (14.1 mL), 2-(dimethylamino)ethanethiol hydrochloride (22.5 mg, 0.159 mmol) and 1.0 M acetic acid (18.4 mL) were added to it. The resulting mixture was stirred at rt for 2 h. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2:1) to give **26** as a colorless oil (22.0 mg, 8%). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 7.68 (tt, 1H, *J* = 6.9, 1.9 Hz), 7.58-7.52 (m, 6H), 7.26 (dd, 2H, *J* = 9.7, 4.6 Hz), 7.20 (dt, 1H, *J* = 10.5, 2.6 Hz), 7.13 (2H, t, *J* = 4.0 Hz), 7.05 (2H, d, *J* = 8.6 Hz) 5.96 (1H, s), 3.79 (t, 2H, *J* = 7.4 Hz), 2.64 (t, 2H, *J* = 7.4 Hz), 0.26 (6H, s); ^{13}C-NMR (125 MHz, DMSO-d_6) δ 140.30, 139.29, 138.05, 137.76, 133.73, 133.10, 129.27, 128.71, 128.33, 127.51, 127.19, 126.35, 51.18, 34.19, 0.53; HRMS (ESI+) *m/z* 434.1187 [(M+Na)$^+$: calcd for $C_{22}H_{25}NO_3SSiNa$, 434.1217].

4.1.18. *N*-(4-(Hydroxydimethylsilyl)phenyl)-*N*-(2-methoxyethyl)benzenesulfonamide (27). To a solution of $PdCl_2$ (9.0 mg, 51.0 μmol), 2-(di-*t*-butylphosphino)biphenyl (30.4 mg, 0.102 mmol) and **20** (377 mg, 1.02 mmol) in 1-methyl-2-pyrrolidinone (10.2 mL) was added diisopropylethylamine (0.523 mL), and the mixture was stirred at 60 °C under an argon atmosphere. 1,2-Diethoxy-1,1,2,2-tetramethyldisilane (0.302 mL, 1.22 mmol) was added to it, and the mixture was stirred at 60 °C for 4 h, then cooled to rt. CH_3CN (22.5 mL), 2-(dimethylamino)ethanethiol hydrochloride (36.1 mg, 0.255 mmol) and 0.1 M acetic acid (29.3 mL) were added to it, and the resulting mixture was stirred at rt for 2 h. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2:1) to give **27** as a colorless oil (14.0 mg, 4%). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 7.69 (dq, 1H, *J* = 10.3, 2.4 Hz), 7.60-7.58 (m, 4H), 7.52-7.50 (m, 2H), 7.05-7.03 (m, 2H), 5.95 (1H, s), 3.74-3.70 (m, 2H), 3.29 (t, 2H, *J* = 5.7 Hz), 3.15 (s, 3H), 0.24 (6H, s); ^{13}C-NMR (125 MHz, DMSO-d_6) δ 140.36, 139.63, 138.24, 133.73, 129.28, 127.68, 127.20, 69.21, 57.85, 49.73, 0.53; HRMS (ESI+) *m/z* 388.0994 [$(M+Na)^+$: calcd for $C_{17}H_{23}NO_4SSiNa$, 388.1009].

4.1.19. Methyl *N*-(4-(hydroxydimethylsilyl)phenyl)-*N*-(phenylsulfonyl)glycinate (28). To a solution of $PdCl_2$ (3.5 mg, 0.0401 mmol), 2-(di-*t*-butylphosphino)biphenyl (11.8 mg, 39.5 μmol) and **21** (165 mg, 0.395 mmol) in 1-methyl-2-pyrrolidinone (3.95 mL) was added diisopropylethylamine (203 μL) and the mixture was stirred at 60 °C under an argon atmosphere. 1,2-Diethoxy-1,1,2,2-tetramethyldisilane (117 μL, 0.474 mmol) was added, and the mixture was stirred at 60 °C for 4 h. The reaction mixture was cooled to rt and CH_3CN (8.78 mL), 2-(dimethylamino)ethanethiol hydrochloride (14.0 mg, 98.8 μmol) and 1.0 M acetic acid (11.4 mL) were added to it. The resulting mixture was stirred at rt for 2 h. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2:1) to give **28** as a colorless oil (4.3 mg, 3%). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 7.68 (ddd, 3H, *J* = 16.2, 10.7, 2.1 Hz), 7.58 (ddd, 2H, *J* = 10.6, 5.7, 2.0 Hz), 7.49 (dd, 2H, *J* = 8.3, 2.0 Hz), 7.15 (td, 2H, *J* = 4.6, 2.9 Hz), 5.93 (1H, s), 4.56 (d, 2H, *J* = 5.2 Hz), 3.61 (d, 3H, *J* = 1.7 Hz), 0.22 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) δ169.31, 140.75, 140.00, 138.99, 134.03, 133.01, 128.89, 127.82, 127.77, 52.62, 52.46, 0.86; HRMS (ESI+) *m/z* 402.0822 [$(M+Na)^+$: calcd for $C_{17}H_{21}NO_5SSiNa$ 402.0802].

