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Development of subtype-selective estrogen receptor modulators using the bis(4-hydroxyphenyl)silanol core as a stable isostere of bis(4-hydroxyphenyl)methanol†

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In this study, we synthesized and evaluated silanol-based bisphenol derivatives as stable isosteres of bis(4-hydroxyphenyl)methanol. The developed silanols exhibited estrogen receptor (ER)-modulating activity. Among them, bis(4-hydroxyphenyl)(methyl)silanol (**5a**) showed a characteristic ER subtype selectivity, namely, antagonistic activity toward ERα and agonistic activity toward ERβ. Docking simulation indicated that the silanol moiety plays a key role in this selectivity. Our results suggest that silanol-based bisphenols offer a unique scaffold for biologically active compounds.

1 Introduction

Silanols are widely used in various fields, including materials chemistry and synthetic chemistry.[1] For example, they undergo cross-coupling reactions and are key components of various silicone materials and ceramics.[2] In the field of biologically active compounds, silanols have been utilized in place of alcohols,[3] since they are more acidic and hydrophobic than the corresponding alcohols, and therefore have distinct profiles of biological activity. We have developed silanol derivatives such as **1** with unique target selectivity.[4] In addition, Tacke and coworkers have developed sila-haloperidol (**2**) and related silicon analogs of dopamine receptor antagonists in order to avoid the formation of neurotoxic metabolites, which are generated by elimination of water during the metabolism of the parent carbon analogs (Fig. 1A).[5] We considered that silanols might be more widely applicable, and here we report the development and biological evaluation of silanol-based bisphenol derivatives as candidate estrogen receptor (ER) ligands.

2 Results and discussion

2.1 Molecular design

Bis(4-hydroxyphenyl)methanol (**3**) is a versatile scaffold of functional molecules such as fluorescein.[6] However, bis(4-hydroxyphenyl)methanols, especially in case of aliphatic substituents (R = alkyl), are readily converted to electrophilic quinone methides (**4**) by elimination of water, and therefore are not available as biologically active compounds (Fig. 1B). On the other hand, bisphenol is a promising core structure of biologically active compounds,[7] particularly modulators of nuclear estrogen receptors (ERs).[8] The ERs are members of the nuclear receptor superfamily of ligand-dependent transcription factors.[9]

There are two subtypes, namely ERα and ERβ,[10] which have distinct target tissue distributions and functional activities, and may have divergent roles. For example, activation of ERα results in the progression of estrogen-dependent breast cancer,

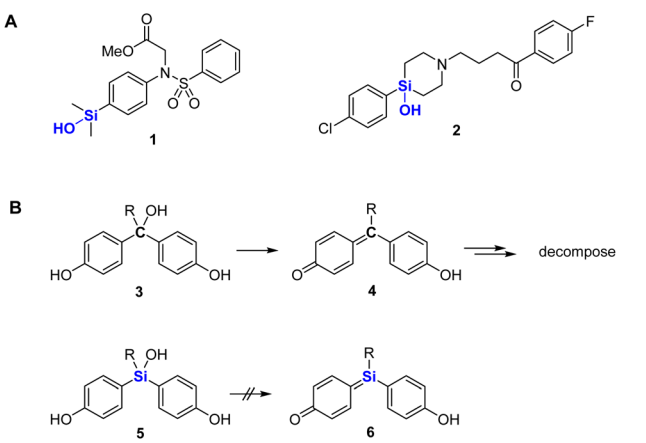

Fig. 1 (A) Structures of some silanol-based biologically active compounds. (B) Structures and properties of bis(4-hydroxyphenyl) methanols (**3**) and bis(4-hydroxyphenyl)silanols (**5**). Compounds **3** are easily converted to quinone methides **4**, whereas silanols **5** cannot generate the corresponding quinone congeners.

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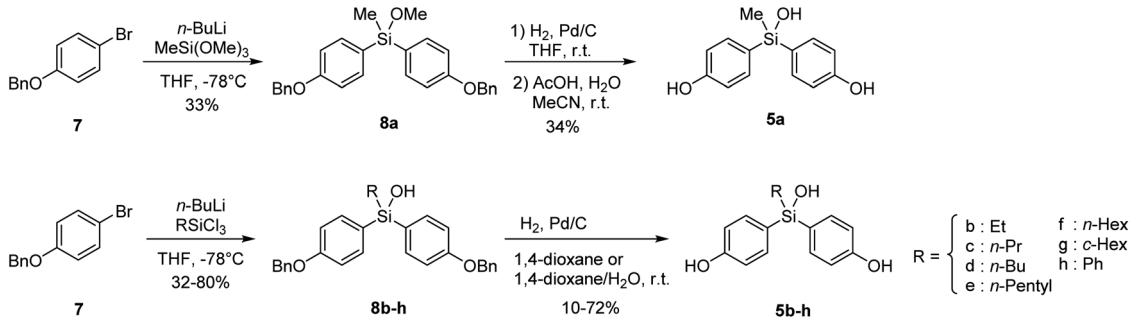
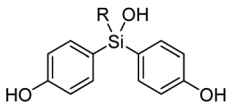


