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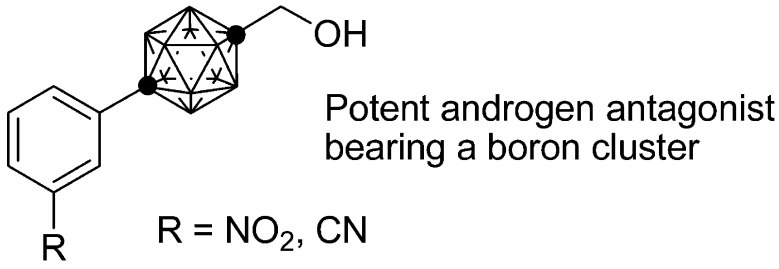

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Potent Androgen Antagonists Based on Carborane as a Hydrophobic Core Structure

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Carboranes (dicarba-*closo*-dodecaboranes) are a class of carbon-containing polyhedral boron-cluster compounds having remarkable chemical and thermal stability and hydrophobic character. These features may allow application of carboranes as a new hydrophobic core structure in biologically active molecules that interact hydrophobically with receptors. We report here the design and synthesis of novel androgen antagonists bearing carborane. The most potent compounds, the arylcarborane derivatives **6e** and **6i**, exhibited antiandrogenic activity greater than that of the well-known antiandrogen hydroxyflutamide in reporter gene assay using NIH3T3 cells transfected with a human AR expression plasmid, as well as in cell growth inhibition assay using androgen-dependent SC-3 cells. Further development of the potent carborane-containing androgen antagonists described here, having a new skeletal structure and unique characteristics, may yield novel therapeutic agents, especially selective androgen receptor modulators.

Introduction

Dicarba-*closo*-dodecaboranes (carboranes),[1] members of the class of carbon-containing boron clusters, have characteristic properties such as spherical geometry, remarkable thermal and chemical stability, and a hydrophobic molecular surface.[2] Medical applications of the carboranes have been mainly in the field of boron neutron capture therapy (BNCT) of cancer, utilizing the high boron content of the carboranes. We have investigated another approach to utilize carboranes in the field of medicinal chemistry and have demonstrated that their hydrophobic character and spherical geometry make them available as a hydrophobic core for biologically active molecules. We have developed potent estrogen agonists[3] and antagonists,[4] and retinoid agonists[5] and antagonists.[6] Our potent estrogen agonist bearing a carborane, 1-hydroxymethyl-12-(4-hydroxyphenyl)-1,12-dicarba-*closo*-dodecaborane (BE120),[4] has an activity greater than that of 17β-estradiol in luciferase reporter gene assay and in estrogen receptor α (ERα) binding assay.[4] These results suggested that the hydrophobic interaction along the spherical carborane cage produces a stronger interaction than that in the case of 17β-estradiol. The use of this new hydrophobic, spherical component, the carborane cage, for molecular drug design should make it possible to develop a wide variety of nuclear receptor ligands.

Androgen receptor (AR), a member of the nuclear receptor superfamily, plays a key role of the development and maintenance of the male reproductive system.[7] Since AR is closely related to prostate cancer, androgen antagonists are used clinically for treatment of prostate cancer.[8] Nonsteroidal agents, such as flutamide (**1**) and bicalutamide (**3**), are preferred, because the steroidal antiandrogen cyproterone acetate (**4**) induces adverse effects owing to its cross-activity at other steroid hormone receptors.[9] Recently, we have presented a new class of nonsteroidal androgen modulators, represented by **5**, which contains carborane in place of the steroidal C, D rings. This design was based on the successful results in the design of carborane-containing ER modulators. The carborane-containing androgen modulator **5** is an antagonist, with potency comparable to that of hydroxyflutamide (**2**).[10] On the basis of the above results, we have examined a new design approach to obtain more potent carborane-containing androgen antagonists.

In our previous study,[10] it was suggested that matching of the carborane structure with the hydrophobic region of the AR ligand binding pocket may account for the high binding affinity to AR, and the resulting conformation of the AR−ligand complex may not interact with cellular coregulators, exhibiting antagonistic activity. On the other hand, typical potent nonsteroidal androgen antagonists with aromatic structure, such as hydroxyflutamide (**2**) and bicalutamide (**3**), have two characteristic moieties, i.e., a benzene ring bearing an electron-withdrawing group (nitro, cyano, trifluoromethyl) and a hydroxyl group. These two polar functionalities are assumed to be the anchors for binding to AR and so are promising candidates for the hydrogen-bonding components of new carborane-containing androgen antagonists. On the basis of the above considerations, we designed putative AR antagonists **6** and

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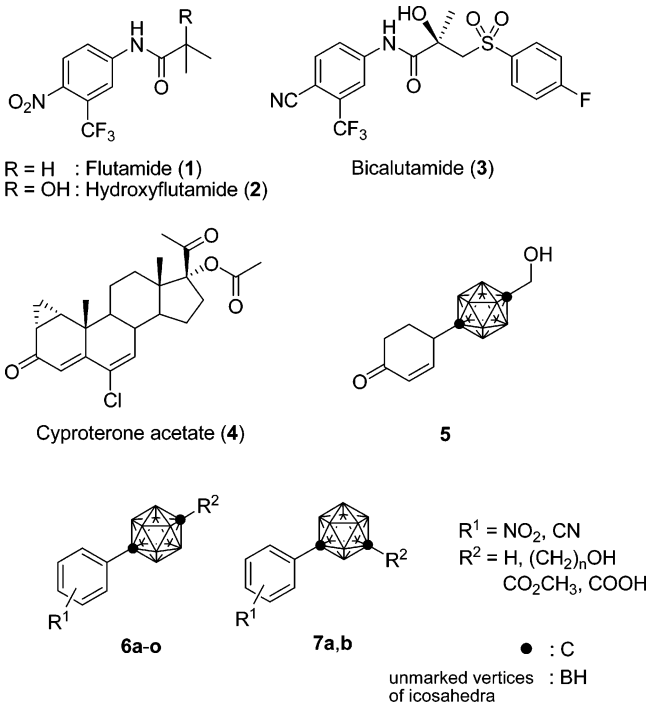
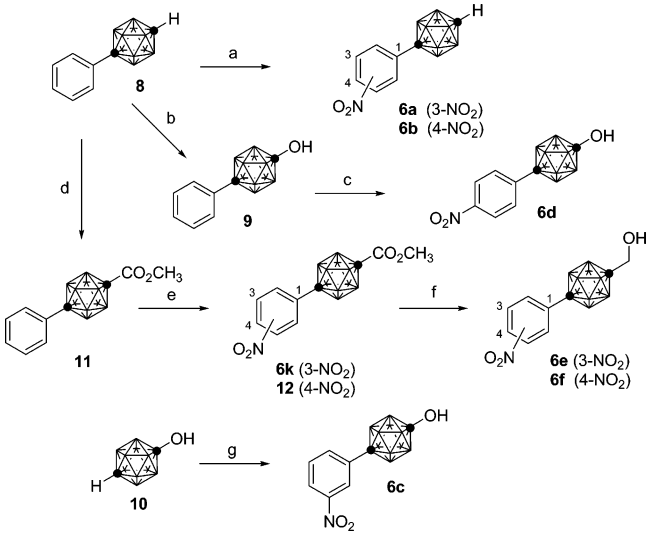


Figure 1. The structures of nonsteroidal androgen antagonists and designed molecules **6a**−**o** and **7a**,**b**.

Scheme 1. Synthesis of Nitro Compounds **6a**−**f**[a]



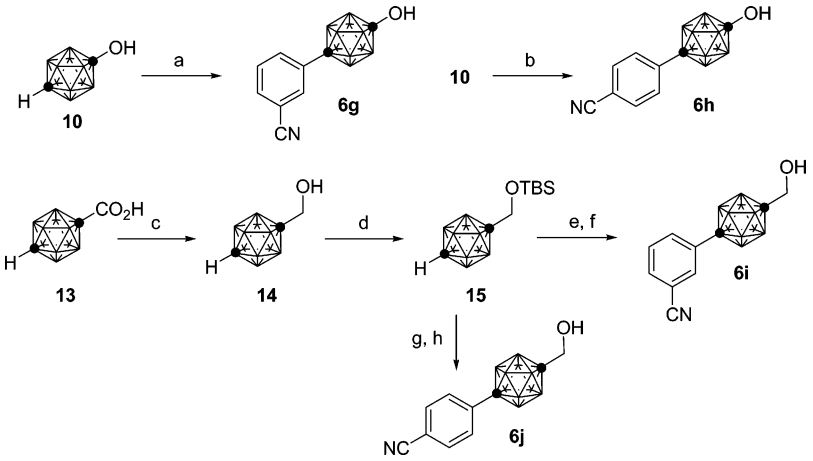
[a] (a) HNO_3,c.H_2SO_4/CH_2Cl_2, rt, 20%(**6a**), 67%(**6b**); (b) *n*-BuLi,$(PhCOO)_2$/benzene, Et_2O, rt, 50%; (c)HNO_3, c.H_2SO_4/CH_2Cl_2, rt, 63%; (d) *n*-BuLi,$ClCO_2CH_3$/Et_2O, rt, 78%; (e) HNO_3, c.H_2SO_4/CH_2Cl_2, rt, 22%(**6k**), 63%(**12**); (f) $LiBH_4$/Et_2O, reflux, quant.; (g) *n*-BuLi, CuCl, 3-NO_2-C_6H_4I, pyridine/DME, reflux, 22%.

7, in which a benzene ring with an electron-withdrawing group and a hydroxyl group are placed at the appropriate contralateral vertices of the hydrophobic carborane cage, as shown in Figure 1. In icosahedral cage structures throughout this paper, closed circles (•) represent carbon atoms and other vertices represent BH units.