4.1.20. *N*-(4-(2-Hydroxypropan-2-yl)phenyl)benzenesulfonamide (29). To a solution of **10** (329 mg, 1.08 mmol) in THF was added methyl magnesium bromide (2.60 mL, 2.37 mmol) under an Ar atmosphere at 0°C, and the mixture was stirred at the same temperature for 3 h. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 3:1) to give **29** as an orange solid (87.3 mg, 28%). ^{1}H-NMR

(500MHz, $CDCl_3$) δ 7.78 (dt, 2H, *J* = 8.4, 1.6 Hz), 7.56-7.52 (m, 1H), 7.44 (dt, 2H, *J*= 12.8, 2.7 Hz), 7.36 (dt, 2H, *J*= 9.2, 2.3 Hz), 7.02 (dt, 2H, *J* = 9.2, 2.4 Hz), 6.64 (s, 1H), 1.52 (s, 6H); MS (ESI+) *m/z* 314 [$(M+Na)^+$].

4.1.21. *N*-(4-(2-((Trimethylsilyl)oxy)propan-2-yl)phenyl)benzenesulfonamide (30). A solution of **29** (275 mg, 0.943 mmol) in DMF (9.40 mL) was stirred at 0°C, and imidazole (257 mg, 3.77 mmol) was added to it. Stirring was continued at 0°C. Trimethylsilyl chloride (239 μL, 1.89 mmol) was added, and the mixture was further stirred at 0°C for 1 h. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. This material was used in the next step without further purification. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.75 (d, 2H, *J* = 8.0 Hz), 7.48 (t, 1H, *J* = 7.4 Hz), 7.38 (t, 2H, *J* = 7.7 Hz), 7.26 (t, 2H, *J* = 4.3 Hz), 7.03 (d, 2H, *J* = 8.6 Hz), 1.48 (s, 6H), 0.00 (s, 9H); MS (ESI+) *m/z* 386 [$(M+Na)^+$].

4.1.22. *N*-(4-(2-Hydroxypropan-2-yl)phenyl)-*N*-(phenylsulfonyl)glycinate (31). To a solution of **30** in DMF (9.40 mL) was added sodium hydride (77.6 mg, 2.26 mmol), and the mixture was stirred at room temperature for 30 min. Methyl bromoacetate (313 μL, 3.39 mmol) was added, and the mixture was stirred at 80°C. The reaction was then quenched with H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2:1), and the trimethylsilyl group was removed to give **31** as a yellow solid (295 mg, 86%). White powder, mp: 96-99°C; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.69 (t, 2H, *J* = 4.3 Hz), 7.58 (t, 1H, *J* = 7.4 Hz), 7.46 (dd, 2H, *J* = 10.6, 5.4 Hz), 7.41 (td, 2H, *J* = 5.7, 3.4 Hz), 7.17-7.14 (2H, m), 4.40 (2H, s), 3.70 (s, 3H), 1.55 (s, 6H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ169.35, 149.36, 139.14, 138.22, 132.95, 128.88, 128.65, 127.83, 125.53, 72.43, 52.82, 52.44, 31.83; HRMS (ESI+) m/z 386.1026 [(M+Na): calcd for $C_{18}H_{21}NO_5SNa$, 386.1033].

4.2. Determination of log*P* value by an HPLC method

We calculated of log*P* values based on the OECD Guideline for Testing Chemicals 117.[S1] The measurements were performed on a Inertsil ODS-4 (5 μM, 4.6 × 150 mm) (GL Science Inc., Japan) by using an HPLC instrument (detector (MD-2010, JASCO), pump (PU-2080, JASCO)) with acetonitrile and H_2O (50%:50%). As reference compounds, thiourea, benzyl alcohol, methyl benzoate, 4-phenyl phenol, benzyl benzoate and dibenzyl were used.

4.3. Biological evaluation by reporter gene assay.

pcDNA3.1(-)-hRORα1, pcDNA3.1(-)-hRORβ1, pcDNA3.1(-)-hRORγ1 and RORE-TK-Luc were provided by Itsuu Laboratory. CMX-Gal4N-hLXRα-LBD, CMX-Gal4N-hLXRβ-LBD, CMX-Gal4N-hFXR-LBD, CMX-β-GAL, and tk-MH100×4 were provided by Professor Dr. Makoto Makishima (Nihon University School of Medicine). pVP16-PXR was constructed by insertion of

hPXR-ORF into the multiple cloning site of pVP16 plasmid (Clontech). HEK 293 cells were cultured in DMEM containing 5% FBS, penicillin and streptomycin mixture at 37 °C in a humidified atmosphere of 5% CO_2 in air. Cells were seeded at a density of 20% confluence/96-well plate 24 h prior to transfection. Cells in each well were co-transfected with 150 ng of a nuclear receptor expression plasmid, 500 ng of a luciferase reporter and 10 ng of CMX-β-GAL expression vector. Transfections were performed by the calcium phosphate co-precipitation method. After 24 h, transfected cells were treated with test compounds or DMSO for 24 h. Treated cells were assayed for luciferase activity with a Wallac ARVO SX 1420 Multilabel Counter (PerkinElmer). The luciferase activity of each sample was normalized by the β-galactosidase activity. Each transfection was carried out in triplicate. Assays were conducted in the concentration range of 0.03 - 30 μM of each tested compound, and EC_{50} values were calculated by sigmoid fitting using Origin data analysis software.

4. 4. Docking simulation

The structure of the LBD of hPXR was prepared from the Protein Data Bank accession 2O9I, chain A [35]. Polar hydrogens and partial atomic charges were assigned using AutoDockTools (ADT). Molecular docking was performed using AutoDock 4.2 with the Genetic Algorithm. AutoDock parameters for silicon atom were Rii = 4.30 and eii = 0.402.

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Graphical abstract