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Design and synthesis of novel androgen receptor antagonists with sterically bulky icosahedral carboranes

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Abstract—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. Here, we report the design and synthesis of novel androgen antagonists bearing a carborane moiety. These compounds, particularly **8a**, **8c**, and **9d**, exhibited anti-androgenic activity similar to that of the well-known anti-androgen flutamide in reporter gene assay using NIH3T3 cells transfected with a human AR expression plasmid. The carborane cage seems to be a privileged hydrophobic pharmacophore for the expression of AR-antagonistic activity.

1. Introduction

Carboranes (dicarba-*closo*-dodecaboranes)[1] are mixed hydrides containing both carbon and boron atoms in the molecular skeleton. The carboranes, the highest known members of the series $C_2B_mH_{m+2}$, contain the icosahedral C_2B_{10} skeleton, which is highly thermally stable and resistant to attack by a wide range of reagents. These icosahedral carboranes have a hydrophobic surface and a spherical geometry, and are considered to be three-dimensional aromatic compounds or inorganic benzenes.[2] The carboranes have been utilized in medicinal chemistry in the field of boron neutron capture therapy (BNCT) for incorporation of large numbers of boron atoms into tumor cells.[3] The clinical use of BNCT has been energetically promoted by two Japanese doctors, Hatanaka and Mishima. Several of their patients became long-term survivors of malignant brain tumors and melanoma.[4,5] We thought that these boron-cluster compounds might be useful in another approach to cancer therapy. The carboranes are stable in vivo,[6] so they might possess a wide range of possible applications in the field of medicinal chemistry. From the standpoint of receptor–ligand complexation, the exceptional hydrophobic character[7,8] and the spherical geometry of the carboranes might allow them to work effectively as hydrophobic pharmacophores. Therefore, we have focused on the utility of carboranes as a hydrophobic component in anti-tumor compounds. Recently, we reported the design, synthesis, and biological evaluation of a range of nuclear receptor modulators, such as estrogen receptor agonists[9–11] and antagonists,[12,13] and retinoic acid receptor agonists[14–16] and antagonists,[17] and a retinoid X receptor antagonist,[18] all of which contain carborane as a hydrophobic pharmacophore. Hydrophobic interaction along the spherical carborane cage with hydrophobic pockets in the ligand binding domains of nuclear receptors seemed to produce a strong interaction, as we had hoped.

Androgen receptor (AR) is a member of the nuclear receptor superfamily of ligand-regulated transcription factors[19] and plays a key role in the development and maintenance of the male reproductive system.[20] Physiological actions, such as prostate enlargement, body hair growth, acne, and muscle development, are initiated by the binding of the steroid hormones, testosterone **1** and/or 5α-dihydrotestosterone **2** (Fig. 1), to the AR, and an intricate machinery, involving translocation of AR into the nucleus, binding to specific DNA sites, formation of transcriptional complex, and activation of the expression of specific genes, begins to work.[19] AR ligands have

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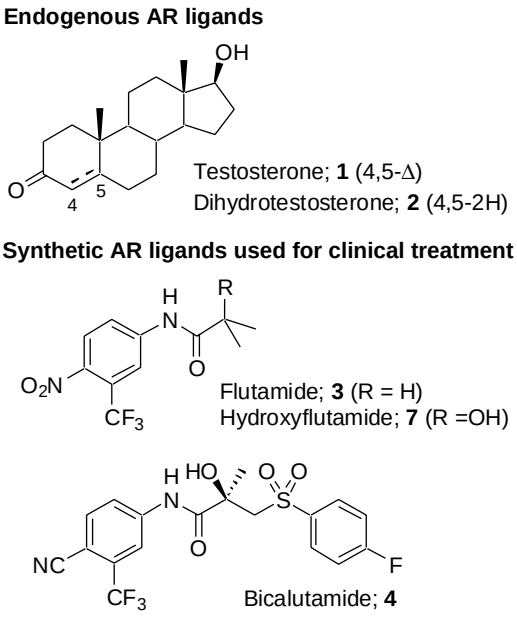


Figure 1. The structures of endogenous and synthetic AR ligands.

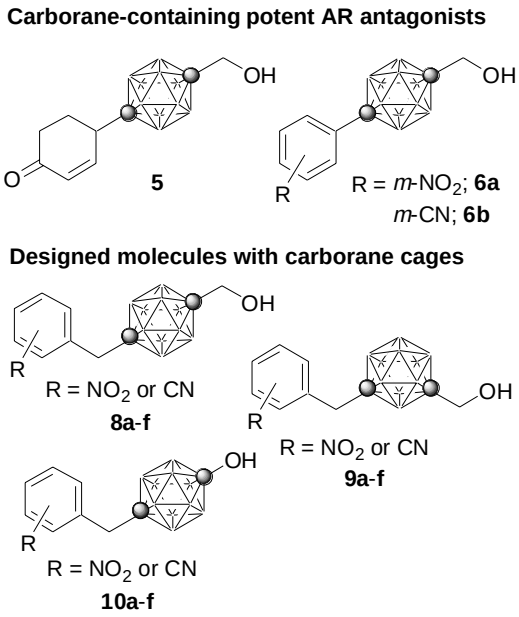


Figure 2. The structures of carborane-containing AR antagonists and new designed molecules **8**–**10**.

been applied clinically; for instance, AR agonists are used for the treatment of aplastic anaemia and AR antagonists for prostate cancer.[21] A number of nonsteroidal AR antagonists, such as flutamide **3**[22,23] and bicalutamide **4**,[24,25] are used clinically for treatment of prostate cancer (Fig. 1). Steroidal AR antagonists are also useful clinically, but are considered less desirable than nonsteroidal AR antagonists, because the steroidal anti-androgens induce adverse effects owing to cross-activity at other steroid hormone receptors.[21]

Recently, we have presented a new class of nonsteroidal androgen antagonists **5**,[26] with a *p*-carborane cage in place of the steroidal C, D rings of the endogenous AR ligands **1** and **2**. We have also developed more potent androgen antagonists **6a** and **6b**,[27] which have cyanophenyl and nitrophenyl groups, respectively, instead of the cyclohexene ring of **5** (Fig. 2). The potency of compound **6** was superior to that of hydroxyflutamide **7** (Fig. 1). It was suggested that hydrophobic interaction of the carborane structure with the hydrophobic region of the AR ligand-binding pocket may account for the high binding affinity to AR, and owing to the bulky carborane cage, the conformation of the AR–ligand complex may not be appropriate for interaction with cellular co-regulators, resulting in antagonistic activity. We have designed a series of cyano or nitrobenzyl derivatives **8**–**10** with a *p*- or *m*-carborane cage to examine further the structure–activity relationships of **6** and to find new carborane skeleton-containing nonsteroidal AR antagonists (Fig. 2). Here, we describe the synthesis and biological evaluation of these carborane-containing benzyl-type derivatives.

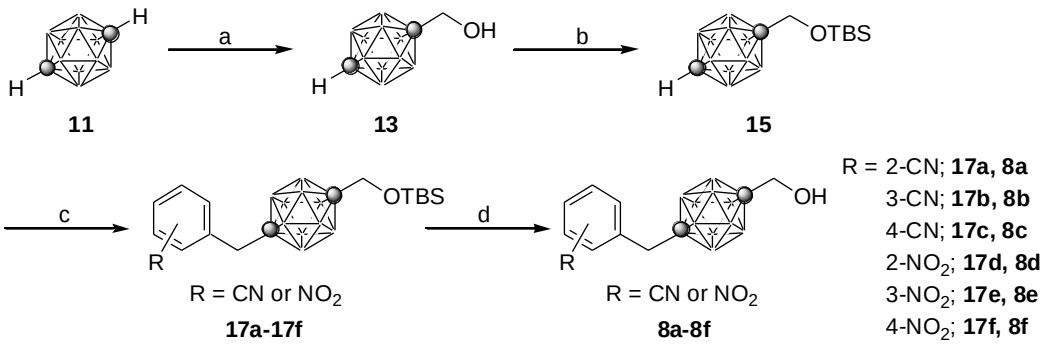
2. Chemistry

The carboranyl methanols **8** and **9** were synthesized as shown in Schemes 1 and 2, respectively. The *p*-carborane **11** and *m*-carborane **12** were treated with *n*-BuLi, and the resulting Li salts were reacted with equimolar paraformaldehyde to give *p*-carboranylmethanols **13** and *m*-carboranylmethanols **14** in 71% yield and 46% yield, respectively;[28] these products reacted readily with *t*-butyldimethylsilyl chloride under usual conditions to give the corresponding protected compounds **15** and **16** in 91% yield and 94% yield, respectively. The Li salts derived from compounds **15** and **16** reacted with a variety of benzyl bromides to give the corresponding compounds **17a**–**f** and **18a**–**f** (>52% yield in the case of *p*-carborane derivatives, >45% yield in the case of *m*-carborane derivatives), and deprotection with tetrabutylammonium fluoride (TBAF) afforded the corresponding benzyl derivatives **8a**–**f** (>81% yield) and **9a**–**f** (>62% yield).