Chemistry. The designed molecules with a nitro group **6a**−**f** were synthesized from 1-phenyl-1,12-dicarba-*closo*-dodecaborane (1-phenyl-*p*-carborane, **8**)[11] as shown in Scheme 1. Nitration of **8** gave a mixture of **6a** and **6b**[12] in the ratio of 1:3. Oxidation of the carborane C−H of **8** employing benzoyl peroxide[13] followed by nitration gave a mixture of nitro derivatives. The major product, *p*-nitro derivative **6d**, was isolated in 63% yield. While, the minor product, *m*-nitro derivative **6c**, was not isolated in sufficient purity. Therefore, compound **6c** was prepared by an alternative procedure. Coupling of the *C*-copper(I) derivative[14] of 1-hydroxy-*p*-carborane (**10**)[15] with 3-iodonitrobenzene gave **6c**. The compound **8** was also converted to the methoxycarbonyl derivative **11** by the reaction of the lithiated form of **8** with methyl chloroformate. Nitration of the compound **11** gave a mixture of **6k** and **12** in the ratio of 1:3. The methoxycarbonyl group of **6k** and **12** was converted to a hydroxymethyl group quantitatively by reduction with $LiBH_4$ to give **6e** and **6f**, respectively. The designed molecules with a cyano group **6g**-**6j** were synthesized by the coupling of the *C*-copper(I) form of *p*-carborane derivatives as shown in Scheme 2. The compounds **6g** and **6h** were obtained by the coupling reaction of **10** with 3-iodo or 4-iodobenzonitrile, respectively. On the other hand, the compounds **6i** and **6j** were prepared by the coupling reaction of 1-*tert*-butyldimethylsilyloxymethyl-*p*-carborane (**15**) with 3-iodo or 4-iodobenzonitrile, respectively. The compound **15** was readily prepared by reduction of commercially available *p*-carborane-1-carboxylic acid (**13**) followed by protection of the hydroxyl group by *tert*-butyldimethylsilyl (TBS) group. To investigate the relation between the activity and separation distance between aromatic nucleus and hydroxyl groups on the skeleton, we designed and synthesized compounds bearing methylene units between the carborane cage and the hydroxyl group (**6m**−**o**) as shown in Scheme 3. The compound **8** was converted to **16** by reaction of the lithiate of **8** with 2-(2-bromoethoxy)tetrahydro-2*H*-pyran followed by deprotection of the THP group with *p*-toluenesulfonic acid. After acetylation of the hydroxyl group of **16**, nitration of **17** afforded 3-nitro derivative **18** (17%) accompanying with 4-nitro derivative **19** (62%). Reductive cleavage of the acetoxy group of **19** gave the compound **6m**. The compounds **6n** and **6o** were synthesized by the coupling of the *C*-copper(I) form of *p*-carborane derivatives with 3-iodonitrobenzene. Reaction of *p*-carborane (**20**) lithiate with 2-(3-bromopropyloxy)tetrahydro-2*H*-pyran or 2-(4-bromobutyloxy)tetrahydro-2*H*-pyran followed by deprotection of the THP group with *p*-toluenesulfonic acid gave **21** and **22**. Protection of the hydroxyl group of **21** and **22** by TBS group gave **23** and **24**, respectively. Coupling of the compounds **23** and **24** with 3-iodonitrobenzene followed by deprotection of the TBS group afforded **6n** and **6o**, respectively. The compounds bearing *m*-carborane (**7a** and **7b**) were prepared by the similar procedure that in the case of **6e** and **6f**, but with 1-phenyl-*m*-carborane (**27**) as a starting material (Scheme 4).

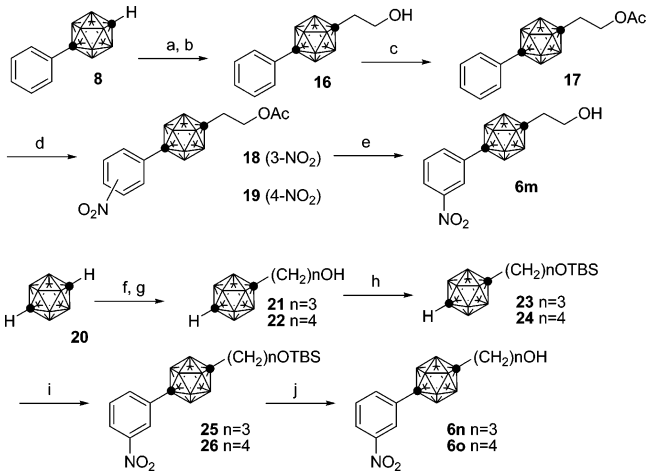
Biology. A competitive binding assay using [1,2-^{3}H]-dihydrotestosterone ([^{3}H]DHT) and hAR was employed for initial screening of the new carborane-containing molecules.[10,16] Table 1 shows the synthesized molecules and their binding activity. The values indicate the percent displacement of specific [^{3}H]DHT binding to hAR by each compound at the concentration of 10 μM.[17] Comparison of **6a** and **6b** with other molecules indicates that a polar functional group at the *C*-vertex of the carborane opposite the phenyl group was essential for binding activity. A comparison of **6e** and **6f**, or **6i** and

Scheme 2. Synthesis of Cyano Compounds **6g**−**j**[a]



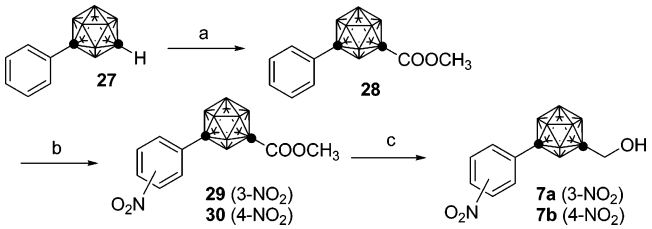
[a] (a) *n*-BuLi, CuCl, 3-CN-C_6H_4I, pyridine/DME, reflux, 34%; (b) *n*-BuLi, CuCl, 4-CN-C_6H_4I, pyridine/DME, reflux, 41%; (c) $LiAlH_4$/Et_2O, reflux, 86%; (d) TBSCl, imidazole/CH_2Cl_2, rt, 96%; (e) *n*-BuLi, CuCl, 3-CN-C_6H_4I, pyridine/DME, reflux, 22%; (f) HCl/THF,MeOH, rt, 95% (g) *n*-BuLi, CuCl, 4-CN-C_6H_4I, pyridine/DME, reflux, 36%; (h) HCl/THF, MeOH, rt, 83%.

Scheme 3. Synthesis of Nitro Compounds **6m**−**o**[a]



[a] (a) *n*-Bu-Li,Br$(CH_2)_2$OTHP/Et_2O, rt, 42%; (b) p-TsOH/MeOH, rt, 96%; (c) *n*-BuLi, AcCl/Et_2O, rt, 87%; (d) HNO_3, c.H_2SO_4/CH_2Cl_2, rt, 17%(**18**), 62%(**19**); (e) $LiBH_4$/Et_2O, rt, quant; (f) *n*-Bu-Li,Br-(CH_2)nOTHP/Et_2O, rt, 29%($n = 3$), 22%($n = 4$); (g) p-TsOH/MeOH, rt, 78% ($n = 3$, **21**), 98% ($n = 4$, **22**); (h) TBSCl, imidazole/CH_2Cl_2, rt, 93%(**23**), 85%(**24**); (i) *n*-BuLi, CuCl, 3-CN-C_6H_4I, pyridine/DME, reflux, 59%(**25**), 60%(**26**); (j) HCl/THF, MeOH, rt, 90%(**6n**), 88%(**6o**).

Scheme 4. Synthesis of Compounds with *m*-Carboranes **7a** and **7b**[a]



[a] (a) n-BuLi, $ClCO_2CH_3$/Et_2O, rt, 68%; (b) HNO_3, c.H_2SO_4/CH_2Cl_2, rt, 22%(**29**), 65%(**30**); (f) $LiBH_4$/ Et_2O, reflux, rt, 98%(**7a**), 86%(**7b**).

6j, indicated that substitution at the meta position was more suitable than at the para position for effective binding to the receptor. The *m*-carborane derivative **7a** was less potent than the corresponding *p*-carborane derivative **6e**. Compounds bearing a trifluoromethyl, methoxyl, or amino group at the meta position in place of nitro or cyano showed only weak affinity for hAR, and introducing a second substitution onto the aromatic ring reduced the binding activity of the lead molecules (data not shown). Therefore, the *m*-nitro or *m*-cyano derivative was considered a reasonable candidate for analyzing the structure−activity relationship. Table 2 shows the synthesized 3-nitrophenyl-*p*-carborane derivatives with altered substitution at the carbon atom (C12) on the carborane cage and their binding activity. The binding of the hydroxymethyl compound **6e** was strong, whereas compounds **6k** and **6l** had low binding activity; therefore, the hydroxyl group is indispensable for binding to AR. The optimal distance between the hydroxyl group and the carborane core was investigated by changing the length of the methylene chain: a distance of one methylene group was most appropriate, and a longer chain reduced the binding affinity (**6m**, **6n**, and **6o**).

