Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 16 (2006) 3943–3946
Bioorganic & Medicinal Chemistry Letters

m-Carborane bisphenol structure as a pharmacophore for selective estrogen receptor modulators

Takumi Ogawa,[a] Kiminori Ohta,[a] Tomohiro Yoshimi,[a] Hiroto Yamazaki,[a] Tomoharu Suzuki,[b] Shigeru Ohta[b] and Yasuyuki Endo[a,*]

[a]*Faculty of Pharmaceutical Sciences, Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan*
[b]*Graduate School of Medical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan*

Received 7 April 2006; revised 2 May 2006; accepted 8 May 2006
Available online 2 June 2006

Abstract—A series of *m*-carborane derivatives was prepared based upon the structures of antiestrogenic drugs and their activities were evaluated by estrogen receptor alpha (ERα) binding assay and transactivation assay using human breast cancer cell line, MCF-7 cells. The *m*-carborane bisphenol **5** exhibited about a thousand times more potent ER agonistic activity than the *o*-carborane bisphenol **11**. The *m*-carborane bisphenol structure appears to be a favorable hydrophobic pharmacophore for the development of novel selective estrogen receptor modulators (SERMs).

Estradiol (E2, **1**) plays important roles in the regulation of the female and male reproductive systems, bone metabolism, and the cardiovascular system as well as the central nervous system, through binding to and activating a specific nuclear receptor, the estrogen receptor (ER).[1] ER is activated by ligand binding to form large complexes with various cofactors, followed by gene transcription through binding to target enhancer of DNA.[1] Differences of distribution and function of cofactors among tissues seem to be connected with the tissue selectivity of certain ER ligands, which are called selective estrogen receptor modulators (SERMs).[2] SERMs can act as agonists for the bone system and as antagonists for cancers, and have been extensively studied for the treatment of reproductive disorders, estrogen-responsive cancers, and osteoporosis. The relative stability of ER-ligand–cofactors complexes, agonist form or antagonist form, in tissues seems to determine whether or not certain ER ligands can act as SERMs.[3]

Tamoxifen (**2a**), which is metabolized in vivo to an active derivative, 4-hydroxytamoxifen (**2b**), is a first-generation SERM, while raloxifen (**3**) is a second-generation SERM. However, these drugs involve a risk of cancers of the female reproductive organs. Currently, researchers are seeking to develop third- or fourth-generation SERMs to circumvent this risk.[4] For this purpose, it is important to understand the structure–activity relationships of existing SERMs. The most noteworthy substituent in these SERMs is the *N*,*N*-dialkylaminoethyl group, which inhibits the binding of coactivators by moving helix-12 to an unfavorable position.[5] (see Chart 1)

Recently, we have reported that dicarba-*closo*-dodecaboranes (carboranes) can act as a hydrophobic structure of various biologically active molecules, including

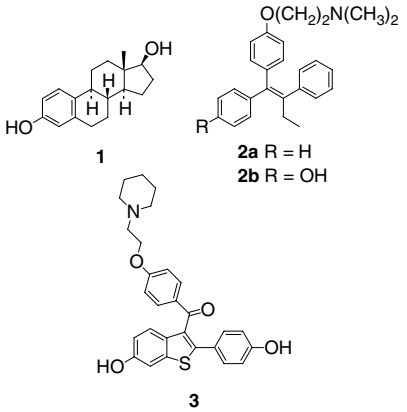


Chart 1. The structures of native ER ligand and SERMs.

Keywords: Estrogen receptor modulator; Medicinal drug design; Hydrophobic interaction; Boron cluster; Carborane.
* Corresponding author. E-mail: yendo@tohoku-pharm.ac.jp

0960-894X/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2006.05.032

ER modulators.[6] Their spherical structures and hydrophobic surface make easy for them to interact with hydrophobic residues of the ligand binding pocket of receptors.[7] We have also reported that the *m*-carborane bisphenol derivative **4** with a basic side chain, the *N*,*N*-dimethylethylamino group, acted as an ERα antagonist in luciferase reporter gene assay (Chart 2).[8] However, we did not examine in detail its activity profile, binding affinity to ERα, and agonistic activity in transcriptional assay.[8]

Therefore, we have focused on the development of SERMs with *m*-carborane bisphenol structure. We designed and synthesized *m*-carborane bisphenol derivatives **4**–**10** and *o*-carborane bisphenol **11**, which have similar geometry to *m*-carborane bisphenol (Chart 3). In this paper, we described the structure–activity relationships at ERα and the biological activities of these designed derivatives.