Scheme 1 Synthesis of the designed bis(4-hydroxyphenyl)silanols **5a–5h**.

Table 1 ER agonistic and antagonistic activity of silanol derivatives determined by means of luciferase reporter gene assay using HEK293 cells transiently transfected with pCX-GAL4-hER-LBD and MH100x4-tk-LUC vectors. Data are presented as mean ± SD



		ERα		ERβ	
Compd	R	EC_{50}[a] (μM)	IC_{50}[b] (μM)	EC_{50}[a] (μM)	IC_{50}[b] (μM)
5a	Me	NA	9.85 ± 1.71	3.35 ± 0.74	NA
5b	Et	(28 ± 7%)[c]	(40 ± 10%)[d]	7.87 ± 2.36	NA
5c	*n*-Pr	(19 ± 5%)[c]	11.2 ± 2.57	(30 ± 4%)[c]	(17% ± 15)[d]
5d	*n*-Bu	NA	9.63 ± 2.78	NA	21.5 ± 33
5e	*n*-Pen	NA	10.0 ± 4.93	NA	3.62 ± 3.5
5f	*n*-Hex	NA	6.09 ± 1.86	NA	4.80 ± 3.85
5g	*c*-Hex	NA	10.5 ± 5.56	NA	0.59 ± 0.31
5h	Ph	NA	(27 ± 6%)[d]	NA	22.2 ± 16.1

[a] Concentration showing 50% of the maximal activity of E2. [b] Concentration inhibiting the activity of 0.3 nM E2 by 50%. [c] Percentage of the maximal activation of E2 at 30 μM. [d] Percent inhibition at 30 μM. NA: no activity.

whereas ERβ inhibits proliferation and invasion of breast cancer cells. Thus, the development of subtype-selective ER modulators is an attractive approach for anticancer drug discovery.[11] Bisphenol derivatives function as modulators of ERs, and the substituents on the central carbon atom of bisphenols greatly influence their ER subtype selectivity.[8] Therefore, introduction of a hydroxyl group on the bisphenol core structure is a reasonable approach to develop novel subtype-selective ER modulators. However, since bis(4-hydroxyphenyl)methanols (**3**) are insufficiently stable, we aimed to synthesize bis(4-hydroxyphenyl)silanols (**5**) as more stable isosteres of bis(4-hydroxyphenyl)methanols (**3**), and to investigate their potency as ER modulators.

2.2 Synthesis

Synthesis of the designed bis(4-hydroxyphenyl)silanols **5a–5h** is summarized in Scheme 1. From 4-benzyloxybromobenzene (**7**) as the starting material, lithiation and arylation with trimethoxymethylsilane gave methoxysilane **8a**, and removal of the benzyl groups and methyl group afforded the desired silanol **5a**. Silanol derivatives **5b–5h** were synthesized similarly, using alkyltrichlorosilane instead of trimethoxysilane. Namely, lithiation of **7** and arylation with alkyltrichlorosilane gave the corresponding silanols **8b–8h**, and removal of the benzyl groups afforded the desired silanols **5b–5h**, respectively (Scheme 1).

2.3 ER modulating activity

The ER-modulating activities of the synthesized bis(4-hydroxyphenyl)silanol derivatives were evaluated by means of luciferase reporter gene assay using HEK293 cells, and the results are summarized in Table 1. Agonistic activities toward each ER subtype were assessed in terms of the increase in luciferase activity and are shown as 50% effective concentration (EC_{50}). Antagonistic activities were assessed in terms of the decrease in the luciferase activity induced by 0.3 nM estradiol (E2) and are shown as 50% inhibitory concentration (IC_{50}). All the synthesized compounds exhibited ER-modulating potency, and compounds **5d–5g** bearing a large aliphatic substituent at the silicon atom exhibited significant antagonistic activity toward both ERα and ERβ. Compound **5h** bearing a phenyl group showed moderate antagonistic activity. Decrease in the bulkiness of the substituent, interestingly, had different effects on the two subtypes. The methyl (**5a**) and propyl (**5c**) derivatives exhibited antagonistic activity towards ERα with potency similar to those of **5d–5g**. On the other hand, propyl derivative **5c** exhibited weak antagonistic activity and partial agonistic activity towards ERβ. Methyl (**5a**) and ethyl (**5b**) derivatives did not exhibit ERβ-antagonistic activity, but showed ERβ-agonistic activity. Thus, the methyl derivative **5a** serves as a unique ER subtype-selective modulator, *i.e.*, an antagonist toward ERα and a full agonist toward ERβ (Fig. 2). Although the activity of **5a** was weaker than the developed ER modulators, the unique subtype selectivity profile of **5a** is interesting and suggestive for development of novel ER modulators.