To evaluate the activity of these carborane-containing compounds as transcriptional agonists and antagonists, cotransfection assay was conducted in mouse fibroblast

Table 1. Binding Affinity of Synthesized Molecules

entry	R^1[a]	R^2[a]	binding affinity[b]
6a	3-NO_2	H	36
6b	4-NO_2	H	29
6c	3-NO_2	OH	75
6d	4-NO_2	OH	53
6e	3-NO_2	CH_2OH	97
6f	4-NO_2	CH_2OH	55
6g	3-CN	OH	66
6h	4-CN	OH	50
6i	3-CN	CH_2OH	95
6j	4-CN	CH_2OH	54
7a	3-NO_2	CH_2OH	54
7b	4-NO_2	CH_2OH	60

Table 2. Binding Affinity of Synthesized Molecules Modified at C12

entry	R^1[a]	R^2[a]	binding affinity[b]
6a	3-NO_2	H	36
6c	3-NO_2	OH	75
6e	3-NO_2	CH_2OH	97
6k	3-NO_2	CO_2CH_3	18
6l	3-NO_2	CO_2H	35
6m	3-NO_2	$(CH_2)_2OH$	63
6n	3-NO_2	$(CH_2)_3OH$	39
6o	3-NO_2	$(CH_2)_4OH$	20

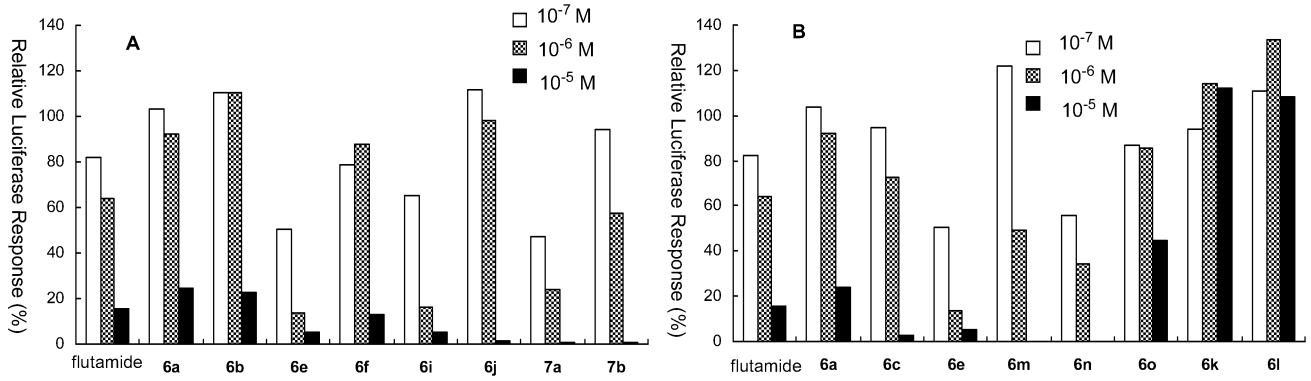


Figure 2. Inhibition of transcriptional activation of DHT by the test compounds (**6** and **7**). NIH3T3 cells were transfected with hAR expression vector, ARE/Luci (firefly Luciferase), and pRL/CMV (Renilla Luciferase) and incubated with the test compounds (10^{-7}−10^{-5} M) plus DHT(10^{-10} M)($n = 2$). Values are percentages of the transcriptional response of DHT (10^{-10} M).

NIH3T3 cells, using an expression plasmid for hAR and reporter plasmids, ARE/Luci (firefly luciferase) and pRL/CMV (*Renilla* luciferase).[18] DHT at 1×10^{-12} to 1×10^{-9} M induced the expression of luciferase in a dose-dependent manner, while none of the test compounds at 1×10^{-7} to 1×10^{-5} M induced luciferase expression. However, most of the test compounds (except for **6o**, **6k**, and **6l**) in the concentration range of 1×10^{-7}−10^{-5} M dose-dependently inhibited the activity of DHT. The results on the inhibition of transcriptional activity of 10^{-10} M DHT by the carborane-containing molecules (**6** and **7**) are summarized in Figure 2. The results of the luciferase reporter gene assay are consistent with the preliminary binding data. The most potent compounds in the binding assay, **6e** and **6i**, also showed the highest antagonistic activity in the transcriptional assay (Figure 2A). Alteration of the substituent at the carbon atom on the carborane cage (**6k** and **6l**) and of the distance between the hydroxyl group and the carborane core (**6b**, **6c**, **6e**, **6m**, **6n**, and **6o**) had similar effects on the activity in both assays (Figure 2B)

The biological activity of the most potent compounds, **6e** and **6i**, was compared with that of hydroxyflutamide (**2**), a well-known active metabolite of flutamide (**1**). Dose−response curves in the competitive binding assay using [^{3}H]DHT and hAR were also obtained for compounds **6e** and **6i**, whose affinities were approximately 10-fold higher than that of 4-hydroxyflutamide (Figure 3A). The antiandrogenic activity of the most potent compounds, **6e** and **6i**, was confirmed by growth promotion/inhibition assay using androgen-dependent SC-3 cells.[16,19] None of the compounds showed growth-promoting activity in the absence of testosterone. On the other hand, these compounds strongly inhibited testosterone-promoted cell growth of SC-3 (Figure 3B). The potency of the antagonistic activity of **6e** and **6i** was over 10-fold higher than that of hydroxyflutamide.

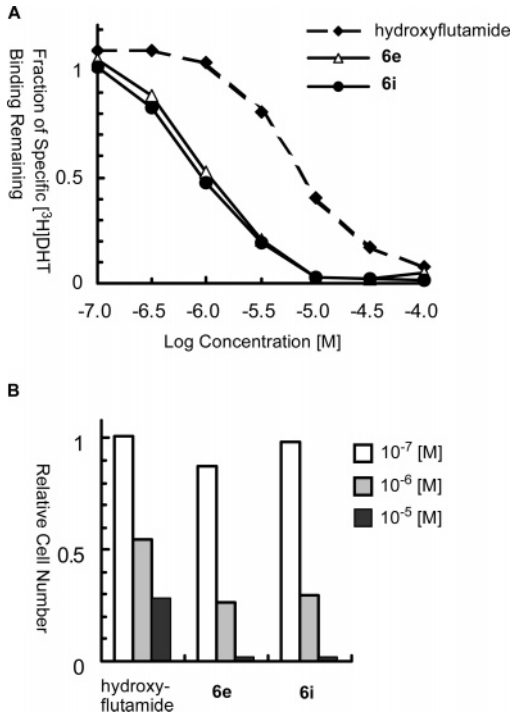


Figure 3. Biological evaluation of **6e** and **6i**. A. Competitive binding assay using hAR and [3H]DHT. ([3H]DHT: 4 nM). B. SC-3 cell growth inhibition in the presence of 10 nM testosterone. Cell number was normalized to that in the absence of testosterone.

Discussion

It is reasonable that the combination of a nitro- or cyanophenyl group and hydroxymethyl group was optimal for nonsteroidal androgen antagonist activity, in view of the reported structure−activity relationship of flutamide.[20] However, it is particularly noteworthy that the compounds bearing a carborane cage as a structural core exhibited more potent antiandrogenic activity than that of hydroxyflutamide. Many nonsteroidal AR antagonists, such as flutamide, bicalutamide, and their analogues, with a carboxamide backbone have been developed, and recently nonsteroidal AR agonists have been obtained by relatively small modifications of the AR antagonist bicalutamide.[21] However, modification of the carboxamide moiety itself has not been investigated much. The binding modes of these aromatic AR antagonists and agonists, and their interaction with cellular coregulators after the binding, have not been clarified. The novel aromatic, carborane-containing AR modulators described here should be useful tools for the analysis of AR−ligand interactions and also as scaffolds for the development of clinically useful nonsteroidal androgen antagonists.

In summary, we have developed novel carborane-containing molecules with potent antiandrogenic activity, exceeding that of hydroxyflutamide. The unique character of the carborane core may provide distinctive characteristics of distribution and metabolism in vivo.

Further structure−function studies could lead to the development of highly selective and potent androgen antagonists, which could be useful as therapeutic agents.

Experimental Section

General. Melting points were obtained on a Yanagimoto micro hot stage without correction. Elemental analyses were carried out in the Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, University of Tokyo, and were within ±0.3% of the theoretical values. ^{1}H NMR spectra were recorded on a JEOL JNM-GSX-400 spectrometer (400 MHz). Chemical shifts are reported in ppm from tetramethylsilane with tetramethylsilane as the internal standard. Data are reported as follows: chemical shift, multiplicity (*s* = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration.

1-Phenyl-1,12-dicarba-*closo*-dodecaborane (8). To a solution of *p*-carborane (5.00 g, 34.7 mmol) in 1,2-dimethoxyethane (120 mL) was added dropwise a 1.60 M solution of *n*-BuLi in *n*-hexane (22.8 mL, 36.5 mmol) at 0 °C under Ar. The mixture was stirred at room temperature for 30 min, CuCl (4.46 g, 45.1 mmol) was added in one portion, and stirring was continued at room temperature for 1 h. Pyridine (21 mL) was added, iodobenzene (7.43 g, 36.4 mmol) was further added in one portion, and the mixture was heated at 100 °C for 48 h. After cooling, the reaction mixture was diluted with diethyl ether and stirred at room temperature for 3 h. Insoluble materials were filtered off through Celite. The filtrate was washed with 2 N HCl, water, and brine, dried over sodium sulfate, and then concentrated. Purification by silica gel flash column chromatography (eluent: hexane) gave **8** (2.67 g, 35%) as a colorless solid. colorless prisms (*n*-hexane): mp 100.5−101 °C; ^{1}H NMR ($CDCl_3$) δ 7.23−7.14 (m, 5H), 2.78 (br s, 1H), 3.2−1.0 (br m, 10H); ^{13}C NMR ($CDCl_3$) δ (ppm) 59.8, 86.4, 127.0, 128.0, 128.3, 136.8; HRMS Calcd for $C_8H_{16}B_{10}$: 220.2255. Found 220.2282.

1-(3-Nitrophenyl)-1,12-dicarba-*closo*-dodecaborane (6a) and 1-(4-Nitrophenyl)-1,12-dicarba-*closo*-dodecaborane (6b). A solution of **9** (220 mg, 1.00 mmol) in dichloromethane (5.0 mL) was added to a mixture of HNO_3 (0.75 mL) and concentrated H_2SO_4 (4.25 mL) at 0 °C. The mixture was stirred at room temperature for 30 min and then poured into ice−water and extracted with dichloromethane. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over sodium sulfate, and then concentrated. Purification by silica gel flash column chromatography (eluent: hexane/ethyl acetate, 10:1) gave **6a** (52 mg, 20%) and **6b** (185 mg, 67%). **6a**: colorless plates (hexane); mp 121−122 °C; ^{1}H NMR ($CDCl_3$) δ 8.10−8.08 (m, 2H), 7.53 (d, J = 7.3 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 3.3−1.6 (br m, 10H), 2.87 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 60.6, 83.9, 122.2, 123.3, 129.1, 132.9, 138.5, 147.9; HRMS Calcd for $C_8H_{15}B_{10}NO_2$: 265.2106. Found 265.2090. **6**b: colorless plates (hexane); mp 177−178 °C; ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J = 9.2 Hz, 2H), 7.38 (d, J = 9.2 Hz, 2H), 3.3−1.6 (br m, 10H), 2.87 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm) 61.0, 84.2, 123.2, 128.3, 143.0, 147.7; HRMS Calcd for $C_8H_{15}B_{10}NO_2$: 265.2106. Found 265.2091.