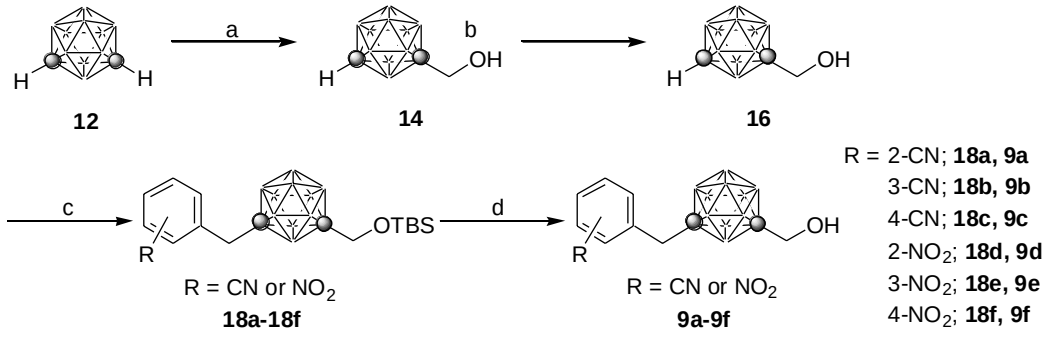
The *p*-carboranol derivatives **10a**–**f** were synthesized from *p*-carborane **11** using a similar strategy. The conventional lithiation at carbon of *p*-carborane **11**, followed by boronation with trimethylborate, gave the corresponding boron ester in situ, and this was oxidized with peracetic acid to give the desired *p*-carboranol **19** (55% yield) in one pot.[29] The hydroxyl group of the *p*-carboranol was protected with a *t*-butyldimethylsilyl group to give the silylated *p*-carboranol **20** in 75% yield. Then C–H on the opposite side to the newly formed O–Si bond was also deprotonated with *n*-BuLi and benzylated to give the corresponding compounds **21a**–**f** (>55% yield), and deprotection of the *t*-butyldimethylsilyl group afforded a variety of *p*-carboranol derivatives **10a**–**f** (>92% yield) (see Scheme 3).

3. Biology

The biological activity of the synthesized compounds was evaluated by means of transient transactivation assay.[30] The co-transfection assay was conducted in mouse

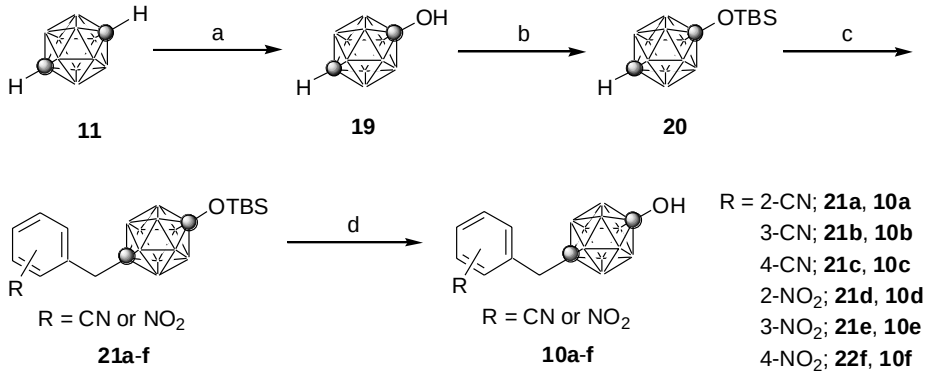


Scheme 1. Synthesis of various benzyl derivatives **8** with *p*-carborane cages. Reagents: (a) *n*-BuLi, $(CHO)_n$, benzene-ether; (b) TBSCl, imidazole, CH_2Cl_2; (c) *n*-BuLi, benzylbromides, THF; (d) TBAF, THF.



a) *n*-BuLi, $(CHO)_n$, benzene-ether; b) TBSCl, imidazole, CH_2Cl_2; c) *n*-BuLi, benzylbromides, THF; d) TBAF, THF

Scheme 2. Synthesis of various benzyl derivatives **9** with *m*-carborane cages. Reagents: (a) *n*-BuLi, $(CHO)_n$, benzene-ether; (b) TBSCl, imidazole, CH_2Cl_2; (c) *n*-BuLi, benzylbromides, THF; (d) TBAF, THF.



Scheme 3. Synthesis of a series of benzyl-*p*-carboranol derivatives **10**. Reagents: (a) *n*-BuLi, $B(MeO)_3$, ether then H_2O_2; (b) TBSCl, Et_3N, CH_2Cl_2; (c) *n*-BuLi, benzylbromides, THF; (d) TBAF, THF.

fibroblast NIH3T3 cells, using an expression plasmid for hAR and reporter plasmids, ARE/Luci (firefly luciferase), and pRL/CMV (*Renilla* luciferase).[30] The endogenous AR agonist dihydrotestosterone **2**, at 1×10^{-12}–1×10^{-9} M, activated AR and induced the expression of luciferase in a dose-dependent manner, while none of the test compounds **8a**–**f**, **9a**–**f**, and **10a**–**f** showed activating activity at 1×10^{-7}–1×10^{-5} M (data not shown). The transcription-antagonistic activity (inhibition of the transcriptional activity of 1×10^{-10} M dihydrotestosterone **2**) of the carborane-containing molecules **8a**–**f**, **9a**–**f**, and **10a**–**f** is shown in Figures 3–5, respectively. All of the test compounds in the concentration range of 1×10^{-7}–1×10^{-5} M dose-dependently inhibited the transactivation of AR induced by 1×10^{-10} M dihydrotestosterone **2**. On the whole, compounds **8a**–**f**, which contain a *p*-carborane cage with a hydroxymethyl group, exhibited more potent AR-antagonistic activity than the *m*-carborane derivatives **9a**–**f** or *p*-carboranol derivatives **10a**–**f**. Among these compounds, the most potent compounds **8a** (IC_{50} = 0.96 nM), **8c** (IC_{50} = 0.85 nM), and **8d** (IC_{50} = 0.83 nM), which have a cyano or a nitro group at the *ortho* or *meta* position in the benzene ring, showed

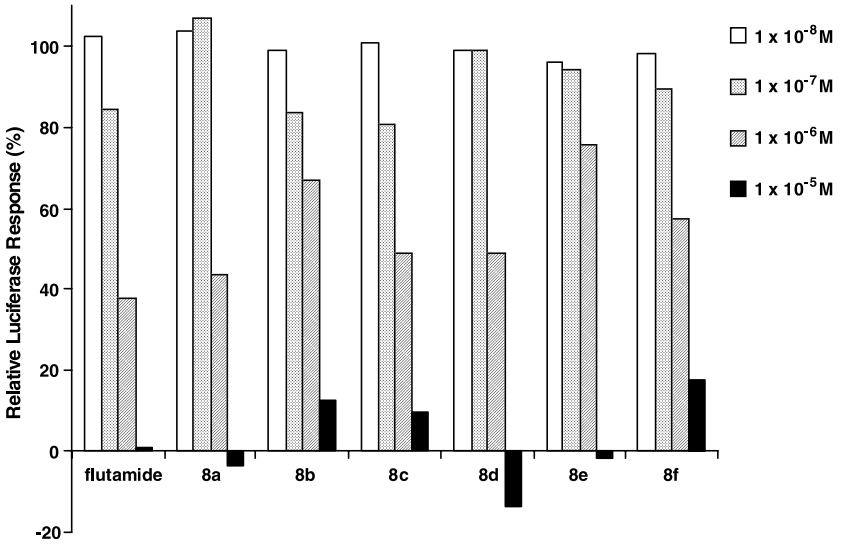


Figure 3. Inhibition of transcriptional activation of dihydrotestosterone **2** by the test compounds **8a**–**f**. NIH3T3 cells were transfected with hAR expression vector, ARE/Luci (firefly Luciferase) and pRL/CMV (*Renilla* Luciferase), and incubated with the test compounds (10^{-8}–10^{-5} M) plus DHT (10^{-10} M). The response of DHT (10^{-10} M) alone was defined as 100%. Values are percentages of the transcriptional response of DHT (10^{-10} M).