2.4 Docking simulation

In order to understand the subtype-selective activity of silanol **5a**, docking simulation using the crystal structures of human ERα (PDB ID: 3ERT)[12] and ERβ (PDB-ID: 3OLS)[13] was performed (Fig. 3 and 4). The homology of the ligand-binding domains of

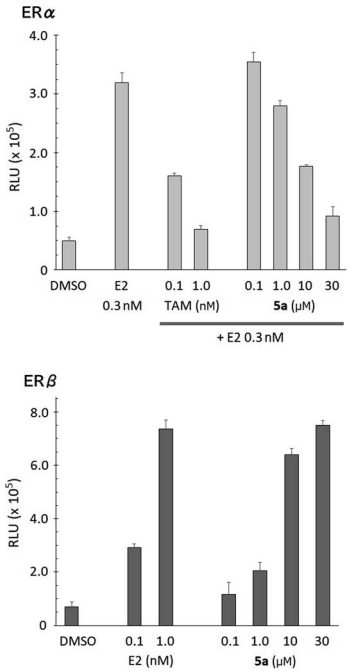


Fig. 2 Dose–response relationship of **5a** in reporter gene assay using HEK293 cells. Compound **5a** induced transcription of ERβ, but suppressed the transcription of ERα induced by E2. Data are presented as mean ± SD. TAM: tamoxifen.

the two ER subtypes is very high, and only two residues in the ligand-binding pocket are different, namely, Leu (Leu384) and Met (Met421) in ERα are replaced by Met (Met336) and Ile (Ile373) in ERβ, respectively. Therefore, we postulated that the interaction with these residues would be the key to the subtype-selective action of **5a**. In the case of ERα, one of the phenolic hydroxyl groups of **5a** interacts with Glu353 and Arg394, which form hydrogen-bonds with the 3-OH group of estradiol. The OH group of silanol is located near Met421. Although the hydrogen bonding between His524 and a ligand is important for ERα agonistic activity, **5a** did not interact with His524 in the calculated structure (Fig. 3 left). On the other hand, in the docked structure with ERβ, compound **5a** forms hydrogen bonds with Glu305 and Arg346, which correspond to Glu353 and Arg394 in ERα, respectively, as well as with His475, which corresponds to His524 in ERα. The OH group of silanol is also located near Met336 (Fig. 4 left). Thus, compound **5a** can form suitable hydrogen bonds for agonistic activity with ERβ. These results suggests that the silanol moiety of **5a** plays a key role in recognizing the structural difference between ERα and ERβ, and the loss of hydrogen bonding with His524 results in the ERα-antagonistic activity of **5a**.

We also performed docking simulation of *n*-hexyl derivative **5f** which acted as an antagonist towards both ERα and ERβ. In the docked structure with ERα, the bisphenol core of compound **5f** takes a similar conformation to that of **5a**, in which the OH group of silanol is located near Met421, and the *n*-hexyl group occupies the hydrophobic cavity (Fig. 3 center). In the docked structure with ERβ, on the other hand, the conformation of compound **5f** is quite different from that of **5a**. One phenolic OH group of **5f** interacts with Glu305 and Arg346, but there is no interaction with His475, and the *n*-hexyl group occupies the cavity that is occupied by the phenol group of **5a** (Fig. 4 center). This calculated structure of **5f** in ERβ is similar to that in ERα, which may explain why the silanol derivatives **5d–5h** bearing a bulky substituent function as antagonists toward both ERα and ERβ. These results suggests that the loss of hydrogen bonding with His524 is responsible for the ERα-antagonistic activity of **5a**.

We performed docking simulation of imaginary methyl and hexyl carbinol analogs with hERα LBD. These carbon analogs adopt conformation similar to the corresponding silanols **5a** and **5f**, respectively (Fig. S1†). However, these carbon analogs are inherently unstable. Thus, the silanol moiety plays a key role in realization of the characteristic activity.