1-Hydroxy-12-phenyl-1,12-dicarba-*closo*-dodecaborane (9). To a solution of **8** (264 mg, 1.20 mmol) in benzene/diethyl ether (2:1, 3 mL) was added dropwise a 1.6 M solution of *n*-BuLi in hexane (1.50 mL, 2.40 mmol) at 0 °C under Ar. The mixture was stirred at room temperature for 30 min. The solution was cooled at 0 °C and benzyl peroxide (145 mg, 0.601 mmol) in benzene/ diethyl ether (2:1, 2 mL) was added dropwise, and then the mixture was stirred at room temperature for 2 h. The reaction was quenched with 10% aqueous HCl and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel flash column chromatography (eluent: hexane/AcOEt, 12:1) gave **9** (142 mg, 50%) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 7.25−7.15 (m, 5H), 3.21 (br, s, 1H), 3.5−1.5 (10 H, br m); Calcd for $C_8H_{16}B_{10}O$: 236.2204. Found 236.2232.

1-Hydroxy-12-(4-nitrophenyl)-1,12-dicarba-*closo*-dodecaborane (6d). A solution of **9** (200 mg, 0.85 mmol) in dichloromethane (4.0 mL) was added to a mixture of HNO_3 (0.75 mL) and concentrated H_2SO_4 (4.25 mL) at 0 °C. The mixture was stirred at room temperature for 30 min and then poured into ice−water and extracted with dichloromethane. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over sodium sulfate, and then concentrated. Purification by silica gel flash column chromatography (eluent: hexane/ethyl acetate, 10:1) gave **6d** (150 mg, 63%). **6d**: colorless plates (hexane); mp 170−171 °C; ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J = 9.2 Hz, 2H), 7.38 (d, J = 9.2 Hz, 2H), 3.3−1.6 (br m, 10H), 2.87 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 69.9, 108.1, 123.3, 128.7, 141.9, 147.8; Anal. Calcd for: $C_8B_{10}H_{15}NO_3$: N, 4.98; C, 34.16; H, 5.37. Found: N, 4.90; C, 34.40; H, 5.37.

1-Hydroxy-12-(3-nitrophenyl)-1,12-dicarba-*closo*-dodecaborane (6c). To a solution of 1-hydroxy-1,12-dicarba-*closo*-dodecaborane (**10**, 100 mg, 0.63 mmol) in 1,2-dimethoxyethane (5 mL) was added dropwise a 1.56 M solution of *n*-BuLi in hexane (0.88 mL, 1.38 mmol) at 0 °C under Ar. The mixture was stirred at room temperature for 30 min, CuCl (161 mg, 1.63 mmol) was added in one portion, and stirring was continued for 1 h. Pyridine (0.38 mL) and then 3-iodonitrobenzene (171 mg, 0.69 mmol) were added to the solution. The mixture was heated at 80 °C for 30 h. After cooling, the mixture was diluted with diethyl ether and stirred at room temperature for 3 h. Insoluble material was filtered off through Celite. Then the filtrate was washed with 2 N HCl, water and brine, dried over sodium sulfate, and then concentrated. Purification by silica gel flash column chromatography (eluent: hexane/ethyl acetate, 5:1) gave **6c** (39 mg, 22%). **6c**: colorless powder (hexane−dichloromethane); mp 175.0−175.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (m, 2H), 7.55 (ddd, J = 8.0, 2.0, 1.1 Hz, 1H), 7.37 (dd, J = 8.8, 8.0 Hz, 1H), 3.5−1.0 (br m, 10H), 3.43 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 69.8, 107.9, 122.7, 123.4, 129.2, 133.4, 137.2, 147.9; Anal. Calcd for: $C_8B_{10}H_{15}NO_3$: N, 4.98; C, 34.16; H, 5.37. Found: N, 4.87; C, 34.39; H, 5.51.

1-Methoxycarbonyl-12-phenyl-1,12-dicarba-*closo*-dodecaborane (11). To a solution of **8** (100 mg, 0.45 mmol) in diethyl ether (3.0 mL) was added dropwise a 1.60 M solution of *n*-BuLi in *n*-hexane (0.38 mL, 0.57 mmol) at 0 °C under Ar. The mixture was stirred at room temperature for 30 min, and methyl chloroformate (70 mL, 0.91 mmol) was added dropwise at 0 °C. The mixture was stirred at room temperature for 1.5 h, and then poured into water and extracted with diethyl ether. The organic layer was washed with brine, dried over sodium sulfate, and then concentrated. Purification by silica gel flash column chromatography (eluent: hexane/dichloromethane, 3:1) gave **11** (98 mg, 78%) as a colorless oil. colorless flakes (*n*-hexane); mp 116−117 °C; ^{1}H NMR ($CDCl_3$) δ 7.25−7.15 (m, 5H), 3.5−1.5 (br m, 10H), 3.65 (s, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm) 54.1, 76.0, 85.4, 126.9, 128.1, 128.5, 136.0, 163.0; HRMS Calcd for $C_{10}H_{18}B_{10}O_2$: 278.2310. Found 278.2327.

1-Methoxycarbonyl-12-(3-nitrophenyl)-1,12-dicarba-*closo*-dodecaborane (6k) and 1-Methoxycarbonyl-12-(4-nitrophenyl)-1,12-dicarba-*closo*-dodecaborane (12). A solution of **11** (95 mg, 0.34 mmol) in dichloromethane (2.0 mL) was added to a mixture of HNO_3 (0.30 mL) and concentrated H_2SO_4 (1.7 mL) at 0 °C. The mixture was stirred at room temperature for 30 min and then poured into ice−water and extracted with dichloromethane. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over sodium sulfate, and then concentrated. Purification by silica gel flash column chromatography (eluent: hexane/ethyl acetate, 10:1) gave **6k** (25 mg, 22%) and **12** (70 mg, 63%). **6k**: colorless needles (hexane); mp 180.5−182.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.11 (ddd, J = 8.2, 2.2, 0.9 Hz, 1H), 8.06 (t, J = 2.1 Hz, 1H), 7.51 (ddd, J = 8.2, 2.1, 0.9 Hz, 1H), 7.39 (t, J = 8.1 Hz, 1H), 3.67 (s, 3H), 3.5−1.5 (br m, 10H); ^{13}C NMR (acetone-d_6) δ (ppm) 55.0, 78.1, 84.2, 122.4, 124.8, 131.1, 134.0, 138.2, 149.0, 162.9; Anal. Calcd for: $C_{10}B_{10}H_{17}NO_4$: N, 4.37; C, 37.15; H, 5.30. Found: N, 4.31; C, 37.30; H, 5.22. **12**: colorless leaflets (*n*-hexane−dichloromethane); mp 147−148.5 °C; 1H NMR ($CDCl_3$) δ 8.04 (d, J = 9.1 Hz, 2H), 7.36 (d, J = 9.1 Hz, 2H), 3.67 (s, 3H), 3.5−1.5 (br m, 10H); ^{13}C NMR (acetone-d_6) δ (ppm) 55.0,

78.2, 84.3, 124.3, 129.3, 142.7, 149.1, 162.8; HRMS Calcd for $C_{10}H_{17}B_{10}NO_4$: 323.2161. Found 323.2175.

1-Hydroxymethyl-12-(3-nitrophenyl)-1,12-dicarba-*closo*-dodecaborane (6e). To a suspension of $LiBH_4$ (3.0 mg, 0.14 mmol) in diethyl ether (1.0 mL) was added a solution of **6k** (24 mg, 0.074 mmol) in diethyl ether (2.0 mL), and the mixture was refluxed for 2 h. The mixture was poured into diluted aqueous HCl and extracted with diethyl ether. The organic layer was washed with water and brine, dried over sodium sulfate, and then concentrated. Purification by silica gel flash column chromatography (eluent: hexane/ethyl acetate, 8:1) gave **6e** (22 mg, quant.). **6e**: colorless needles (hexane); mp 148.5−149.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (ddd, J = 8.1, 2.2, 1.1 Hz, 1H), 8.08 (t, J = 2.1 Hz, 1H), 7.53 (ddd, J = 8.1, 2.1, 1.1 Hz, 1H), 7.38 (dt, J = 0.9, 7.9 Hz, 1H), 3.56 (d, J = 7.5 Hz, 2H), 3.5−1.5 (brm,10H), 1.62 (t, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 65.9, 80.1, 82.4, 122.4, 123.4, 129.2, 133.1, 138.1, 148.0; Anal. Calcd for: $C_9B_{10}H_{17}NO_3$: N, 4.74; C, 36.60; H, 5.80. Found: N, 4.70; C, 36.67; H, 5.63.

1-Hydroxymethyl-12-(4-nitrophenyl)-1,12-dicarba-*closo*-dodecaborane (6f). Compound **6f** was prepared from **12** by the same method as that used for preparation of **6e**. Purification by silica gel flash column chromatography (eluent: hexane/ethyl acetate, 8:1) gave **6f** (quant.). **6f**: colorless needles (hexane); mp 164.0−165.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J = 9.1 Hz, 2H), 7.38 (d, J = 9.1 Hz, 2H), 3.56 (d, J = 7.3 Hz, 2H), 3.5−1.5 (br m, 10H), 1.62 (t, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 66.0, 80.3, 82.7, 123.3, 128.4, 142.6, 147.8; Anal. Calcd for: $C_9B_{10}H_{17}NO_3$: N, 4.74; C, 36.60; H, 5.80. Found: N, 4.74; C, 36.67; H, 5.62.