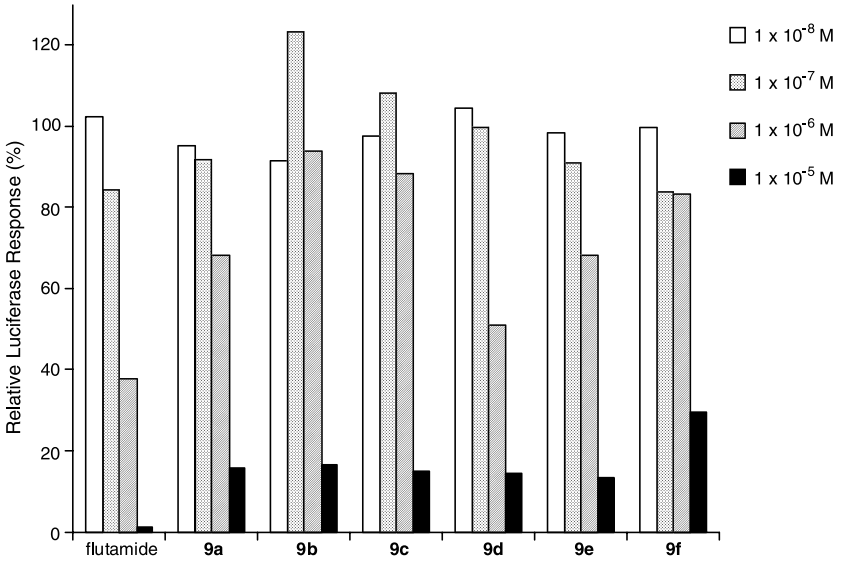


Figure 4. Inhibition of transcriptional activation of dihydrotestosterone **2** by the test compounds **9a**–**f**. NIH3T3 cells were transfected with hAR expression vector, ARE/Luci (firefly Luciferase) and pRL/CMV (*Renilla* Luciferase), and incubated with the test compounds (10^{-8}–10^{-5} M) plus DHT (10^{-10} M). The response of DHT (10^{-10} M) alone was defined as 100%. Values are percentages of the transcriptional response of DHT (10^{-10} M).

similar activity to flutamide **3** (IC_{50} = 0.63 nM). These potent AR antagonists and flutamide were compared dose-dependently on sigmoid curve (Fig. 6).

4. Results and discussion

In general, the manifestation of agonistic or antagonistic activity towards various nuclear receptors may depend upon conformational alteration of helix-12 in the ligand-binding domain. When helix-12 is located in an appropriate position to interact with co-regulators, agonistic activity is expressed. In contrast, antagonistic activity is expressed when helix-12 cannot interact with co-regulators.[31]

The structural requirements for AR ligands have been revealed by X-ray co-crystallographic analyses of the complexes of the ligand-binding domain of AR and its T877A mutant with dihydrotestosterone **2**.[32,33] The carbonyl group of dihydrotestosterone **2** hydrogen bonds through a water molecule to the Arg-752 residue and the Gln-711 residue of the AR ligand-binding domain, and the 17β-hydroxyl group of **2** hydrogen bonds to

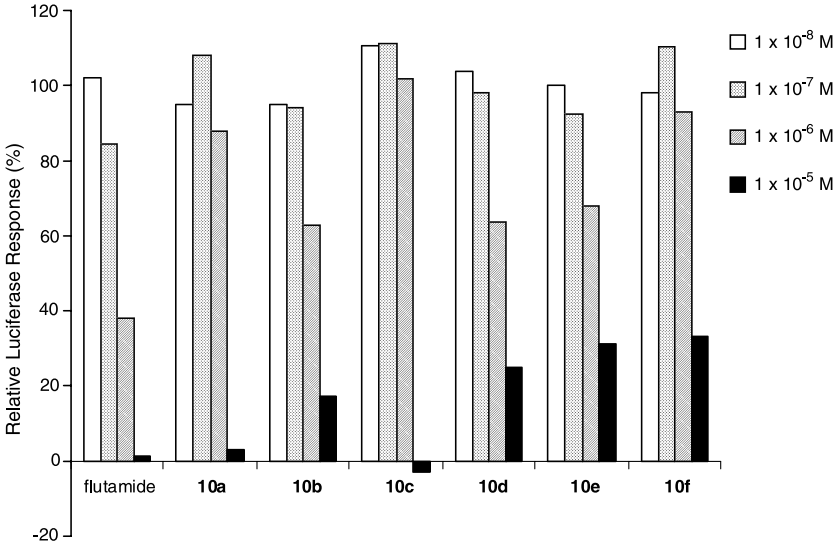


Figure 5. Inhibition of transcriptional activation of dihydrotestosterone **2** by the test compounds **10a**–**f**. NIH3T3 cells were transfected with hAR expression vector, ARE/Luci (firefly Luciferase), and pRL/CMV (*Renilla* Luciferase), and incubated with the test compounds (10^{-8}–10^{-5} M) plus DHT (10^{-10} M). The response of DHT (10^{-10} M) alone was defined as 100%. Values are percentages of the transcriptional response of DHT (10^{-10} M).

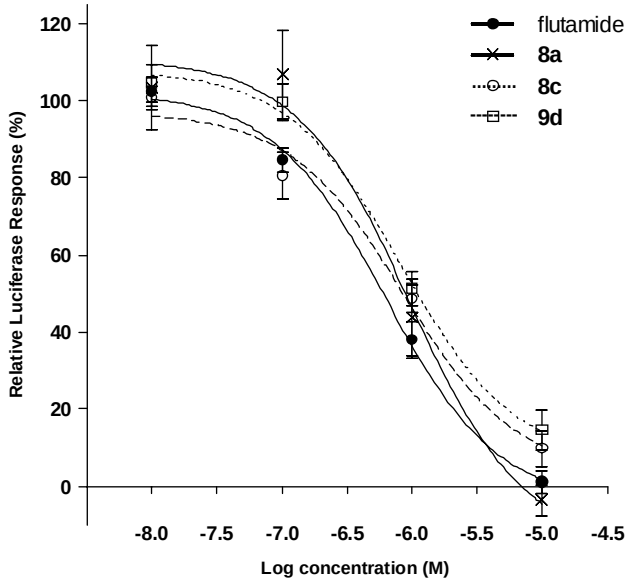


Figure 6. Dose-dependent sigmoid curve of flutamide and most potent compounds, such as **8a**, **8c**, and **9d**. These results were obtained from transient transactivation assay using NIH3T3 cells transfected with hAR expression vector. The transcriptional response of DHT (10^{-10} M) alone was defined as 100%. Values of a vertical axis are percentages of the transcriptional response of DHT (10^{-10} M).

the Thr-877 residue and the Asn-705 residue. More recently, the co-crystal structure of the mutant T877A AR ligand-binding domain with a synthetic AR ligand containing a 4-nitronaphthyl group has been reported by Salvati and co-workers, and it was clear that the 4-nitro group makes similar contacts with both Arg-752 and Gln-711.[34] Polar functionalities, such as cyano and nitro groups, appended to synthetic AR modulators, are assumed to be the anchors for binding to AR, and so are promising candidates for the hydrogen-bonding components of novel carborane-containing androgen antagonists. Our results suggest that the hydrogen-bonding acceptors, cyano and nitro groups, could be aligned suitably to interact with both Arg-752 and Gln-711, provided that there is a methylene group between the carboranes and the phenyl group.

The carborane cage may play an important role in the expression of AR-antagonistic activity through destabilizing the interaction between AR and co-activator; this idea is consistent with the observation that there were no remarkable differences in anti-androgenic activity among the test compounds. In other words, a clash between the spherical bulky carborane cage and the Thr-877 residue may lead to displacement of helix-12 through movement of helix-3 and/or helix-10/11, blocking interaction of the AR–ligand complex with cellular co-regulators to manifest anti-androgenic activity.[34]

5. Conclusion

In conclusion, we have found a series of novel AR-antagonistic *p*- and *m*-carborane derivatives bearing a cyano or nitrobenzyl group. The derivatives **8a**, **8c**, and **9d** showed similar AR-antagonistic potency to the well-known synthetic AR antagonist, flutamide **3**. The AR-antagonistic activity seems not to depend much on the location of the cyano or nitro group, but rather may be due to the steric bulkiness of the carborane moiety. The carborane may influence the stability of the ligand complex with the AR ligand-binding region via hydrophobic interaction with the hydrophobic region of the AR ligand-binding pocket, resulting in high binding affinity to AR. We suggest that the carborane cage may be a privileged hydrophobic pharmacophore for the expression of AR-antagonistic activity.

6. Experimental

6.1. General considerations

Melting points were determined with a Yanaco micro melting point apparatus without correction. ^{1}H NMR and ^{13}C NMR spectra were recorded with a JEOL JNM-EX-270 spectrometer in $CDCl_3$. Chemical shifts for ^{1}H NMR spectra were referenced to tetramethylsilane (0.0 ppm) as an internal standard. Chemical shifts for ^{13}C NMR spectra were referenced to residual ^{13}C present in the deuterated solvent. The chemical shifts are reported in parts per million (δ scale) and all coupling constants (J) are in hertz (hertz). The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double doublet), dt (double triplet), and br (broad). Mass spectra were recorded on a JEOL JMS-DX-303 spectrometer. Elemental analyses were performed by a Perkin Elmer 2400 CHN analyzer. Column chromatography was carried out using Merck silica gel 60 (0.063–0.200 μm). TLC was performed on Merck silica gel 60 F_{254} and the spots were detected under UV light (wavelength 254 nm).

