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Synthesis and structure–activity relationships of 1-benzylindane derivatives as selective agonists for estrogen receptor beta

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ABSTRACT

The estrogen receptor beta (ERβ) selective agonist is considered a promising candidate for the treatment of estrogen deficiency symptoms in ERβ-expressing tissues, without the risk of breast cancer, and multiple classes of compounds have been reported as ERβ selective agonists. Among them, 6-6 bicyclic ring-containing structures (e.g., isoflavone phytoestrogens) are regarded as one of the cyclized analogues of isobutestrol **5b**, and suggest that other cyclized scaffolds comprising 5-6 bicyclic rings could also act as selective ERβ ligands. In this study, we evaluated the selective ERβ agonistic activity of 1-(4-hydroxybenzyl)indan-5-ol **7a** and studied structure–activity relationship (SAR) of its derivatives. Some functional groups improved the properties of **7a**; introduction of a nitrile group on the indane-1-position resulted in higher selectivity for ERβ (**12a**), and further substitution with a fluoro or a methyl group to the pendant phenyl ring was also preferable (**12b**, **d**, and **e**). Subsequent chiral resolution of **12a** identified that *R*-**12a** has a superior profile over *S*-**12a**. This is comparable to diarylpropionitrile (DPN) **5c**, one of the promising selective ERβ agonists and indicates that this indane-based scaffold has the potential to provide better ERβ agonistic probes.

1. Introduction

Estrogens play a crucial role in the development, maintenance, and functioning of the reproductive system and nonreproductive tissues such as cardiovascular, musculoskeletal, immune, and central nervous systems in both males and females.[1,2] While estrogens can be beneficial for health, the proliferative effect of estrogens may increase the risk of cancer in the breast and uterus.[3,4] Hormone replacement therapy (HRT) reduces many symptoms such as hot flashes, sweating, and bone loss in postmenopausal women; however, long-term use of estrogens increases the risk of breast cancer.[5,6]

The multiple actions of estrogens are exerted through two estrogen receptors, ERα[7,8] and ERβ,[9,10] which have different patterns of tissue distribution and biological regulation.[11] The ERα, expressed at high levels in the uterus and breast is now considered to involve a proliferative effect and can bring about malignant growth in these tissues, whereas ERβ has an antiproliferative effect on breast cancer cells.[12,13] Thus, an ERβ selective ligand is considered to exert beneficial effects on ERβ-expressing tissues, such as the prostate, colon, and brain, without the risk of breast cancer.[14,15]

Although ERα and ERβ share less than 60% sequence homology in the ligand-binding domain (LBD), the ligand-binding pockets (LBPs) of the two isoforms have a difference of only two amino acids; Leu384 and Met421 in ERα are substituted with Met336 and Ile373 in ERβ, respectively.[16] In fact, 17β-estradiol (**E2**, an endogenous estrogen) binds to both ERs without selectivity.

To date, multiple classes of compounds have been reported as ERβ selective agonists.[17,18] Among them, 1,2-bis(4-hydroxyphenyl)ethane **5a** is one of the common templates for ER ligands, and the exact motif or its oxygen-containing analogues are incorporated into many scaffolds (Fig. 1). The representative phytoestrogen genistein **2a**,[19] daidzein enteric metabolite *S*-equol **2b**,[20] and synthetic ligands ERB-041 **3a**,[21] WAY-292 **3b**,[21] and SERBA-1 **4**,[22] are relatively rigid molecules comprising fused-ring frameworks. On the other hand, ERβ ligands with more structural flexibility, such as bibenzyl-diol derivatives **5a**–**c**, are also known. Diarylpropionitrile (DPN) **5c** is an attractive ligand with a 72-fold binding selectivity relative to **E2**,[23] and isobutestrol **5b** with a nonpolar ethyl group instead of the cyano group in DPN **5c** also exerts an 18-fold relative binding selectivity for ERβ.[24]

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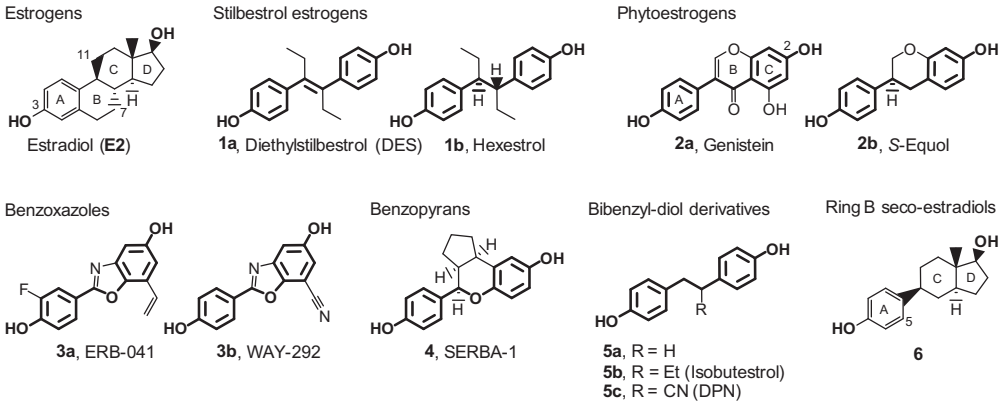


Figure 1. Estradiol and ERβ ligands.

