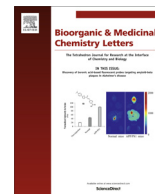




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Altered activity profile of a tertiary silanol analog of multi-targeting nuclear receptor modulator T0901317



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ABSTRACT

We report the design, synthesis, and physicochemical/biological evaluation of novel silanol derivative **6** (sila-T) as a silanol analog of multi-target nuclear receptor modulator T0901317 (**5**). Compound **6** showed intermediate hydrophobicity between the corresponding alcohol **13** and perfluoroalcohol **5**. While **5** exhibited potent activities toward liver X receptor α and β , farnesoid X receptor, pregnane X receptor (PXR) and retinoic acid receptor-related orphan receptor (ROR) γ , silanol **6** exhibited activity only toward PXR and RORs. Incorporation of silanol instead of perfluoroalcohol is a promising option for developing novel target-selective, biologically active compounds.

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The alcoholic hydroxy group is one of the most important functional groups in biologically active compounds.¹ It can be involved in hydrogen bonding and other polar contacts, functions as a nucleophilic reactive species, and markedly influences the absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles of compounds. Physicochemical properties such as the acidity of the hydroxy group and the hydrophobicity of a neighboring group also affect the biological activity. For example, in nuclear receptor ligands such as vitamin D receptor (VDR) ligands,^{2,3} liver X receptor (LXR) ligands and pregnane X receptor (PXR) ligands,⁴ modification of the acidity or hydrophobicity of the tertiary alcohol therein significantly affects the biological activities. Therefore, the use of novel substitutes for the alcoholic hydroxy group is a promising approach for structural development of drug candidates.

One possible approach for exploiting novel isosteric structures of alcoholic hydroxy groups is utilization of heteroatom functionalities. In the case of acidic carboxy groups, application of several heteroatom-hydroxy functionalities, such as sulfonic acid, phosphonic acid, hydroxamic acid and boronic acid, has been intensively investigated in the field of medicinal chemistry.^{1,5} Regarding development of alternatives to the alcoholic hydroxy group, incorporation of heteroatoms is also useful, and silanol has potential as an isosteric substructure of alcoholic hydroxy

groups.^{6–8} The silicon atom is isoelectronic with carbon, and therefore various silicon/carbon exchanges (sila-substitutions) of biologically active compounds have been investigated, particularly for optimization of hydrophobic moieties.^{9–16} There have also been some studies on the use of silanol as a hydrophilic structure. A representative example is a series of silanediol-based protease inhibitors, such as **1** and **2**.^{17–19} Silanediols in these compounds function as mimics of the transition state in substrate hydrolysis. Another example is provided by cyclic silanol derivatives including sila-venlafaxine (**3**) and sila-haloperidol (**4**) (Fig. 1).^{20–22} In the case

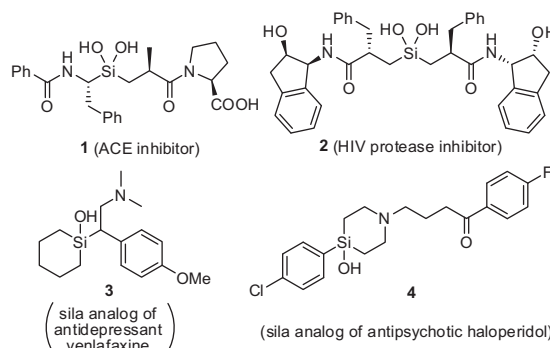


Figure 1. Examples of silanol-based biologically active compounds.

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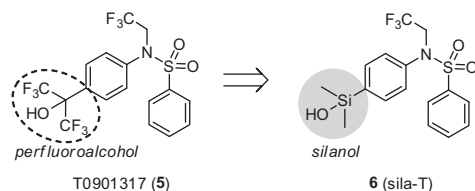


Figure 2. Design scheme of the silanol analog of T0901317 (sila-T; **6**).

of sila-haloperidol, dehydration to afford the toxic pyridinium metabolite is blocked, because the Si=C double bond is intrinsically thermodynamically instable.²¹ Although other examples have also been reported, utilization of silanol in medicinal chemistry is still quite limited compared to other hydrophobic substructures.

To expand the utility of silanols, we focused on the similarity between silanol and perfluoroalcohol. Perfluoroalcohols show higher acidity and hydrophobicity than the corresponding hydrocarbon-based alcohols, owing to the differences of electronegativity and molecular volume between alkyl groups and the corresponding perfluoroalkyl groups. Silanols also show somewhat higher acidity and hydrophobicity than the corresponding alcohols because of the differences of electronic properties and molecular volume between silanols and the corresponding alcohols.²³ The 1,1,1,3,3,3-hexafluoro-2-hydroxypropyl group, one of the perfluoroalcoholic functionalities, is a key structural motif of T0901317 (**5**), which is a benzenesulfonamide-based compound that exhibits agonistic activity toward multiple nuclear receptors, including LXR α and LXR β ,²⁴ PXR (also SXR; steroid and xenobiotic receptor),^{4,25} farnesoid X receptor (FXR),²⁶ and inverse agonistic activity toward retinoic acid receptor-related orphan receptors (RORs).²⁷ Previous researches revealed that the substituents around the hydroxy group have a significant influence on the activity and selectivity.^{4,28} So, we planned to investigate the activity profile of silanol **6** (named sila-T), a silanol analog of perfluoroalcohol-based T0901317 (**5**) (Fig. 2).