1-(3-Nitrophenyl)-1,12-dicarba-*closo*-dodecaborane-1-carboxylic Acid (6l). To a solution of **6k** (90 mg, 0.28 mmol) in tetrahydrofuran (3.0 mL) was added dropwise aqueous 1 N potassium hydroxide (1.0 mL) at room temperature. The mixture was stirred for 12 h at 40 °C, and then the reaction was quenched with aqueous 2 N HCl and extracted with AcOEt. The organic layer was washed with water and brine, dried over sodium sulfate, and then concentrated. Purification by silica gel flash column chromatography (eluent: hexane/ethyl acetate/acetic acid, 10:4:1) gave **6l** (46%). **6l**: colorless needles (hexane−dichloromethane); mp 220 °C (decomp) ^{1}H NMR ($CDCl_3$) δ 8.11 (ddd, J = 8.1, 2.2, 1.0 Hz, 1H), 8.06 (d, J = 2.0 Hz, 1H), 7.51 (ddd, J = 8.0, 2.0, 1.1 Hz, 1H), 7.40 (t, J = 8.1 Hz, 1H), 3.5−1.0 (br m, 10H); ^{13}C NMR ($CDCl_3$) δ (ppm) 83.4, 100.6, 122.2, 123.7, 129.4, 132.8, 137.8, 148.0, 166.2; Anal. Calcd for: $C_9B_{10}H_{15}NO_4$: N, 4.53; C, 34.95; H, 4.89. Found: N, 4.40; C, 35.25; H, 4.81.

1-Hydroxy-12-(3-cyanophenyl)-1,12-dicarba-*closo*-dodecaborane (6g). Compound **6g** was prepared from **10** and 3-iodobenzonitrile in the same manner as that used for the preparation of **6c**. Purification by silica gel flash column chromatography (eluent: hexane/ethyl acetate, 10:1) gave **6g** (34%). **6g**: colorless powder (hexane); mp 212.3-213.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.52 (m, 1H), 7.51 (m, 1H), 7.46 (ddd, J = 8.2, 2.0, 1.1 Hz, 1H), 7.30 (t, J = 8.2 Hz, 1H), 3.5−1.0 (br m, 10H), 3.31 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 87.5, 107.9, 112.5, 118.0, 129.1, 131.1, 131.9, 132.0, 136.8; Anal. Calcd for: $C_9B_{10}H_{15}NO$: N, 5.36; C, 41.37; H, 5.79. Found: N, 5.39; C, 41.18; H, 5.77.

1-Hydroxy-12-(4-cyanophenyl)-1,12-dicarba-*closo*-dodecaborane (6h). Compound **6h** was prepared from **10** and 4-iodobenzonitrile in the same manner as that used for the preparation of **6c**. Purification by silica gel flash column chromatography (eluent: hexane/ethyl acetate, 10:1) gave **6h** (41%). **6h**: colorless needles (hexane); mp 218.0−219.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.47 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.9 Hz, 2H), 3.5−1.0 (br m, 10H), 3.36 (br s,1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 70.2, 108.2, 112.4, 117.9, 128.4, 131.9, 140.1; Anal. Calcd for: $C_9B_{10}H_{15}NO$: N, 5.36; C, 41.37; H, 5.79. Found: N, 5.36; C, 41.17; H, 5.68.

1-Hydroxymethyl-1,12-dicarba-*closo*−dodecaborane (14). To a suspension of $LiAlH_4$ (400 mg, 10.5 mmol) in diethyl ether (10 mL) was added a solution of *p*-carborane-1-carboxylic acid **13** (2.00 g, 10.6 mmol) in diethyl ether (10 mL), and the mixture was refluxed for 1 h. The mixture was poured into 2 N HCl and extracted with diethyl ether. The organic layer was washed with water and brine, dried over sodium sulfate, and then concentrated. Purification by silica gel flash column chromatography (eluent: hexane/ethyl acetate, 10:1) gave **14** (320 mg, 86%) as a colorless solid. **14**:colorless cubes (*n*-hexane−dichloromethane); mp 209−211 °C; ^{1}H NMR ($CDCl_3$) δ 3.47 (d, J = 7.3 Hz, 2H), 3.5−1.0 (br m, 10H), 2.7 (br s, 1H), 1.55 (t, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 59.3, 66.6, 84.9; HRMS Calcd for $C_3H_{14}B_{10}O$: 174.2048. Found 174.2071.

1-*tert*-Butyldimethylsilyloxymethyl-1,12-dicarba-*closo*-dodecaborane (15). A mixture of **14** (1.59 g, 9.14 mmol), imidazole (2.49 g, 36.6 mmol), and TBSCl (4.13 g, 27.4 mmol) in dichloromethane (30 mL) was stirred at room temperature for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layer was washed with water and brine, dried over sodium sulfate, and then concentrated. Purification by silica gel flash column chromatography (eluent: hexane/ethyl acetate, 10:1) gave **15** (2.54 g, 96%) as a colorless solid. colorless prisms (*n*-hexane); mp 36 °C; ^{1}H NMR ($CDCl_3$) δ 3.41 (s, 2H), 3.5−1.0 (br m, 10H), 2.7 (br s, 1H), 0.85 (s, 9H), −0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm) −5.6, 18.2, 25.7, 59.0, 66.7, 85.1; HRMS Calcd for $C_9H_{28}B_{10}OSi$: 288.2913. Found 288.2899.

1-Hydroxymethyl-12-(4-cyanophenyl)-1,12-dicarba-*closo*-dodecaborane (6j). To a solution of **15** (300 mg, 1.04 mmol) in 1,2-dimethoxyethane (10 mL) was added dropwise a 1.56 M solution of *n*-BuLi in hexane (0.73 mL, 1.15 mmol) at 0 °C under Ar. The mixture was stirred at room temperature for 30 min, CuCl (134 mg, 1.35 mmol) was added in one portion, and stirring was continued at room temperature for 1 h. Pyridine (0.62 mL) was added, 4-iodobenzonitrile (261 mg, 1.13 mmol) was further added in one portion, and the mixture was heated at 80 °C for 20 h. After cooling, the reaction mixture was diluted with diethyl ether and stirred at room temperature for 3 h. Insoluble materials were filtered off through Celite. The filtrate was washed with 2 N HCl, water, and brine, dried over sodium sulfate, and then concentrated. Purification by silica gel column chromatography (eluent: *n*-hexane−ethyl acetate, 20:1) gave 1-*tert*-butyldimethylsilyloxymethyl-12-(4-cyanophenyl)-1,12-dicarba-*closo*-dodecaborane (140 mg, 36%): colorless leaflets (*n*-hexane); mp 123−124 °C; ^{1}H NMR ($CDCl_3$) δ 7.47 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 3.5−1.0 (br m, 10H), 3.49 (s, 2H), 0.87 (s, 9H), −0.01 (s, 6H).; HRMS Calcd for $C_{16}H_{31}B_{10}NOSi$: 389.3178. Found 389.3144. To a solution of the TBS ether (140 mg, 0.36 mmol) in THF (5.0 mL) and methanol (4.0 mL) was added 2 N HCl (1.0 mL), and the mixture was stirred at room temperature for 3 h. Then the reaction was quenched with water and extracted with ethyl acetate, and the organic layer was washed with brine, dried over sodium sulfate, and then concentrated. Purification by silica gel column chromatography (eluent: *n*-hexane−ethyl acetate, 5:1) gave **6j** (83.1 mg, 83%). **6j**: colorless needles (*n*-hexane -dichloromethane); mp 151.5−153.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.48 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 3.56 (d, J = 7.3 Hz, 2H), 3.5−1.0 (br m, 10H), 1.64 (t, J = 7.3 Hz, 1H), 3.5−1.0 (br m, 10H); ^{13}C NMR ($CDCl_3$) δ (ppm) 66.0, 80.7, 82.6, 112.6, 118.0, 128.1, 131.9, 140.9; Anal. Calcd for: $C_{10}B_{10}H_{17}NO$: N, 5.09; C, 43.62; H, 6.22. Found: N, 4.89; C, 43.43; H, 6.11.

1-Hydroxymethyl-12-(3-cyanophenyl)-1,12-dicarba-*closo*-dodecaborane (6i). Compound **6i** was prepared from **15** and 3-iodobenzonitrile in the same manner as that used for the preparation of **6j**. Intermediate,1-*tert*-Butyldimethylsilyloxymethyl-12-(3-cyanophenyl)-1,12-dicarba-*closo*-dodecaborane (22%). colorless leaflets (*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 7.5 (m, 2H), 7.44 (ddd, J = 8.1 Hz, 2.1 Hz, 1.1 Hz, 1H), 7.29 (ddd, J = 8.1 Hz, 8.1 Hz, 0.6 Hz, 1H), 3.5−1.0 (br m, 10H), 3.50 (s, 2H), 0.86 (s, 9H), −0.01 (s, 6H).; HRMS Calcd for $C_{16}H_{31}B_{10}NOSi$: 389.3178. Found 389.3139. After deprotection of the TBS group, purification by silica gel flash column chromatography (eluent: hexane−ethyl acetate, 20:1) gave **6i** (95%). **6i**: colorless needles (hexane−dichloromethane); mp 131.0−132.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.52 (dt, J = 7.5, 1.4 Hz,

1H), 7.49 (m, 1H), 7.44 (ddd, J = 8.3, 2.1, 1.1 Hz, 1H), 7.31 (ddd, J = 8.2, 7.5, 0.6 Hz, 1H), 3.56 (d, J = 7.3 Hz, 2H), 3.5−1.0 (br m, 10H), 1.65 (t, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 65.9, 80.2, 82.4, 112.6, 118.1, 129.1, 130.8, 131.6, 131.9, 137.7; Anal. Calcd for: $C_{10}B_{10}H_{17}NO$: N, 5.09; C, 43.62; H, 6.22. Found: N, 5.09; C, 43.59; H, 6.19.