6.1.1. Hydroxymethyl-1,12-dicarba-*closo*-dodecaborane (13). To a solution of *p*-carborane (10.0 g, 69.3 mmol) in 60 mL of dry benzene and 30 mL of dry ether a solution of 1.57 M of *n*-BuLi in hexane (52 mL, 83.2 mmol) was added dropwise at 0 °C under an argon (Ar) atmosphere, and the mixture was stirred at room temperature for 1 h. The mixture was cooled to 0 °C and paraformaldehyde (3.12 g, 104 mmol) was added. The reaction mixture was stirred at 10 °C for 11 h, then quenched with 10% HCl aqueous solution, and the resulting solution was extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$, and then concentrated. Purification by silica gel column chromatography (*n*-hexane/AcOEt = 10:1) gave **13** as a colorless solid (8.65 g, 71%): colorless cubes (CH_2Cl_2/*n*-hexane); mp 209–211 °C (lit.[35] mp 208–208.5 °C); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.0–3.5 (br m, 10H), 1.55 (t, 1H, J = 7.3 Hz), 2.70 (br s, 1H), 3.47 (d, 2H, J = 7.3 Hz); MS (EI) *m*/*z*: 174 (M^+, 100%).

6.1.2. 1-Hydroxymethyl-1,7-dicarba-*closo*-dodecaborane (14). Compound **14** was prepared in a similar manner to that described for **13** (46% yield): colorless prisms (CH_2Cl_2/*n*-hexane); mp 226 °C (lit.[35] mp 222–224 °C); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.0–3.5 (br m, 10H), 2.26 (t, 1H, J = 7.1 Hz), 2.86 (br s, 1H), 3.81 (d, 2H, J = 6.8 Hz); MS (EI) *m*/*z*: 174 (M^+, 100%).

6.1.3. 1-*tert*-Butyldimethylsiloxymethyl-1,12-dicarba-*closo*-dodecaborane (15). A mixture of **13** (8.65 g, 49.09 mmol), imidazole (5.0 g, 73.6 mmol) and *tert*-butyldimethylsilyl chloride (11.1 g, 73.6 mmol) in 50 mL of CH_2Cl_2 was stirred at room temperature for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and the resulting solution was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over $MgSO_4$, then concentrated. Purification by silica gel column chromatography (*n*-hexane/AcOEt = 10:1) gave **15** as a colorless solid (12.9 g, 91%): colorless prisms (*n*-hexane); mp 36 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): −0.04 (s, 6H), 0.85 (s, 9H), 1.0–3.5 (br m, 10H), 2.70 (br s, 1H), 3.47 (s, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −5.6, 18.2, 25.7, 59.0, 66.7, 85.1; MS (EI) *m*/*z*: 288 (M^+), 231 (100%); HRMS Calcd for $C_9H_{28}B_{10}OSi$: 288.2913. Found 288.2899.

6.1.4. 1-*tert*-Butyldimethylsiloxymethyl-1,7-dicarba-*closo*-dodecaborane (16). Compound **16** was prepared in a similar manner to that described for **14** (94% yield): colorless cubes (*n*-hexane); mp 35.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): −0.10 (s, 6H), 0.80 (s, 9H), 1.0–3.5 (br m, 10H), 2.79 (br s, 1H), 3.64 (s, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −5.6, 18.2, 25.7, 54.6, 65.5, 77.7; MS (EI) *m*/*z*: 288 (M^+), 232 (100%); HRMS Calcd for $C_9H_{28}B_{10}OSi$: 288.2913. Found 288.2894.

6.1.5. 1-*tert*-Butyldimethylsiloxymethyl-12-(2-cyanobenzyl)-1,12-dicarba-*closo*-dodecaborane (17a). To a solution of **15** (300 mg, 1.04 mmol) in 2 mL of dry THF a solution of 1.59 M of *n*-BuLi in hexane (0.79 mL, 1.25 mmol) was added dropwise at 0 °C under an Ar atmosphere. The mixture was stirred at room temperature for 30 min, then cooled to 0 °C, and α-bromo-*o*-tolunitrile (245 mg, 1.25 mmol) was added. The resulting mixture was stirred at room temperature for 4 h, quenched with 10% aqueous HCl solution, and extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$, and then concentrated. Purification by silica gel column chromatography (*n*-hexane/AcOEt = 30:1) gave **17a** as a colorless solid (355 mg, 81%): colorless needles (CH_2Cl_2/*n*-hexane); mp 103 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 0.06 (s, 6H), 0.82 (s, 9H), 1.0–3.5 (br m, 10H), 3.16 (s, 2H), 3.41 (s, 2H), 7.14 (dd, 1H, J = 7.7 Hz), 7.35 (ddd, 1H, J = 1.5 Hz, 7.6 Hz, 7.7 Hz), 7.50 (ddd, 1H, J = 1.5 Hz, 7.6 Hz, 7.7 Hz), 7.58 (dd, 1H, J = 1.5 Hz, 7.7 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −5.7, 18.1, 25.6, 43.1, 65.8, 78.3, 80.6, 112.2, 118.4, 128.8, 131.0, 133.0, 134.1, 138.1; MS (EI) *m*/*z*: 403 (M^+), 347 (100%); Anal. Calcd for $C_{17}H_{33}B_{10}NOSi$: C, 50.58; H, 8.24; N, 3.47. Found: C, 50.54; H, 8.11; N, 3.41.

6.1.6. 1-*tert*-Butyldimethylsiloxymethyl-12-(3-cyanobenzyl)-1,12-dicarba-*closo*-dodecaborane (17b). Compound **17b** was prepared in a similar manner to that described for **17a** (100% yield): colorless needles (*n*-hexane); mp 61–62 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): −0.06 (s, 6H), 0.83 (s, 9H), 1.0–3.5 (br m, 10H), 2.92 (s, 2H), 3.41 (s, 2H), 7.20 (d, 1H, J = 7.7 Hz), 7.26 (s, 1H), 7.37 (t, 1H, J = 7.7 Hz), 7.54 (d, 1H, J = 7.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −5.7, 18.1, 25.6, 43.1, 65.8, 78.3, 80.7, 112.3, 118.5, 129.0, 131.0, 133.1, 134.2, 138.2; MS (EI) *m*/*z*: 403 (M^+), 347 (100%); Anal. Calcd for $C_{17}H_{33}B_{10}NOSi$: C, 50.58; H, 8.24; N, 3.47. Found: C, 50.73; H, 8.38; N, 3.49.

6.1.7. 1-*tert*-Butyldimethylsiloxymethyl-12-(4-cyanobenzyl)-1,12-dicarba-*closo*-dodecaborane (17c). Compound **17c** was prepared in a similar manner to that described for **17a** (83% yield): colorless cubes (CH_2Cl_2/*n*-hexane); mp

117–118 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): −0.06 (s, 6H), 0.82 (s, 9H), 1.0–3.5 (br m, 10H), 2.94 (s, 2H), 3.40 (s, 2H), 7.07 (d, 2H, J = 8.4 Hz), 7.55 (d, 2H, J = 8.4 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −5.7, 18.1, 25.6, 43.6, 65.9, 78.2, 80.8, 111.3, 118.6, 130.6, 132.0, 142.0; MS (EI) *m*/*z*: 403 (M^+), 347 (100%); Anal. Calcd for $C_{17}H_{33}B_{10}NOSi$: C, 50.58; H, 8.24; N, 3.47. Found: C, 50.68; H, 8.21; N, 3.38.

6.1.8. 1-*tert*-Butyldimethylsiloxymethyl-12-(2-nitrobenzyl)-1,12-dicarba-*closo*-dodecaborane (17d). Compound **17d** was prepared in a similar manner to that described for **17a** (65% yield): pale yellow prisms (CH_2Cl_2/*n*-hexane); mp 92–93 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): −0.07 (s, 6H), 0.82 (s, 9H), 1.0–3.5 (br m, 10H), 3.39 (s, 2H), 3.46 (s, 2H), 7.10 (dd, 1H, J = 1.6 Hz, 7.6 Hz), 7.40 (ddd, 1H, J = 1.6 Hz, 7.4 Hz, 8.1 Hz), 7.50 (ddd, 1H, J = 1.5 Hz, 7.4 Hz, 7.6 Hz), 7.88 (dd, 1H, J = 1.3 Hz, 7.9 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −6.0, 18.1, 25.6, 38.9, 65.9, 78.3, 80.9, 125.0, 128.7, 131.3, 132.5, 133.8, 149.1; MS (EI) *m*/*z*: 423 (M^+), 366 (100%); Anal. Calcd for $C_{16}H_{33}B_{10}NO_3Si$: C, 45.36; H, 7.85; N, 3.31. Found: C, 45.57; H, 7.91; N, 3.16.