3 Conclusions

In order to expand the utility of silicon-based molecular construction in medicinal chemistry, we designed and synthesized a series of silanol-based bisphenol derivatives as stable isosteres of bis(4-hydroxyphenyl)methanol derivatives, which readily undergo dehydration to form electrophilic quinone methide species. The synthesized silanol derivatives served as ligands of ERα and ERβ, and methyl silanol **5a** exhibited a unique subtype selectivity profile, namely, antagonist activity toward ERα and agonist activity toward ERβ. Docking simulation suggested that the interaction of the silanol moiety with methionine (Met421 in ERα or Met336 in ERβ) and hydrophobic

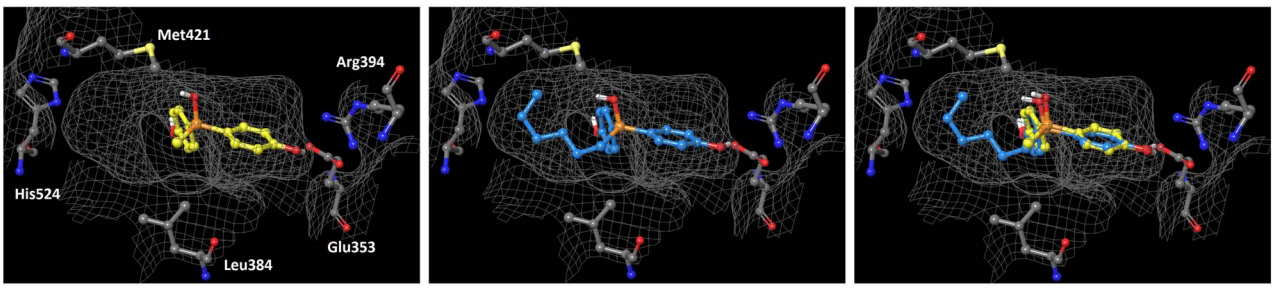


Fig. 3 Docking models of silanol **5a** and **5f** with hERα LBD (PDB ID: 3ERT) obtained with AutoDock 4.2.[14] The protein surface is indicated as a grey mesh. (Left) Docking model of **5a** (yellow) in the hERα LBD. (Center) Docking model of **5f** (cyan) in the hERα LBD. (Right) Superimposition of the docking models of **5a** and **5f**.

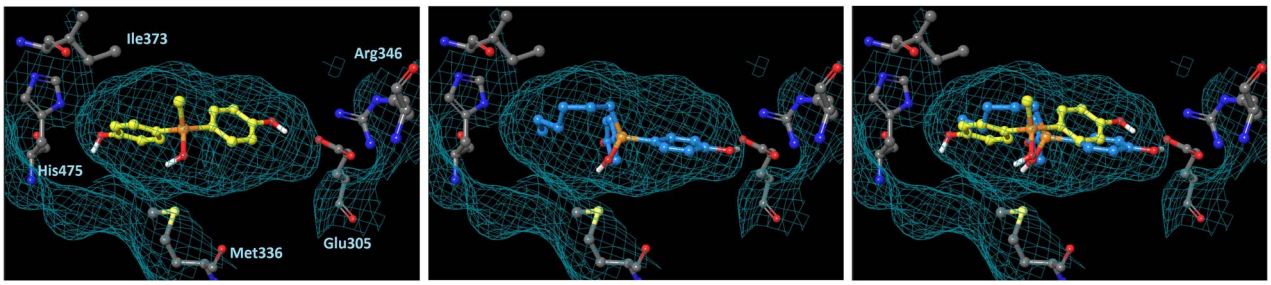


Fig. 4 Docking models of silanol **5a** and **5f** with hERβ LBD (PDB ID: 3OLS) obtained with AutoDock 4.2. The protein surface is indicated as a blue mesh. (Left) Docking model of **5a** (yellow) in the hERβ LBD. (Center) Docking model of **5f** (cyan) in the hERβ LBD. (Right) Superimposition of the docking models of **5a** and **5f**.

interaction of the alkyl substituent are key factors. Since both antagonistic activity toward ERα and agonistic activity toward ERβ are desirable for anticancer activity,[11] the compounds developed in this study may be promising lead compounds for cancer drug discovery.

4 Experimental

The detailed procedures for synthesis of compounds, biological evaluation and docking simulation is given in the ESI file.†

Conflicts of interest

There are no conflicts to declare.

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