1-(2-Hydroxyethyl)-12-phenyl-1,12-dicarba-*closo*-dodecaborane (16). To a solution of **8** (1.0 g, 4.55 mmol) in diethyl ether (20 mL) was added dropwise a 1.59 M solution of *n*-BuLi in hexane (3.43 mL, 5.46 mmol) at 0 °C under Ar. The mixture was stirred at room temperature for 30 min and cooled to 0 °C, *O*-tetrahydropyranyl-2-bromoethanol (1.43 g, 6.83 mmol) was added dropwise, and stirring was continued at room temperature for 20 h. The reaction was quenched with water, and the whole was extracted with diethyl ether. The organic layer was washed with brine, dried over sodium sulfate, and concentrated. Purification by silica gel flash column chromatography (eluent: ethyl acetate, 20:1) gave the C-alkylated product (42%). ^{1}H NMR ($CDCl_3$) δ 7.2 (m, 5H), 4.5 (m, 1H), 3.8 (m, 1H), 3.55 (m, 1H), 3.5−1.5 (br, m, 10H), 3.45 (m, 1H), 3.2 (m, 1H), 2.0 (m, 1H), 1.7 (m, 1H), 1.5 (m, 6H); The compound (550 mg, 1.58 mmol) was dissolved in MeOH (10 mL), and TsOH·H_2O (15 mg, 0.08 mmol) was added. The mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and then the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and concentrated to give **16** (96%). ^{1}H NMR ($CDCl_3$) δ 7.2 (m, 5H), 3.5−1.0 (br, m, 10H), 3.49 (t, J = 7.0 Hz, 2H), 1.96 (t, J = 7.0 Hz, 2H); HRMS Calcd for $C_{10}H_{20}B_{10}O$ 264.2517, Found 264.2539.

1-(2-Acetoxyethyl)-12-phenyl-1,12-dicarba-*closo*-dodecaborane (17). To a solution of **16** (400 mg, 1.56 mmol) in diethyl ether (12 mL) was added dropwise a 1.59 M solution of *n*-BuLi in hexane (1.1 mL, 1.75 mmol) at 0 °C under Ar. The mixture was stirred at room temperature for 10 min and cooled to 0 °C, acetyl chloride (150 mg, 1.91 mmol) was added dropwise, and stirring was continued at room temperature for 20 min. The reaction was quenched with water, and the whole was extracted with diethyl ether. The organic layer was washed with brine, dried over sodium sulfate, and concentrated to give **17** (87%). ^{1}H NMR ($CDCl_3$) δ 7.2 (m, 5H), 3.88 (t, J = 7.0 Hz, 2H), 3.5−1.0 (br, m, 10H), 2.02 (t, J = 7.0 Hz, 2H), 2.02 (s, 3H); HRMS Calcd for $C_{12}H_{22}B_{10}O_2$ 306.2622, Found 306.2643.

1-(2-Acetoxyethyl)-12-(3-nitrophenyl)-1,12-dicarba-*closo*-dodecaborane (18) and 1-(2-Acetoxyethyl)-12-(4-nitrophenyl)-1,12-dicarba-*closo*-dodecaborane (19). Compound **18** and **19** were prepared from **17** (416 mg, 1.35 mmol) in the same manner as that used for the preparation of **6k** and **12**. Purification by silica gel flash column chromatography (eluent: hexane−ethyl acetate, 10:1) gave **19** (297 mg, 63%) and **18** (81 mg, 17%). **19**: ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J = 9.1 Hz, 2H), 7.37 (d, J = 9.1 Hz, 2H), 3.88 (t, J = 6.9 Hz, 2H), 3.5−1.0 (br m, 10H), 2.04 (t, J = 6.9 Hz, 2H), 2.03 (s, 3H); **18**: ^{1}H NMR ($CDCl_3$) δ 8.08 (m, 1H), 8.07 (m, 1H), 7.52 (ddd, J = 7.9 Hz, 1.9 Hz, 1.0 Hz, 1H), 7.37 (dd, J = 8.1 Hz, 7.9 Hz, 1H), 3.88 (t, J = 6.8 Hz, 2H), 3.5−1.5 (br m, 10H); 2.04 (t, J = 6.8 Hz, 2H), 2.03 (s, 3H); HRMS Calcd for $C_{12}H_{21}B_{10}NO_4$ 351.2473, Found 351.2459.

1-(2-Hydroxyethyl)-12-(3-nitrophenyl)-1,12-dicarba-*closo*-dodecaborane (6m). To a suspension of $LiBH_4$ (7.2 mg, 0.33 mmol) in diethyl ether (1.0 mL) was added a solution of **19** (100 mg, 0.33 mmol) in diethyl ether (2.0 mL), and the mixture was refluxed for 30 min. The mixture was poured into diluted aqueous HCl and extracted with diethyl ether. The organic layer was washed with water and brine, dried over sodium sulfate, and then concentrated to gave **6m** (quant.). **6m**: colorless needles (hexane−dichloromethane); mp 143.5−145.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.09 (m, 1H), 8.07 (m, 1H), 7.52 (ddd, J = 7.8, 2.0, 1.1 Hz, 1H), 7.37 (m, 1H), 3.5−1.0 (br m, 10H), 3.49 (t, J = 6.9 Hz, 2H), 1.97 (t, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 40.0, 61.3, 78.8, 106.0, 122.4, 123.3, 129.2, 133.1, 138.1, 147.9; Anal. Calcd for: $C_{10}B_{10}H_{19}NO_3$: N, 4.53; C, 38.82; H, 6.19. Found: N, 4.57; C, 39.00; H, 6.12.

1-(3-Hydroxypropyl)-12-phenyl-1,12-dicarba-*closo*-dodecaborane (21). To a solution of *p*-carborane **20** (2.0 g, 13.9 mmol) in diethyl ether (30 mL) was added dropwise a 1.59 M solution of *n*-BuLi in hexane (9.18 mL, 14.6 mmol) at 0 °C under Ar. The mixture was stirred at room temperature for 30 min and cooled to 0 °C, *O*-tetrahydropyranyl-3-bromopropan-1-ol (4.65 g, 20.8 mmol) was added dropwise, and stirring was continued at room temperature for 20 h. The reaction was quenched with water, and the whole was extracted with diethyl ether. The organic layer was washed with brine, dried over sodium sulfate, and concentrated. Purification by silica gel flash column chromatography (eluent: ethyl acetate, 5:1) gave the C-monoalkylated product (29%). ^{1}H NMR ($CDCl_3$) δ 4.47 (t, J = 3.6 Hz, 1H), 3.78 (m, 1H), 3.54 (m, 1H), 3.5−1.5 (br, m, 10H), 3.46 (m, 1H), 3.21 (dt, J = 9.6 Hz, 6.1 Hz, 1H), 2.64 (br, s, 1H), 1.8−1.4 (m, 10H); The compound (1.15 g, 4.02 mmol) was dissolved in MeOH (10 mL), and TsOH·H_2O (38 mg, 0.20 mmol) was added. The mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and then the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and concentrated to give **20** (78%). ^{1}H NMR ($CDCl_3$) δ 3.5−1.0 (br, m, 10H), 3.48 (t, J = 5.9 Hz, 2H), 2.64 (br, s, 1H), 1.72 (m, 2H), 1.42 (m, 2H); HRMS Calcd for $C_4H_{16}B_{10}O$: 188.2204. Found 188.2223.

1-(3-*tert*-Butyldimethylsilyloxypropyl)-1,12-dicarba-*closo*-dodecaborane (23). Compound **23** was prepared from **21** and 3-iodobenzonitrile in the same manner as that used for the preparation of **15**. Purification by silica gel flash column chromatography (eluent: hexane−ethyl acetate, 10:1) gave **23** (93%). ^{1}H NMR ($CDCl_3$) δ 3.5−1.0 (br, m, 10H), 3.42 (t, J = 6.0 Hz, 2H), 2.63 (br, s, 1H), 1.69 (m, 2H), 1.36 (m, 2H), 0.85 (s, 9H), −0.01 (s, 6H).

1-(3-Hydroxypropyl)-12-(3-nitrophenyl)-1,12-dicarba-*closo*-dodecaborane (6n). Coupling reaction of **23** with 3-iodonitrobenzene and deprotection of the TBS group were carried out by the same procedure as that used for the preparation of **6j**. Purification by silica gel flash column chromatography (eluent: hexane−ethyl acetate, 2:1) gave **6n** (53%). **6n**: colorless needles (hexane−dichloromethane); mp 145.0−147.0 °C; ^{1}H NMR ($CDCl_3$) δ 8.09 (ddd, J = 8.0, 2.1, 1.0 Hz, 1H), 8.07 (d, J = 1.8 Hz, 1H), 7.53 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 7.36 (t, J = 8.5 Hz, 1H), 3.52 (q, J = 5.7 Hz, 2H), 3.5−1.0 (br m, 10H), 1.81 (m, 2H), 1.46 (m, 2H), 1.17 (t, J = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 32.4, 34.4, 61.8, 78.8, 81.7, 122.4, 123.3, 129.1, 138.2, 147.9; Anal. Calcd for: $C_{11}B_{10}H_{21}NO_3$: N, 4.33; C, 40.85; H, 6.55. Found: N, 4.30; C, 40.72; H, 6.59.

1-(4-Hydroxybutyl)-12-phenyl-1,12-dicarba-*closo*-dodecaborane (22). Compound **22** was prepared from *p*-carborane **20** and *O*-tetrahydropyranyl-4-bromobutan-1-ol in the same manner as that used for the preparation of **21**. Purification by silica gel flash column chromatography (eluent: hexane−ethyl acetate, 10:1) gave **22** (22%). ^{1}H NMR ($CDCl_3$) δ 3.56 (m, 2H), 3.5−1.0 (br, m, 10H), 2.63 (br, s, 1H), 1.63 (m, 2H), 1.38 (m, 2H), 1.24 (m, 2H). HRMS Calcd for $C_5H_{18}B_{10}O$: 202.2360. Found 202.2379.