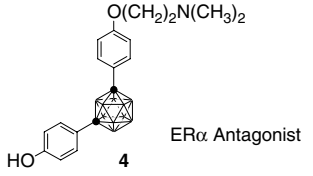


Chart 2. *m*-Carborane derivative having ER antagonistic activity.

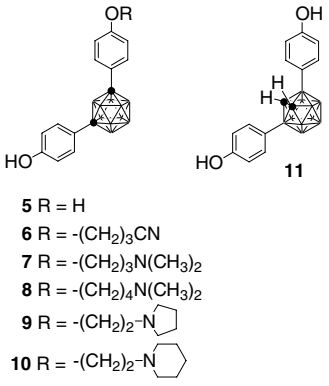
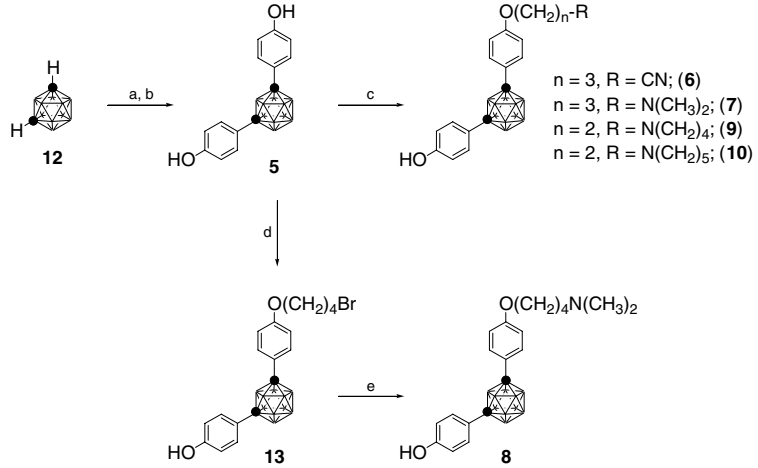


Chart 3. Designed molecules as candidate SERMs.

The designed molecules **6**–**10** were synthesized from *m*-carborane **12** as shown in Scheme 1. Compound **12** was treated with *n*-BuLi and CuCl (I), and reacted with 4-iodoanisole under Ullmann coupling conditions,[9] followed by demethylation with BBr_3 to afford a bisphenol **5** in 62% yield. Compound **5** was reacted with various alkyl halides to afford the corresponding monophenol derivatives **6**–**10** (except for **8**) in 20–30% yield.[10] Compound **8** was synthesized stepwise from **5** through the intermediate **13** in 10% yield since *N*,*N*-dimethylaminobutyl chloride did not react with **5** and was decomposed under the reaction conditions. The synthesis of the *o*-carborane bisphenol **11** is summarized in Scheme 2. Iodine atoms were introduced onto the boron atoms at the 3 and 6 positions of *o*-carborane **14** through decomposition and reconstruction of the *o*-carborane cage. The *o*-carborane cage was easily transformed into a *nido*-compound under basic conditions, and reaction with BI_3 gave 3-iodo-*o*-carborane **15** in 74% yield.[11] Compound **15** was also deboronated to afford the corresponding *nido*-compound, and the synthesis of 3,6-diiodo-*o*-carborane **16** was achieved in 52% yield under same conditions as those used for **15**.[10] Compound **16** reacted with 4-methoxyphenyl magnesium bromide under Pd-catalyzed cross-coupling conditions to afford compound **17** in 42% yield,[12] and this was easily transformed into the *o*-carborane bisphenol **11** by treatment with BBr_3 in quantitative yield.

A competitive binding assay using [6,7-^{3}H]17β-estradiol (K_d = 0.4 nM) and human recombinant ERα was employed for initial screening of the synthesized compounds.[13] Table 1 summarizes the binding affinity data. All the test compounds competed with ^{3}H-labeled E2 and bound to the ERα ligand binding pocket in a concentration-dependent manner. The binding affinities of **4** and **7**–**10**, linked with an aminoalkyl group, were



Scheme 1. Synthetic scheme of *m*-carborane derivatives **6**–**10**. Reagents: (a) *n*-BuLi, DME, then CuCl(I), 4-iodoanisole, pyridine; (b) BBr_3, CH_2Cl_2; (c) alkyl halides, K_2CO_3, acetone/DMF (1:1); (d) 1,4-dibromobutane, K_2CO_3, acetone/DMF (1:1); (e) 50% dimethylamine in water, THF.