6.1.9. 1-*tert*-Butyldimethylsiloxymethyl-12-(3-nitrobenzyl)-1,12-dicarba-*closo*-dodecaborane (17e). Compound **17e** was prepared in a similar manner to that described for **17a** (52% yield): pale yellow leaflets (*n*-hexane); mp 68–69 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): −0.06 (s, 6H), 0.82 (s, 9H), 1.0–3.5 (br m, 10H), 3.00 (s, 2H), 3.41 (s, 2H), 7.30 (m, 1H), 7.45 (dd, 1H, J = 7.9 Hz, 8.1 Hz), 7.84 (dd, 1H, J = 1.8 Hz, 2.3 Hz), 8.12 (ddd, 1H, J = 1.2 Hz, 2.3 Hz, 8.1 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −5.7, 18.1, 25.6, 43.2, 65.9, 78.3, 80.8, 122.4, 124.6, 129.1, 135.9, 138.7, 148.0; MS (EI) *m*/*z*: 423 (M^+), 367 (100%); HRMS Calcd for $C_{16}H_{33}B_{10}NO_3Si$: 423.3233. Found 423.3206.

6.1.10. 1-*tert*-Butyldimethylsiloxymethyl-12-(4-nitrobenzyl)-1,12-dicarba-*closo*-dodecaborane (17f). Compound **17f** was prepared in a similar manner to that described for **17a** (58% yield): colorless prisms (CH_2Cl_2/*n*-hexane); mp 116 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 0.06 (s, 6H), 0.82 (s, 9H), 2.99 (s, 2H), 3.41 (s, 2H), 7.13 (d, 2H, J = 8.7 Hz), 8.12 (d, 2H, J = 8.7 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −5.7, 18.2, 25.6, 43.3, 65.9, 77.2, 80.9, 123.5, 130.7, 144.0, 147.3; MS (EI) *m*/*z*: 423 (M^+), 366 (100%); Anal. Calcd for $C_{16}H_{33}B_{10}NO_3Si$: C, 45.36; H, 7.85; N, 3.31. Found: C, 45.52; H, 7.87; N, 3.24.

6.1.11. 1-*tert*-Butyldimethylsiloxymethyl-7-(2-cyanobenzyl)-1,7-dicarba-*closo*-dodecaborane (18a). Compound **18a** was prepared in a similar manner to that described for **17a** (82% yield): colorless cotton (*n*-hexane); mp 40–41 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 0.22 (s, 6H), 1.0–3.5 (br m, 10H), 1.08 (s, 9H), 3.70 (s, 2H), 3.91 (s, 2H), 7.50 (m, 1H), 7.61 (ddd, 1H, J = 1.2 Hz, 7.6 Hz, 7.7 Hz), 7.76 (dd, 1H, J = 1.5 Hz, 7.7 Hz), 7.83 (td, 1H, J = 1.2 Hz, 7.7 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −5.5, 18.2, 25.7, 40.6, 65.4, 73.8, 77.7, 113.3, 117.6, 128.1, 131.5, 132.4, 132.8, 140.0; MS (EI) *m*/*z*: 403 (M^+), 347 (100%); HRMS Calcd for $C_{17}H_{33}B_{10}NOSi$: 403.3335. Found 403.3376.

6.1.12. 1-*tert*-Butyldimethylsiloxymethyl-7-(3-cyanobenzyl)-1,7-dicarba-*closo*-dodecaborane (18b). Compound **18b** was prepared in a similar manner to that described for **17a** (88% yield): colorless cotton (*n*-hexane); mp 51–52 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 0.22 (s, 6H), 1.0–3.5 (br m, 10H), 1.08 (s, 9H), 3.45 (s, 2H), 3.89 (s, 2H), 7.57 (m, 1H), 7.56–7.68 (m, 2H), 7.80 (ddd, 1 H, J = 1.5 Hz, 7.6 Hz, 7.7 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −5.5, 18.2, 25.6, 42.4, 65.3, 74.1, 77.7, 112.5, 118.3, 129.1, 131.1, 133.1, 134.2, 138.0; MS (EI) *m*/*z*: 403 (M^+), 346 (100%); Anal. Calcd for $C_{17}H_{33}B_{10}NOSi$: C, 50.58; H, 8.24; N, 3.47. Found: C, 50.75; H, 8.32; N, 3.47.

6.1.13. 1-*tert*-Butyldimethylsiloxymethyl-7-(4-cyanobenzyl)-1,7-dicarba-*closo*-dodecaborane (18c). Compound **18c** was prepared in a similar manner to that described for **17a** (82% yield): colorless prisms (CH_2Cl_2/*n*-hexane); mp 97–98 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 0.22 (s, 6H), 1.0–3.5 (br m, 10H), 1.09 (s, 9H), 3.47 (s, 2H), 3.89 (s, 2H), 7.45 (d, 2H, J = 8.2 Hz), 7.83 (d, 2H, J = 8.2 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −5.6, 18.2, 25.7, 42.8, 65.3, 74.0, 77.6, 108.4, 111.5, 118.3, 130.5, 132.0, 141.7; MS (EI) *m*/*z*: 403 (M^+), 346 (100%); Anal. Calcd for $C_{17}H_{33}B_{10}NOSi$: C, 50.58; H, 8.24; N, 3.47. Found: C, 50.80; H, 8.04; N, 3.39.

6.1.14. 1-*tert*-Butyldimethylsiloxymethyl-7-(2-nitrobenzyl)-1,7-dicarba-*closo*-dodecaborane (18d). Compound **18d** was prepared in a similar manner to that described for **17a** (84% yield): colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 0.22 (s, 6H), 1.0–3.5 (br m, 10 H), 1.08 (s, 9H), 3.89 (s, 2H), 3.99 (s, 2H), 7.48 (dd, 1H, J = 1.5 Hz, 7.6 Hz), 7.67 (ddd, 1H, J = 1.5 Hz, 7.6 Hz 8.1 Hz), 7.79 (dt, 1H, J = 1.3 Hz, 7.6 Hz), 8.17 (dd, 1H, J = 1.3 Hz, 8.2 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −5.6, 18.2, 25.7, 38.3, 65.4, 73.9, 77.6, 125.0, 128.8, 131.1, 132.7, 133.8, 148.8; MS (EI) *m*/*z*: 423 (M^+), 367 (100%); HRMS Calcd for $C_{16}H_{33}B_{10}NO_3Si$: 423.3233. Found 423.3220.

6.1.15. 1-*tert*-Butyldimethylsiloxymethyl-7-(3-nitrobenzyl)-1,7-dicarba-*closo*-dodecaborane (18e). Compound **18e** was prepared in a similar manner to that described for **17a** (51% yield): colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 0.22 (s, 6H), 1.0–3.5 (br m, 10 H), 1.07 (s, 9H), 3.54 (s, 2H), 3.90 (s, 2H), 7.21 (s, 1H), 7.69–7.76 (m, 2H), 8.38 (d, 1H, J = 7.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −5.6, 18.2, 25.6, 42.4, 65.3, 74.1, 77.7, 122.5, 124.5, 129.3, 135.9, 138.5, 148.0; MS (EI) *m*/*z*: 423 (M^+), 366 (100%); HRMS Calcd for $C_{16}H_{33}B_{10}NO_3Si$: 423.3233. Found 423.3220.

6.1.16. 1-*tert*-Butyldimethylsiloxymethyl-7-(4-nitrobenzyl)-1,7-dicarba-*closo*-dodecaborane (18f). Compound **18f** was prepared in a similar manner to that described for **17a** (45% yield): colorless cubes (*n*-hexane); mp 65.5–67.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 0.22 (s, 6H), 1.0–3.5 (br m, 10H), 1.08 (s, 9H), 2.53 (s, 2H), 3.90 (s, 2H), 7.51 (d, 2H, J = 8.6 Hz), 8.39 (d, 2H, J = 8.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −5.6, 18.2, 25.6, 42.5, 65.3, 73.8, 77.7, 123.5, 130.7, 143.7, 147.2; MS (EI) *m*/*z*: 423 (M^+), 367 (100%); Anal.

Calcd for $C_{16}H_{33}B_{10}NO_3Si$: C, 45.36; H, 7.83; N, 3.31. Found: C, 45.10; H, 7.62; N, 3.21.