1-(4-*tert*-Butyldimethylsilyloxybutyl)-1,12-dicarba-*closo*-dodecaborane (24). Compound **24** was prepared from **22** in the same manner as that used for the preparation of **23**. Purification by silica gel flash column chromatography (eluent: hexane−ethyl acetate, 10:1) gave **24** (85%). ^{1}H NMR ($CDCl_3$) δ 3.50 (t, J = 6.2 Hz, 2H), 3.5−1.0 (br, m, 10H), 2.62 (br, s, 1H), 1.60 (m, 2H), 1.30 (m, 2H), 1.21 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H).

1-(4-Hydroxybutyl)-12-(3-nitrophenyl)-1,12-dicarba-*closo*-dodecaborane (6o). Coupling reaction of **24** with 3-iodonitrobenzene and deprotection of the TBS group were carried out by the same procedure as that used for the preparation of **6j**. Purification by silica gel flash column chromatography (eluent: hexane−ethyl acetate, 2:1) gave **6o** (53%). **6o**: colorless needles (hexane−dichloromethane); mp 121.0−122.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.09 (dd, J = 8.0, 2.1, 1.0 Hz, 1H), 8.07 (d, J = 1.8 Hz, 1H), 7.53 (ddd, J = 8.0, 2.0, 1.0

Hz, 1H), 7.36 (t, J = 8.5 Hz, 1H), 3.58 (q, J = 5.6 Hz, 2H), 3.5−1.0 (br m, 10H), 1.71 (m, 2H), 1.40 (m, 2H), 1.29 (m, 2H), 1.20 (t, J = 4.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 25.9, 32.0, 37.8, 62.3, 82.1, 98.5, 122.4, 123.2, 129.1, 133.2, 138.3, 147.9; Anal. Calcd for: $C_12B_{10}H_{23}NO_3$: N, 4.15; C, 42.71; H, 6.87. Found: N, 4.17; C, 42.58; H, 6.81.

1-Methoxycarbonyl-7-phenyl-1,7-dicarba-*closo*-dodecaborane (28). Compound **28** was prepared from 1-phenyl-*m*-carborane (**27**) in the same manner as that used for the preparation of **11**. Purification by silica gel flash column chromatography (eluent: hexane−dichloromethane, 5:1) gave **28** (68%). ^{1}H NMR ($CDCl_3$) δ 7.5−7.25 (m, 5H), 3.77 (s, 3H), 3.5−1.5 (br m, 10H); ^{13}C NMR ($CDCl_3$) δ (ppm) 54.1, 76.0, 85.4, 126.9, 128.1, 128.5, 136.0, 163.0; HRMS Calcd for $C_{10}H_{18}B_{10}O_2$: 278.2310. Found 278.2336.

1-Methoxycarbonyl-7-(3-nitrophenyl)-1,12-dicarba-*closo*-dodecaborane (29) and 1-Methoxy-carbonyl-7-(4-nitrophenyl)-1,12-dicarba-*closo*-dodecaborane (30). Compounds **29** and **30** were prepared from **28** in the same manner as that used for the preparation of **6k** and **12**. Purification by silica gel flash column chromatography (eluent: hexane−ethyl acetate, 10:1) gave **30** (65%) and **29** (22%). **30**: ^{1}H NMR ($CDCl_3$) δ 8.13 (d, J = 9.1 Hz, 2H), 7.62 (d, J = 9.1 Hz, 2H), 3.79 (s, 3H), 3.5−1.0 (br m, 10H); HRMS Calcd for $C_{10}H_{17}B_{10}NO_4$: 323.2161. Found 323.2184. **29**: ^{1}H NMR ($CDCl_3$) δ 8.32 (dt, J = 2.0 Hz, 1H), 8.19 (ddd, J = 8.1 Hz, 2.0 Hz, 0.9 Hz, 1H), 7.76 (ddd, J = 8.1 Hz, 2.0 Hz, 0.9 Hz, 1H), 7.49 (dd, J = 8.1 Hz, 7.9 Hz, 1H), 3.79 (t, J = 6.8 Hz, 2H), 3.5−1.5 (br m, 10H); HRMS Calcd for $C_{10}H_{17}B_{10}NO_4$: 323.2161. Found 323.2181.

1-Hydroxymethyl-7-(3-nitrophenyl)-1,7-dicarba-*closo*-dodecaborane (7a). Compound **7a** was prepared from **29** in the same manner as that used for the preparation of **6e**. Purification by silica gel flash column chromatography (eluent: hexane−ethyl acetate, 6:1) gave **7a** (98%). **7a**: colorless needles (hexane); mp 90.0−92.0 °C; ^{1}H NMR ($CDCl_3$) δ 8.31 (t, J = 2.2 Hz, 1H), 8.18 (ddd, J = 8.1, 2.2, 0.9 Hz, 1H), 7.75 (ddd, J = 8.0, 2.0, 0.9 Hz, 1H), 7.47 (t, J = 8.1 Hz, 1H), 3.90 (d, J = 7.3 Hz, 2H), 3.5−1.5 (br m, 10H), 1.97 (t, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 66.1, 76.6, 78.4, 123.7, 124.5, 130.3, 134.5, 137.8, 148.9; Anal. Calcd for: $C_9B_{10}H_{17}NO_3$: N, 4.74; C, 36.60; H, 5.80. Found: N, 4.72; C, 36.67; H, 5.61.

1-Hydroxymethyl-7-(4-nitrophenyl)-1,7-dicarba-*closo*-dodecaborane (7b). Compound **7b** was prepared from **30** in the same manner as that used for the preparation of **6e**. Purification by silica gel flash column chromatography (eluent: hexane−ethyl acetate, 6:1) gave **7b** (86%). **7b**: colorless needles (hexane); mp 98.0−99.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.12 (d, J = 9.1 Hz, 2H), 7.61 (d, J = 9.1 Hz, 2H), 3.89 (d, J = 7.2 Hz, 2H), 3.5−1.5 (br m, 10H), 1.95 (t, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 65.3, 76.0, 77.6, 123.5, 129.0, 141.5, 148.0; Anal. Calcd for: $C_9B_{10}H_{17}NO_3$: N, 4.74; C, 36.60; H, 5.80. Found: N, 4.64; C, 36.71; H, 5.55.

Receptor Binding Assay. A hAR-LBD expression plasmid vector which encodes GST-hARLBD (627−919 aa, EF domain) fusion protein under the *lac* promoter (provided by Prof. S. Kato, University of Tokyo) was transfected into *E. coli* strain *HB-101*. An overnight culture (10 mL) of the bacteria was added to 1 L of LB medium and incubated at 27 °C until its optical density reached 0.6−0.7 at 600 nm. Following the addition of IPTG to a concentration of 1 mM, incubation was continued for an additional 4.5 h. Cells were harvested by centrifugation at 4000*g* at 4 °C for 15 min and stored at −80 °C until use. All subsequent operations were performed at 4 °C. The bacterial pellet obtained from 40 mL of culture was resuspended in 1 mL of ice-cold TEGDM buffer (10 mM Tris-HCl pH 7.4, 1 mM EDTA, 10% glycerol, 10 mM DTT, 10 mM sodium molybdate). This suspension was subjected to sonication using 10 × 10 s bursts on ice, and crude GST-hARLBD fraction was prepared by centrifugation of the suspension at 12 000*g* for 30 min at 4 °C. This crude receptor fraction was diluted with buffer (20 mM Tris-HCl pH 8.0, 0.3 M KCl, 1 mM EDTA) to a protein concentration of 0.3−0.5 mg/mL and used in binding assays as hAR-LBD fraction. Aliquots of the hAR-LBD fraction were incubated in the dark at 4 °C with [^{3}H]-DHT (NEN, 4 nM final concentration), triamcinolone acetonide (1 μM final concentration), and reference or test compounds (dissolved in DMSO). Nonspecific binding was assessed by addition of a 200-fold excess of nonradioactive DHT. After 15 h, a Dextran T-70/γ-globulin-coated-charcoal suspension was added to the ligand/protein mixture (1% Norit A, 0.05% γ-globulin, 0.05% Dextran T-70 final concentration each) and the whole was incubated at 4 °C for 10 min. The charcoal was removed by centrifugation for 5 min at 1300*g*, and the radioactivity of the supernatant was measured in Atomlight (NEN) by using a liquid scintillation counter.

Transfection and Luciferase Assays. Assay of androgenic activity was performed by means of ARE-luciferase reporter assay using NIH3T3 cells. Culture was conducted in phenol red-free DMEM (Sigma Chemical Co.) containing penicillin, streptomycin, and dextran-charcoal-treated calf serum for 2−3 days. Transient transfections of NIH3T3 cells were performed using Transfast (Promega Co., Madison, WI), according to the manufacturer's protocol. Transfections were done in 48-well plates at 2 × 10^4 cells/well with 50 ng of pSG5-hAR, 300 ng of p(ARE)$_2$-luc, and 10 ng of pRL/CMV (Promega Co.) as an internal standard. Twenty-four hours after addition of the sample (final concentration, 10^{-5}−10^{-7} M) and 1 × 10^{-10} DHT, cells were harvested with 25 μL of cell lysis buffer (Promega Co.), and the firefly and renilla luciferase activities were determined with a Dual Luciferase Assay Kit (Promega Co.) by measuring luminescence with a Wallac Micro-Beta scintillation counter (PerkinElmer Life Sciences, Boston, MA). Firefly luciferase reporter activity was normalized to renilla luciferase activity from pRL/CMV.