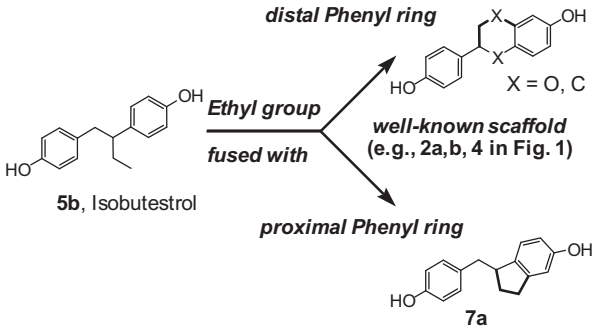


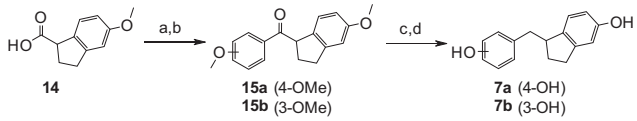
Figure 2. Compounds of interest.

As illustrated in Figure 2, the cyclized scaffold of **5b** fused between the ethyl group and the distal phenyl ring provides well-known ERβ selective ligands with a 6-6 bicyclic ring (e.g., compounds **2a**, **2b**, and **4**). Fusing the ethyl group of **5b** to the proximal phenyl ring affords a 1-benzylindane framework, and it is also expected to be a promising scaffold as ERβ selective ligand; however, little is known about the estrogenic actions of such compounds. In a previous report, 1-(4-hydroxybenzyl)indan-5-ol **7a** with a 5-6 bicyclic ring may have exhibited antigonadotropic activity and a weak estrogenic effect;[25] however, the actions for ERs and ERβ selectivity remain unidentified. Therefore, we were intrigued by the possibility of a 1-benzylindane scaffold as novel ERβ selective ligands, and investigated whether **7a** and its derivatives have selective ERβ agonistic activity.

Herein, we report that **7a** is an attractive template for ERβ selective agonists and disclose the SARs of the 1-benzylindane derivatives, some of which have excellent agonistic activities and high selectivities for ERβ in terms of binding affinities and transcriptional activities.

2. Chemistry

The synthesis of racemic compounds evaluated in this article is illustrated in Schemes 1–6. Hydroxy-substituted indane derivatives and ring-expanded analogues bearing benzyl groups were prepared from carboxylic acid **14** or ketones **16c**,**d**, **17**, and **18**. Compounds **7a**,**b** were obtained by reduction of the carbonyl group with Et_3SiH and subsequent demethylation of the methoxy groups by BBr_3 for the benzoyl derivatives **15a**,**b**, prepared by addition of the corresponding phenyl Grignard reagents to the Weinreb amide obtained from **14** (Scheme 1). When using ketones as starting materials, catalytic hydrogenation of the benzylic hydroxy groups



Scheme 1. Reagents and conditions: (a) MeONHMe·HCl, EDCI·HCl, HOBt·H_2O, Et_3N, CH_2Cl_2, 0 °C to rt; (b) 4-(or 3-)MeO–PhMgBr, THF, 0 °C to rt; (c) Et_3SiH, TFA, 0 °C to rt; (d) BBr_3, CH_2Cl_2, −78 °C to rt.

generated by addition of benzyl Grignard reagent, followed by demethylation, afforded compounds **7c**,**d**, **8**, and **9** (Scheme 2).

Using the above intermediate **15a**, the ethyl-substituted derivative **10** was obtained via Wittig olefination and catalytic hydrogenation of the double bond, followed by demethylation (Scheme 3).

The synthesis of 1-alkylated-1-benzylindane derivatives **11a**–**d** was achieved by alkylation of cyanide **23** with alkyl iodides in the presence of NaH and subsequent conversion of the nitrile groups into 4-methoxybenzyl groups before demethylation. The nitrile groups of the alkylated intermediates were reduced into aldehydes **24a**–**d** using DIBAL-H and then reacted with lithiated anisole, followed by removal of the resulting hydroxy group as described above (Scheme 4).

The 1-cyano derivatives **12a**–**g** were more easily prepared by introduction of various benzyl groups onto the nitrile-substituted carbon under modified conditions of the above alkylation and subsequent demethylation (Scheme 5).

Homologation of the aldehyde obtained by reduction of the above intermediate **27a** was achieved by acidic hydrolysis of the methyl enol ether prepared by the Wittig reaction, and conversion of the formyl group into a nitrile group by heating with hydroxylamine hydrochloride, followed by demethylation of the 1-cyanomethyl product **29**, afforded compound **13** (Scheme 6).

Preparations of each enantiomer of the key compounds **7a** and **12a** are described in Schemes 7 and 8. In the synthesis of the 1-unsubstituted-1-benzylindane enantiomers *S*-**7a** and *R*-**7a**, the corresponding chiral benzoyl intermediates *R*-**15a** and *S*-**15a** were prepared, respectively. Chiral resolution was achieved by flash column chromatography on silica gel of the diastereomixture of chiral oxazolidinone derivatives *R*,*R*-**30** and *R*,*S*-**30**, obtained by acylation of the oxazolidinone nitrogen with the acid chloride of **14** using *n*-BuLi as a base. In each separated diastereomer, the other isomer was not detected by NMR spectroscopy. After removal of the chiral auxiliary using lithium hydrogen peroxide, *S*-**7a** and *R*-**7a** were synthesized in a manner similar to that of racemate **7a**. The optical purity of each enantiomer was confirmed to be >98% ee by high performance liquid chromatography (HPLC) analysis (Scheme 7).