6.1.17. 1-Hydroxymethyl-12-(2-cyanobenzyl)-1,12-dicarba-*closo*-dodecaborane (8a). To a solution of **17a** (200 mg, 0.5 mmol) in 2 mL of dry THF a solution of 1 M of TBAF in THF (0.75 mL, 0.75 mmol) was added, and the reaction mixture was stirred at room temperature for 30 min. The reaction was quenched with water and the solution was extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$, and then concentrated. Purification by silica gel column chromatography (*n*-hexane/AcOEt = 10:1 to 3:1) gave **8a** as a colorless solid (109 mg, 100%): colorless flakes (CH_2Cl_2/*n*-hexane); mp 130 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.0–3.5 (br m, 10H), 1.67 (br s, 1H), 3.19 (s, 2H), 3.46 (s, 2H), 7.14 (d, 1H, J = 7.7 Hz), 7.36 (ddd, 1H, J = 1.2 Hz, 7.6 Hz, 7.7 Hz), 7.51 (ddd, 1H, J = 1.5 Hz, 7.6 Hz, 7.7 Hz), 7.60 (dd, 1H, J = 1.2 Hz, 7.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): 41.4, 65.7, 78.4, 80.6, 113.2, 117.7, 128.1, 131.6, 132.4, 132.9, 140.1; MS (EI) *m*/*z*: 289 (M^+, 100%); Anal. Calcd for $C_{11}H_{19}B_{10}NO$: C, 45.65; H, 6.62; N, 4.84. Found: C, 45.88; H, 6.30; N, 4.76.

6.1.18. 1-Hydroxymethyl-12-(3-cyanobenzyl)-1,12-dicarba-*closo*-dodecaborane (8b). Compound **8b** was prepared in a similar manner to that described for **8a** (99% yield): colorless leaflets (CH_2Cl_2/*n*-hexane); mp 118–118.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.0–3.5 (br m, 10H), 1.80 (br s, 1H), 2.94 (s, 2H), 3.46 (s, 2H), 7.20 (ddd, 1H, J = 1.3 Hz, 1.6 Hz, 7.7 Hz), 7.26 (s, 1H), 7.39 (dd, 1H, J = 7.3 Hz, 7.7 Hz), 7.55 (ddd, 1H, J = 1.3 Hz, 1.5 Hz, 7.7 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): 43.2, 65.7, 78.7, 80.6, 112.3, 118.5, 129.1, 131.1, 133.2, 134.3, 138.1; MS (EI) *m*/*z*: 289 (M^+, 100%); Anal. Calcd for $C_{11}H_{19}B_{10}NO$: C, 45.65; H, 6.62; N, 4.84. Found: C, 45.70; H, 6.34; N, 4.80.

6.1.19. 1-Hydroxymethyl-12-(4-cyanobenzyl)-1,12-dicarba-*closo*-dodecaborane (8c). Compound **8c** was prepared in a similar manner to that described for **8a** (100% yield): colorless prisms (CH_2Cl_2/*n*-hexane); mp 177.5–178 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.0–3.5 (br m, 10H), 1.60 (br s, 1H), 2.95 (s, 2H), 3.46 (s, 2H), 7.07 (d, 2H, J = 8.1 Hz), 7.56 (d, 2H, J = 8.1 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): 43.7, 65.8, 78.7, 80.5, 111.4, 118.5, 130.5, 132.0, 141.7; MS (EI) *m*/*z*: 289 (M^+, 100%); Anal. Calcd for $C_{11}H_{19}B_{10}NO$: C, 45.65; H, 6.62; N, 4.84. Found: C, 45.89; H, 6.41; N, 4.81.

6.1.20. 1-Hydroxymethyl-12-(2-nitrobenzyl)-1,12-dicarba-*closo*-dodecaborane (8d). Compound **8d** was prepared in a similar manner to that described for **8a** (100% yield): pale yellow needles (CH_2Cl_2/*n*-hexane); mp 123.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.0–3.5 (br m, 10H), 1.72 (br s, 1H), 3.02 (s, 2H), 3.46 (s, 2H), 7.30 (m, 1H), 7.45 (dd, 1H, J = 7.7 Hz, 8.2 Hz), 7.84 (dd, 1H, J = 1.8 Hz, 2.1 Hz), 8.13 (ddd, 1H, J = 1.2 Hz, 2.1 Hz, 8.2 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): 39.0, 65.8, 78.7, 80.5, 125.0, 128.7, 131.0, 132.5, 133.7, 148.9; MS (EI) *m*/*z*: 309 (M^+), 262 (100%); Anal. Calcd for $C_{10}H_{19}B_{10}NO_3$: C, 38.82; H, 6.19; N, 4.53. Found: C, 39.08; H, 5.96; N, 4.51.

6.1.21. 1-Hydroxymethyl-12-(3-nitrobenzyl)-1,12-dicarba-*closo*-dodecaborane (8e). Compound **8e** was prepared in a similar manner to that described for **8a** (81% yield): colorless needles (CH_2Cl_2/*n*-hexane); mp 115.5–116 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.0–3.5 (br m, 10H), 1.68 (br s, 1H), 3.44 (s, 2H), 3.48 (s, 2H), 7.26 (dd, 1H, J = 1.5 Hz, 7.6 Hz), 7.42 (ddd, 1H, J = 1.5 Hz, 7.4 Hz, 8.1 Hz), 7.52 (ddd, 1H, J = 1.5 Hz, 7.4 Hz, 7.6 Hz), 7.90 (dd, 1H, J = 1.5 Hz, 8.1 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): 43.16, 65.70, 78.69, 80.52, 122.50, 124.52, 129.19, 135.94, 138.49, 147.98; MS (EI) *m*/*z*: 309 (M^+), 292 (100%); Anal. Calcd for $C_{10}H_{19}B_{10}NO_3$: C, 38.82; H, 6.19; N, 4.53. Found: C, 38.94; H, 5.99; N, 4.49.

6.1.22. 1-Hydroxymethyl-12-(4-nitrobenzyl)-1,12-dicarba-*closo*-dodecaborane (8f). Compound **8f** was prepared in a similar manner to that described for **8a** (94% yield): pale yellow leaflets (CH_2Cl_2/*n*-hexane); mp 123.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.0–3.5 (br m, 10H), 1.59 (br s, 1H), 3.01 (s, 2H), 3.47 (s, 2H), 7.13 (d, 2H, J = 8.7 Hz), 8.13 (d, 2H, J = 8.7 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): 43.3, 65.7, 78.5, 80.7, 123.5, 130.7, 143.8, 147.2; MS (EI) *m*/*z*: 309 (M^+, 100%); Anal. Calcd for $C_{10}H_{19}B_{10}NO_3$: C, 38.82; H, 6.19; N, 4.53. Found: C, 38.79; H, 5.97; N, 4.43.

6.1.23. 1-Hydroxymethyl-7-(2-cyanobenzyl)-1,7-dicarba-*closo*-dodecaborane (9a). Compound **9a** was prepared in a similar manner to that described for **8a** (62% yield): colorless needles (CH_2Cl_2/*n*-hexane); mp 116–117 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.0–3.5 (br m, 10H), 2.79 (br s, 1H), 3.49 (s, 2H), 3.74 (s, 2H), 7.28 (d, 1H, J = 7.9 Hz), 7.41 (t, 1H, J = 7.6 Hz), 7.58 (t, 1H, J = 7.6 Hz), 7.65 (d, 1H, J = 7.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): 40.6, 64.9, 74.0, 77.7, 113.0, 117.7, 128.2, 131.5, 132.6, 132.9, 140.0; MS (EI) *m*/*z*: 289 (M^+, 100%); Anal. Calcd for $C_{11}H_{19}B_{10}NO$: C, 45.65; H, 6.62; N, 4.84. Found: C, 45.89; H, 6.61; N, 4.74.

6.1.24. 1-Hydroxymethyl-7-(3-cyanobenzyl)-1,7-dicarba-*closo*-dodecaborane (9b). Compound **9b** was prepared in a similar manner to that described for **8a** (95% yield): colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.0–3.5 (br m, 10H), 3.06 (br s, 1 H), 3.26 (s, 2H), 3.73 (s, 2H), 7.38 (dd, 1H, J = 3.3 Hz, 7.7 Hz), 7.40 (s, 1H), 7.45 (t, 1H, J = 7.7 Hz), 7.59 (d, 1H, J = 7.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): 42.1, 64.8, 74.3, 77.7, 112.1, 118.3, 129.2, 131.1, 133.0, 134.4, 137.9; MS (EI) *m*/*z*: 289 (M^+, 100%); HRMS Calcd for $C_{11}H_{19}B_{10}NO$: 289.2470. Found 289.2443.

6.1.25. 1-Hydroxymethyl-7-(4-cyanobenzyl)-1,7-dicarba-*closo*-dodecaborane (9c). Compound **9c** was prepared in a similar manner to that described for **8a** (87% yield): colorless prisms (CH_2Cl_2/*n*-hexane); mp 117–118 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.0–3.5 (br m, 10H), 2.75 (br s, 1H), 3.26 (s, 2H), 3.71 (s, 2H), 7.22 (d, 2H, J = 8.2 Hz), 7.60 (d, 2H, J = 8.2 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): 42.6, 64.8, 74.2, 77.6, 111.2, 118.3, 130.5, 132.1, 141.7; MS (EI) *m*/*z*: 289 (M^+, 100%); Anal. Calcd for $C_{11}H_{19}B_{10}NO$: C,

45.65; H, 6.62; N, 4.84. Found: C, 45.87; H, 6.55; N, 4.79.