SC-3 Growth Inhibition Assay. Shionogi Carcinoma-3 (SC-3) cells were cloned from Shionogi Carcinoma 115 cells, which were established from a mouse breast cancer. SC-3 shows androgen-dependent growth. In this assay, androgenic and antiandrogenic activities of test compounds were determined in terms of SC-3 growth promotion and inhibition, respectively. SC-3 cells were cultured in the presence of MEM supplemented with 10% FBS and 10 nM testosterone at 37 °C under 5% CO_2. All experiments were performed in triplicate or more. For SC-3 cell growth-inhibition assay, the cells were trypsinized and diluted to 3.0 × 10^4 cell/mL with MEM supplemented with 10% charcoal resin-stripped fetal bovine serum. This cell suspension was transferred to 96-well microtiter plates, and various concentrations of test compound (from 100 nM to 10 μM DMSO solution) and/or testosterone ethanol solution (final concentration 10 nM) were added. Then the plates were incubated at 37 °C 5% CO_2 for 3 days, and the cell number was determined using the WST-1 method with a Cell Counting Kit and an MPR-A4i2 micro plate reader (TOSOH, Japan). The number of cells on wells with testosterone alone was defined as 100%. The concentration of test compounds that inhibited the increase of the cell number induced by 10 nM testosterone by 50% was quantified (IC_{50}) after log−logit transformation.

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Supporting Information Available: Elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent reviews on medicinal applications, see: Hawthorne, M. F. The role of chemistry in the development of boron neutron capture therapy of cancer. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 950−984. Soloway, A. H.; Tjarks, W.; Barnum, J. G. The chemistry of neutron capture therapy. *Chem. Rev.* **1998**, *98*, 1515−1562.

(2) Fauchere, J. L.; Do, K. Q.; Jow, P. Y. C.; Hansch, C. Unusually strong lipophilicity of 'fat' or 'super' amino acids, including a new reference value for glycine. *Experientia* **1980**, *36*, 1203−1204. Yamamoto, K.; Endo, Y. Utility of boron clusters for drug design. Hansch-Fujita hydrophobic parameters π of dicarba-*closo*-dodecaboranyl groups. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2389−2392. Endo, Y.; Yamamoto, K.; Kagechika, H. Utility of boron clusters for drug design. Relation between estrogen receptor binding affinity and hydrophobicity of phenols bearing various types of carboranyl groups. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4089−4092.

(3) Endo, Y.; Iijima, T.; Yamakoshi, Y.; Yamaguchi, M.; Fukasawa, H.; Shudo, K. Potent estrogenic agonists bearing dicarba-*closo*-dodecaborane as a hydrophobic pharmacophore. *J. Med. Chem.* **1999**, *42*, 1501−1504. Endo, Y.; Iijima, T.; Yamakoshi, Y.; Kubo, A.; Itai, A. Structure−activity study of estrogenic agonists bearing dicarba-*closo*-dodecaborane. Effect of geometry and separation distance of hydroxyl groups at the ends of molecules. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3313−3318. Endo, Y.; Iijima, T.; Yamakoshi, Y.; Fukasawa, H.; Miyaura, C.; Kubo, A.; Itai, A. Potent estrogen agonists based on carborane as a hydrophobic skeletal structure: A new medicinal application of boron clusters. *Chem. Biol.* **2001**, *8*, 341−355.

(4) Endo, Y.; Yoshimi, T.; Iijima, T.; Yamakoshi, Y. Estrogenic antagonists bearing dicarba-*closo*-dodecaborane as a hydrophobic pharmacophore. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3387−3392. Endo, Y.; Yoshimi, T.; Yamakoshi, Y. New estrogenic antagonists bearing dicarba-*closo*-dodecaborane as a hydrophobic pharmacophore. *Chem. Pharm. Bull.* **2000**, *48*, 312−314.

(5) Iijima, T.; Endo, Y.; Tsuji, M.; Kawachi, E.; Kagechika, H.; Shudo, K. Dicarba-*closo*-dodecaboranes as a pharmacophore. Retinoidal antagonists and potential agonists. *Chem. Pharm. Bull.* **1999**, *47*, 398−404. Endo, Y.; Iijima, T.; Ohta, K.; Kagechika, H.; Kawachi, E.; Shudo, K. Dicarba-*closo*-dodecaboranes as a pharmacophore. Novel potent retinoidal agonists. *Chem. Pharm. Bull.* **1999**, *47*, 585−587. Endo, Y.; Iijima, T.; Yaguchi, K.; Kawachi, E.; Kagechika, H. Structure−activity study of retinoid agonists bearing substituted dicarba-*closo*-dodecaborane. Relation between retinoidal activity and conformation of two aromatic nuclei. BioMed. *Chem. Lett.* **2001**, *11*, 1307−1311.

(6) Endo, Y.; Yaguchi, K.; Kawachi, E.; Kagechika, H. Polymethylcarborane as a novel bioactive moiety: derivatives with potent retinoid antagonistic activity. *BioMed. Chem. Lett.* **2000**, *10*, 1733−1736.

(7) Neumann, F. In *Pharmacology and clinical uses of inhibitors of hormone secretion and action*; Furr, B. J. A., Wakeling, A. E., Eds.; Bailliere Tindall: London, 1987; p 132.

(8) Mooradian, A. D.; Morley, J. E.; Korenman, S. G. Biological actions of androgens. *Endocr. Rev.* **1987**, *8*, 1−28.

(9) Zhi, L.; Martinborough, E. Selective androgen receptor modulators (SARMs). *Annu. Rep. Med. Chem.* **2001**, *36*, 169−180.

(10) Fujii, S.; Hashimoto, Y.; Suzuki, T.; Ohta, S.; Endo, Y. A new class of androgen receptor antagonists bearing carborane in place of a steroidal skeleton. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 227−230.

(11) Zakharkin, L. I.; Kovredov, A. I. Preparation of 1-aryl-*o*-, 1-aryl-*m*-, and 1-aryl-*p*-carboranes via copper derivatives of *o*-, *m*-, and *p*-carboranes. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1974**, 740.

(12) Hawthorne, M. F.; Berry, T. E.; Wegner, P. A. The electronic properties of the 1,2- and 1,7-dicarba-*closo*-dodecaborane(12) groups bonded at carbon. *J. Am. Chem. Soc.* **1965**, *87*, 4746−4750. Endo, Y.; Taoda, Y. Electronic Effects of Dicarba-*closo*-dodecaboranes. Friedel−Crafts Acylation of 1-Phenyl-*closo*-dodecaboranes. *Tetrahedron Lett.* **1999**, *40*, 9073−9076.

(13) Zakharkin, L. I.; Zhigareva, G. G. Preparation and properties of 1-hydroxycarboranes. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1970**, 2153−2156.

(14) Coult, R.; Fox, M. A.; Gill, W. R.; Herbertson, P. L.; MacBride, J. A. H.; Wade, K. C−Arylation and C-heteroarylation of icosahedral carboranes via their copper(I) derivatives. *J. Organometal. Chem.* **1993**, *462*, 19−29. Fox, M. A.; MacBride, J. A. H.; Peace, R. J.; Wade, K. Transmission of electronic effects by icosahedral carboranes; skeletal carbon-13 chemical shifts and ultraviolet−visible spectra of substituted aryl-*p*-carboranes (1, 12-dicarba-*closo*-dodecaboranes). *J. Chem. Soc., Dalton Trans.* **1998**, 401−411.

(15) Zharov, I.; Saxena, A.; Michl, J.; Miller, R. D. C−Hydroxydicarba-*closo*-dodecaboranes. *Inorg. Chem.* **1997**, *36*, 6033−6038.

(16) Ishioka, T.; Kubo, A.; Koiso, Y.; Nagasawa, K.; Itai, A.; Hashimoto, Y. Novel nonsteroidal/nonanilide type androgen antagonists with an isoxazolone moiety. *Bioorg. Med. Chem.* **2002**, *10*, 1555−1566.

(17) We used [^{3}H]DHT instead of [^{3}H]testosterone, which had been used in the investigation by Ishioka et al.[13] Under our experimental conditions, 4 nM [^{3}H]DHT was enough to saturate the binding site in the hAR ligand binding domain. All binding data indicate the mean values of the two isolated assays.

(18) Kitamura, S.; Suzuki, T.; Ohta, S.; Fujimoto, N. Antiandrogenic activity and metabolism of the organophosphorus pesticide fenthion and related compounds. *Environ. Health Perspect.* **2003**, *111*, 503−8.

(19) Hiraoka, D.; Nakamura, N.; Nishizawa, Y.; Uchida, N.; Noguchi, S.; Matsumoto, K.; Sato, B. Inhibitory and stimulatory effects of glucocorticoid on androgen-induced growth of murine Shionogi carcinoma 115 in vivo and in cell culture. *Cancer Res.* **1987**, *47*, 6560−6564. Kasayama, S.; Saito, H.; Kouhara, H.; Sumitani, S.; Sato, B. Suramin interrupts androgen-inducible autocrine loop involving heparin binding growth factor in mouse mammary cancer (Shionogi carcinoma 115) cells. *J. Cell. Physiol.* **1993**, *154*, 254−261. Tyrrell, C. J.; Denis, L.; Newling, D.; Soloway, M.; Channer, K.; Cockshott, I. D. Casodex 10−200 mg daily, used as monotherapy for the treatment of patients with advanced prostate cancer. An overview of the efficacy, tolerability and pharmacokinetics from three Phase II dose-ranging studies. *Eur. Urol.* **1998**, *9*, 39−53.

(20) Tucker, H.; Crook, J. W.; Chesterson, G. J. Nonsteroidal antiandrogens. Synthesis and structure−activity relationships of 3-substituted derivatives of 2-hydroxypropionanilides.*J. Med. Chem.* **1988**, *31*, 954−959. Morris, J. J.; Hughes, L. R.; Glen, A. T.; Taylor, P. J. Nonsteroidal antiandrogens. Design of novel compounds based on an infrared study of the dominant conformation and hydrogen-bonding properties of a series of anilide antiandrogens. *J. Med. Chem.* **1991**, *34*, 447−455.

(21) Marhefka, C. A.; Gao, W.; Chung, K.; Kim, J.; He, Y.; Yin, D.; Bohl, C.; Dalton, J. T.; Miller, D. D. Design, synthesis, and biological characterization of metabolically stable selective androgen receptor modulators. *J. Med. Chem.* **2004**, *47*, 993−998.

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