Scheme 1 shows the synthesis of the designed silanol derivative **6**. Sulfonamide formation using 4-bromoaniline (**7**) and benzenesulfonyl chloride gave sulfonamide **8**, and then N-alkylation with 2,2,2-trifluoroethyl triflate afforded compound **9**. The bromo group of **9** was converted to dimethylsilanol using Denmark's conditions,²⁹ namely, in the presence of PdCl₂ and 2-(di-*tert*-butylphosphino) biphenyl (BPTBP), compound **9** reacted with 1,2-diethoxy-1,1,2,2-tetramethyldisilane to afford a ethoxydimethylsilyl derivative as an intermediate, and then removal of the ethyl group gave the desired silanol **6** (Scheme 1).

In order to investigate the structure-activity relationship, the corresponding alcohol derivative **13** was also synthesized as shown in Scheme 2. Reaction with ethyl 4-aminobenzoate (**10**) and benzenesulfonyl chloride gave sulfonamide **11**, which was N-alkylated to afford compound **12**. Treatment of compound **12** with methylmagnesium bromide gave the desired alcohol **13** (Scheme 2).

We next investigated the physicochemical properties of the synthesized compounds and parent T0901317 (**5**). Hydrophobicity was determined in terms of the octanol–water partition coefficient

Table 1

Determined and calculated physicochemical properties of compounds **5**, **6** and **13**

| | 5 | 6 | 13 |
|--|----------|----------|-----------|
| Log $P_{o/w}$ ^a | 5.38 | 4.23 | 3.70 |
| Partial volume (PhXR ₂ OH) (Å ³) ^b | 170.7 | 154.4 | 141.3 |
| pK _a ^c | 7.5 | 12.5 | 14.6 |

^a Determined by HPLC method.³⁰

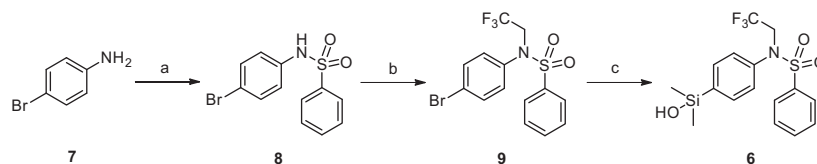
^b Calculated by MOPAC software (methods: PM3 EF).³¹

^c Estimated by ACD/Chemsketch software.³²

($P_{o/w}$), using an HPLC method.³⁰ Silanol **6** exhibited a log $P_{o/w}$ value of 4.23, which is larger than that of corresponding alcohol **13** (log $P_{o/w}$; 3.70). Previous results indicated that C/Si-exchange of alkylsilanes increases the hydrophobicity of the compounds by 0.5–0.7 in log $P_{o/w}$ value,¹⁶ and the present result suggests that this is also the case with silanols. Compound **5** exhibited a log $P_{o/w}$ value of 5.38, significantly larger than that of corresponding alcohol **13**, and the hydrophobicity of silanol is intermediate between those of the alcohol and perfluoroalcohol. The difference of hydrophobicity can be mainly attributed to the difference of molecular volume, and the calculated values of partial volume of the compounds (PhXR₂OH) are consistent with the order of hydrophobicity. The acidity of the compounds was also calculated. The estimated pK_a value of compound **6** (12.5) is smaller than that of alcohol **13** (14.6), while both values are considerably larger than that of compound **5** (7.5). Though the acidity of silanols may be larger than that of corresponding alcohols, it is considerably smaller than that of perfluoroalcohols (Table 1).

Next, the ligand potencies of the compounds toward hLXR α , hLXR β , hFXR, hPXR (SXR), and hROR α , β and γ were evaluated by means of luciferase reporter gene assay in HEK293 cells. Compound **5** exhibited significant agonistic activity toward LXR α and β , FXR and PXR, and inverse agonistic activity toward ROR γ .³³ On the other hand, compound **13** bearing a hydrocarbon-based alcohol instead of the perfluoroalcohol moiety of **5** exhibited no significant activity toward any of these nuclear receptors. These results indicate that high hydrophobicity and/or potent acidity of compound **5** is essential for biological activity toward these nuclear receptors. As for the silanol derivative **6**, it exhibited neither agonistic nor antagonistic activity toward LXRs, and showed only modest partial agonistic activity toward FXR. In contrast to the case of LXRs and FXR, compound **6** exhibited inverse agonistic activity toward RORs. In addition, silanol **6** exhibited significant agonistic activity toward PXR. The PXR agonistic activity of silanol **6** is comparable to that of representative PXR agonist rifampicin (EC₅₀ value for PXR; 1.1 μ M, maximum efficacy is 75% compared to **5** in the same assay system). This result suggests that the silanol group could function as an isoster of the perfluoroalkyl group in the case of PXR ligands. The silanol functionality may be a useful option for development of other target-selective bioactive compounds (Table 2).

X-Ray crystal structures of compound **5** complexed with hLXR α ,³⁴ hLXR β ,³⁵ hPXR⁴ and hROR γ ²⁸ have been reported, and we conducted docking simulations using the crystal structures.³⁶ In the co-crystal structures with ROR γ , the hexafluorohydroxypropyl group of compound **5** does not form a hydrogen bond to



Scheme 1. Synthesis of silanol derivative **6** (sila-T). Reagents and conditions: (a) benzenesulfonyl chloride, pyridine, THF, rt, 93%; (b) NaH, CF₃CH₂OTf, DMF, 80 °C, 68%; (c) (i) PdCl₂, BPTBP, *i*-Pr₂EtN, (Me₂SiOEt)₂, NMP, 60 °C; (ii) AcOH, MeCN, Me₂N(CH₂)₂SH-HCl, 26%.

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