6.1.26. 1-Hydroxymethyl-7-(2-nitrobenzyl)-1,7-dicarba-*closo*-dodecaborane (9d). Compound **9d** was prepared in a similar manner to that described for **8a** (84% yield): brown needles (CH_2Cl_2/*n*-hexane); mp 81–81.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.0–3.5 (br m, 10H), 2.71 (br s, 1H), 3.71 (s, 2H), 3.78 (s, 2H), 7.26 (dd, 1H, J = 1.3 Hz, 7.6 Hz), 7.47 (dt, 1H, J = 1.5 Hz, 8.1 Hz), 7.58 (ddd, 1H, J = 1.3 Hz, 7.6 Hz, 8.1 Hz), 7.96 (dd, 1H, J = 1.3 Hz, 8.1 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): 38.2, 65.2, 74.2, 77.2, 125.3, 129.1, 131.2, 133.0, 133.9, 148.9; MS (EI) *m*/*z*: 309 (M^+, 100%); Anal. Calcd for $C_{10}H_{19}B_{10}NO_3$: C, 38.82; H, 6.19; N, 4.53. Found: C, 38.73; H, 6.10; N, 4.40.

6.1.27. 1-Hydroxymethyl-7-(3-nitrobenzyl)-1,7-dicarba-*closo*-dodecaborane (9e). Compound **9e** was prepared in a similar manner to that described for **8a** (85% yield): yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.0–3.5 (br m, 10H), 2.43 (br s, 1 H), 3.34 (s, 2H), 3.75 (s, 2H), 7.48 (ddd, 1H, J = 1.5 Hz, 2.1 Hz, 7.6 Hz), 7.52 (dd, 1H, J = 7.6 Hz, 7.7 Hz), 7.96 (dd, 1 H, J = 1.5 Hz, 1.8 Hz), 8.16 (ddd, 1 H, J = 1.8 Hz, 2.1 Hz, 7.9 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): 42.3, 65.0, 74.3, 77.6, 122.6, 124.5, 129.4, 135.9, 138.3, 148.0; MS (EI) *m*/*z*: 309 (M^+), 292 (100%); HRMS Calcd for $C_{10}H_{19}B_{10}NO_3$: 309.2368. Found 309.2380.

6.1.28. 1-Hydroxymethyl-7-(4-nitrobenzyl)-1,7-dicarba-*closo*-dodecaborane (9f). Compound **9f** was prepared in a similar manner to that described for **8a** (70% yield): yellow cubes (CH_2Cl_2/*n*-hexane); mp 61–61.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.0–3.5 (br m, 10H), 2.44 (br s, 1H), 3.33 (s, 2H), 3.74 (s, 2H), 7.29 (d, 2H, J = 8.6 Hz), 8.17 (d, 2H, J = 8.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): 42.4, 65.1, 74.2, 77.2, 123.7, 130.8, 143.7, 147.4; MS (EI) *m*/*z*: 309 (M^+), 292 (100%); Anal. Calcd for $C_{10}H_{19}B_{10}NO_3$: C, 38.82; H, 6.19; N, 4.53. Found: C, 39.21; H, 6.07; N, 4.40.

6.1.29. 1-Hydroxy-1,12-dicarba-*closo*-dodecaborane (19). A solution of 1.59 M of *n*-BuLi in hexane (1.4 mL, 2.18 mmol) was added dropwise to a solution of *p*-carborane (300 mg, 2.08 mmol) in 3 mL of dry ether at 0 °C under an Ar atmosphere, and the mixture was stirred at room temperature for 30 min. It was cooled to −30 °C and trimethyl borate (0.28 mL, 2.5 mmol) was added in one portion. The reaction mixture was warmed to 0 °C over 1 h. A mixture of 1 mL of 30% H_2O_2 and 1 mL AcOH was added to it, and the resulting solution was stirred at room temperature for 14 h. Saturated aqueous $NaHSO_3$ (4 mL) and 10% NaOH (6 mL) were added to the reaction mixture, and the solution was stirred at room temperature for 1 h, and then extracted with ether. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated. Purification by silica gel column chromatography (*n*-hexane/AcOEt = 30:1) gave **19** as a colorless solid (184 mg, 55%): colorless needles (CH_2Cl_2/*n*-hexane); mp 148–149.5 °C (lit.[36] mp 148 °C); ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.0–3.5 (br m, 10H), 2.43 (br s, 1H); MS (EI) *m*/*z*: 160 (M^+, 100%).

6.1.30. 1-*tert*-Butyldimethylsiloxy-1,12-dicarba-*closo*-dodecaborane (20). A mixture of **19** (60 mg, 0.38 mmol), Et_3N (156 μL, 1.12 mmol), and *tert*-butyldimethylsilyl chloride (170 mg, 1.12 mmol) in 3 mL of CH_2Cl_2 was stirred at room temperature for 2 h. The reaction was quenched with 10% aqueous HCl solution and the solution was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over $MgSO_4$, and then concentrated. Purification by silica gel column chromatography (*n*-hexane) gave **20** as a colorless oil (79 mg, 75%): colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 0.08 (s, 6H), 0.74 (s, 9H), 1.0–3.5 (br m, 10H), 2.37 (br s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −4.3, 17.6, 25.1, 47.6, 111.6; MS (EI) *m*/*z*: 274 (M^+), 217 (100%); HRMS Calcd for $C_8H_{26}B_{10}OSi$: 274.2756. Found 274.2774.

6.1.31. 1-*tert*-Butyldimethylsiloxy-12-(2-cyanobenzyl)-1,12-dicarba-*closo*-dodecaborane (21a). Compound **21a** was prepared in a similar manner to that described for **17a** (55% yield): colorless cotton (*n*-hexane); mp 120–122 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 0.04 (s, 6H), 0.72 (s, 9H), 1.0–3.5 (br m, 10H), 3.20 (s, 2H), 7.15 (dd, 1H, J = 1.2 Hz, 7.7 Hz), 7.35 (dt, 1H, J = 1.5 Hz, 7.6 Hz), 7.50 (dt, 1H, J = 1.5 Hz, 7.6 Hz, 7.7 Hz), 7.57 (dd, 1H, J = 1.5 Hz, 7.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −4.36, 17.60, 25.02, 39.64, 67.36, 109.05, 113.11, 117.52, 127.86, 131.29, 132.17, 132.57, 140.53; MS (EI) *m*/*z*: 389 (M^+), 332 (100%); Anal. Calcd for $C_{16}H_{31}B_{10}NOSi$: C, 49.32; H, 8.02; N, 3.59. Found: C, 49.20; H, 7.98; N, 3.54.

6.1.32. 1-*tert*-Butyldimethylsiloxy-12-(3-cyanobenzyl)-1,12-dicarba-*closo*-dodecaborane (21b). Compound **21b** was prepared in a similar manner to that described for **17a** (77% yield): colorless needles (CH_2Cl_2/*n*-hexane); mp 98 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 0.05 (s, 6H), 0.72 (s, 9H), 1.0–3.5 (br m, 10H), 2.95 (s, 2H), 7.21 (d, 1H, J = 7.7 Hz), 7.25 (s, 1H), 7.37 (dd, 1H, J = 7.6 Hz, 7.7 Hz), 7.52 (d, 1H, J = 7.7 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −4.40, 17.57, 24.99, 41.29, 67.62, 108.99, 112.21, 118.26, 128.87, 130.83, 132.82, 133.91, 138.54; MS (EI) *m*/*z*: 389 (M^+), 332 (100%); HRMS Calcd for $C_{16}H_{31}B_{10}NOSi$: 389.3178. Found 389.3207.

6.1.33. 1-*tert*-Butyldimethylsiloxy-12-(4-cyanobenzyl)-1,12-dicarba-*closo*-dodecaborane (21c). Compound **21c** was prepared in a similar manner to that described for **17a** (73% yield): colorless leaflets (CH_2Cl_2/*n*-hexane); mp 178–179 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm) 0.04 (s, 6H), 0.72 (s, 9H), 1.0–3.5 (br m, 10H), 2.97 (s, 2H), 7.07 (d, 2H, J = 8.2 Hz), 7.55 (d, 2H, J = 8.4 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −4.33, 17.65, 25.04, 41.83, 67.52, 109.03, 111.28, 118.43, 130.32, 131.89, 142.35; MS (EI) *m*/*z*: 389 (M^+), 332 (100%); Anal. Calcd for $C_{16}H_{31}B_{10}NOSi$: C, 49.32; H, 8.02; N, 3.59. Found: C, 49.36; H, 7.80; N, 3.44.

6.1.34. 1-*tert*-Butyldimethylsiloxy-12-(2-nitrobenzyl)-1,12-dicarba-*closo*-dodecaborane (21d). Compound **21d** was prepared in a similar manner to that described for **17a** (71%

yield): pale yellow cubes (*n*-hexane); mp 104.5–106 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm) 0.03 (s, 6H), 0.71 (s, 9H), 1.0–3.5 (br m, 10H), 3.50 (s, 2H), 7.11 (dd, 1H, J = 1.6 Hz, 7.6 Hz), 7.41 (dt, 1H, J = 1.6 Hz, 8.1 Hz), 7.51 (dt, 1H, J = 1.5 Hz, 7.4 Hz), 7.88 (dd, 1H, J = 1.3 Hz, 8.1 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −4.5, 17.6, 25.0, 37.1, 67.5, 114.9, 125.0, 128.7, 131.8, 132.6, 133.7, 149.0; MS (EI) *m*/*z*: 409 (M^+), 352 (100%); HRMS Calcd for $C_{15}H_{31}B_{10}NO_3Si$: 409.3076. Found 409.3065.

6.1.35. 1-*tert*-Butyldimethylsiloxy-12-(3-nitrobenzyl)-1,12-dicarba-*closo*-dodecaborane (21e). Compound **21e** was prepared in a similar manner to that described for **17a** (60% yield): pale yellow leaflets (*n*-hexane); mp 109.5–110.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$), δ (ppm) 0.05 (s, 6H), 0.72 (s, 9H), 1.0–3.5 (br m, 10H), 3.04 (s, 2H), 7.31 (m, 1H), 7.45 (dd, 1H, J = 7.7 Hz, 8.2 Hz), 7.84 (dd, 1H, J = 1.8 Hz, 2.3 Hz), 8.11 (ddd, 1H, J = 1.2 Hz, 2.3 Hz, 8.2 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −4.3, 25.1, 41.4, 67.6, 109.1, 122.3, 123.6, 129.0, 135.7, 139.1, 147.1; MS (EI) *m*/*z*: 409 (M^+), 352 (100%); Anal. Calcd for $C_{15}H_{31}B_{10}NO_3Si$: C, 43.98; H, 7.63; N, 3.42. Found: C, 44.24; H, 7.77; N, 3.33.

6.1.36. 1-*tert*-Butyldimethylsiloxy-12-(4-nitrobenzyl)-1,12-dicarba-*closo*-dodecaborane (21f). Compound **21f** was prepared in a similar manner to that described for **17a** (71% yield): pale yellow flakes (CH_2Cl_2/*n*-hexane); mp 148–150.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm) 0.04 (s, 6H), 0.71 (s, 9H), 1.0–3.5 (br m, 10H), 3.02 (s, 2H), 7.13 (d, 2H, J = 8.6 Hz), 8.11 (d, 2H, J = 8.7 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): −4.32, 17.65, 25.05, 41.51, 67.32, 109.14, 123.34, 130.46, 144.34, 147.08; MS (EI) *m*/*z*: 409 (M^+), 352 (100%); Anal. Calcd for $C_{15}H_{31}B_{10}NO_3Si$: C, 43.98; H, 7.63; N, 3.42. Found: C, 43.73; H, 7.41; N, 3.28.

6.1.37. 1-Hydroxy-12-(2-cyanobenzyl)-1,12-dicarba-*closo*-dodecaborane (10a). Compound **10a** was prepared in a similar manner to that described for **8a** (quant.): colorless leaflets (acetone/*n*-hexane); mp 172–173 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm) 1.0–3.5 (br m, 10H), 3.19 (s, 2H), 7.14 (d, 1H, J = 7.7 Hz), 7.36 (dt, 1H, J = 1.0 Hz, 7.6 Hz), 7.51 (dt, 1 H, J = 1.5 Hz, 7.7 Hz), 7.59 (d, 1H, J = 7.7 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm): 39.7, 67.9, 106.6, 112.9, 117.5, 128.1, 131.5, 132.6, 132.9, 140.6; MS (EI) *m*/*z*: 275 (M^+, 100%); Anal. Calcd for $C_{10}H_{17}B_{10}NO$: C, 43.62; H, 6.22; N, 5.09. Found: C, 43.64; H, 6.27; N, 4.96.

6.1.38. 1-Hydroxy-12-(3-cyanobenzyl)-1,12-dicarba-*closo*-dodecaborane (10b). Compound **10b** was prepared in a similar manner to that described for **8a** (quant.): colorless needles (acetone/*n*-hexane); mp 201–201.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm) 1.0–3.5 (br m, 10H), 2.95 (s, 2H), 7.20 (d, 1H, J = 7.7 Hz), 7.25 (s, 1H), 7.38 (dd, 1H, J = 7.6 Hz, 7.7 Hz), 7.55 (d, 1H, J = 7.7 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm) 41.4, 68.3, 106.2, 112.4, 118.5, 129.2, 131.2, 133.1, 134.2, 138.5; MS (EI) *m*/*z*: 275 (M^+, 100%); Anal. Calcd for $C_{10}H_{17}B_{10}NO$: C, 43.62; H, 6.22; N, 5.09. Found: C, 43.92; H, 6.27; N, 4.82.

6.1.39. 1-Hydroxy-12-(4-cyanobenzyl)-1,12-dicarba-*closo*-dodecaborane (10c). Compound **10c** was prepared in a similar manner to that described for **8a** (quant.): colorless needles (acetone/*n*-hexane); mp 215–216 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm) 2.97 (s, 2H), 4.22 (br s, 1H), 7.07 (d, 2H, J = 8.1 Hz), 7.55 (d, 2H, J = 8.1 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm) 41.9, 68.1, 106.2, 111.3, 118.4, 130.4, 132.0, 142.2; MS (EI) *m*/*z*: 275 (M^+, 100%); Anal. Calcd for $C_{10}H_{17}B_{10}NO$: C, 43.62; H, 6.22; N, 5.09. Found: C, 43.54; H, 5.97; N, 4.82.

6.1.40. 1-Hydroxy-12-(2-nitrobenzyl)-1,12-dicarba-*closo*-dodecaborane (10d). Compound **10d** was prepared in a similar manner to that described for **8a** (quant.): green cubes (CH_2Cl_2/*n*-hexane); mp 148.5–150.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm) 1.0–3.5 (br m, 10H), 3.28 (br s, 1H), 3.47 (s, 2H), 7.10 (dd, 1H, J = 1.5 Hz, 7.6 Hz), 7.42 (dt, 1H, J = 1.6 Hz, 8.1 Hz), 7.52 (dt, 1H, J = 1.3 Hz, 7.4 Hz), 7.88 (dd, 1H, J = 1.3 Hz, 7.9 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm) 37.3, 68.1, 106.2, 124.9, 128.7, 131.5, 132.6, 133.6, 148.7; MS (EI) *m*/*z*: 295 (M^+), 278 (100%); Anal. Calcd for $C_9H_{17}B_{10}NO_3$: C, 36.60; H, 5.80; N, 4.73. Found: C, 36.70; H, 5.73; N, 4.66.

6.1.41. 1-Hydroxy-12-(3-nitrobenzyl)-1,12-dicarba-*closo*-dodecaborane (10e). Compound **10e** was prepared in a similar manner to that described for **8a** (92% yield): colorless leaflets (CH_2Cl_2/*n*-hexane); mp 146–147 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm) 1.0–3.5 (br m, 10H), 3.03 (s, 2H), 4.77 (br s, 1H), 7.30 (d, 1H, J = 7.6 Hz), 7.45 (t, 1H, J = 7.9 Hz), 7.84 (s, 1H), 8.11 (d, 1H, J = 8.1 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm) 41.42, 68.27, 106.14, 122.58, 124.44, 129.25, 135.84, 138.93, 148.01; MS (EI) *m*/*z*: 295 (M^+), 142 (100%); Anal. Calcd for $C_9H_{17}B_{10}NO_3$: C, 36.60; H, 5.80; N, 4.73. Found: C, 36.60; H, 5.66; N, 4.65.

6.1.42. 1-Hydroxy-12-(4-nitrobenzyl)-1,12-dicarba-*closo*-dodecaborane (10f). Compound **10f** was prepared in a similar manner to that described for **8a** (92% yield): pale yellow leaflets (CH_2Cl_2/*n*-hexane); mp 160–160.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm) 1.0–3.5 (br m, 10H), 3.01 (s, 2H), 7.13 (d, 2H, J = 8.6 Hz), 8.11 (d, 2H, J = 8.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ (ppm) 41.6, 68.0, 106.1, 123.4, 130.5, 144.1, 147.1; MS (EI) *m*/*z*: 295 (M^+, 100%); Anal. Calcd for $C_9H_{17}B_{10}NO_3$: C, 36.60; H, 5.80; N, 4.73. Found: C, 36.73; H, 5.76; N, 4.68.

6.2. 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.

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