

## Regular Article

Development of Boron-Cluster-Based Progesterone Receptor Antagonists Bearing a Pentafluorosulfanyl (SF<sub>5</sub>) Group

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The progesterone receptor (PR) plays an important role in various physiological processes, especially in the female reproductive system, and abnormalities of PR function are associated with several diseases, including some types of cancer. Non-steroidal PR ligands are of interest as candidate drugs for treatment of PR-related diseases without the serious adverse effects that may be caused by steroidal ligands. For the development of non-steroidal PR ligands, both a hydrophobic backbone and a polar functional group corresponding to the 3-carbonyl group of progesterone, which interacts with Gln725 and Arg766 of the PR-ligand binding domain, are critically important. We previously showed that carborane is a useful hydrophobic pharmacophore for PR antagonists, and in this work, we introduced the pentafluorosulfanyl (SF<sub>5</sub>) group as a novel polar functional group of carborane-based non-steroidal PR antagonists. All the synthesized SF<sub>5</sub>-containing carborane derivatives exhibited PR-antagonistic activity at micromolar or submicromolar concentration. Among them, compounds **11** are potent progesterone antagonists with submicromolar IC<sub>50</sub> values.

**Key words** progesterone receptor; antagonist; carborane; pentafluorosulfanyl group

## Introduction

The progesterone receptor (PR) is a member of the nuclear receptor superfamily. Its endogenous agonist, progesterone (**1**, Fig. 1), binds to the PR ligand-binding domain (PR-LBD), resulting in the activation of transcription of target genes, whose promoters contain PR-response elements.<sup>1)</sup> PR is involved in the regulation of various physiological processes, especially those involved in the female reproductive system, including regulation of uterine cell proliferation/differentiation,<sup>2,3)</sup> mammary gland growth/differentiation,<sup>4)</sup> the ovulation cycle,<sup>5)</sup> and sexual behaviors.<sup>6)</sup> Various synthetic PR agonists and antagonists have been clinically employed<sup>7–9)</sup> for contraception, induction of abortion, hormone replacement therapy, and treatment of gynecological disorders. The synthetic PR antagonist mifepristone (**2**, Fig. 1) is a representative abortifacient,<sup>10)</sup> and is also effective in the treatment of endometriosis,<sup>11)</sup> uterine leiomyoma,<sup>12)</sup> and breast cancer.<sup>13)</sup> However, all PR ligands in clinical use, including **2**, possess a steroidal structure, which may cause significant adverse effects due to cross-activity with other steroid hormone receptors.<sup>14)</sup> To avoid these adverse effects, several non-steroidal PR ligands have been developed, such as tanaproget (**3**)<sup>15)</sup> and sulfonamide derivative **4**<sup>16)</sup> (Fig. 1). In the design of such ligands, a polar functional group and a hydrophobic pharmacophore that mimics the steroid skeleton are critically important for the interaction of the ligands with the PR-LBD. In the case of **3**, X-ray crystallographic analysis of the complex of **3** with the PR-LBD revealed that the cyano group of **3** interacts with Gln725 and Arg766 of PR-LBD, which are the same amino acid residues that interact with the 3-carbonyl group of **1**.<sup>15)</sup>

In the previous study, we developed non-steroidal PR antagonists bearing a boron-cluster carborane as the hydrophobic core structure.<sup>17–20)</sup> Carboranes, or more precisely dicarbalo-dodecaboranes (C<sub>2</sub>B<sub>10</sub>H<sub>12</sub>), are carbon-containing boron

clusters with an icosahedral cage structure, and there are three isomers, depending on the positions of the two carbon atoms, that is, *ortho*-, *meta*-, and *para*-carborane.<sup>21)</sup> Carboranes have high thermal and chemical stability, and exceptionally high hydrophobicity,<sup>22–24)</sup> and we have applied them as hydrophobic core structures of various bioactive compounds, especially ligands of various nuclear receptors, such as retinoid receptors,<sup>25)</sup> androgen receptor,<sup>26)</sup> and vitamin D receptor.<sup>27)</sup> Among the synthesized compounds, we found that the phenyl carborane derivatives **5–7** (Fig. 2) exhibited PR-antagonistic activity.<sup>18,20)</sup> A docking study of **5** with the PR-LBD indicated that the carborane moiety of **5** occupies the space corresponding to the steroid CD ring of progesterone (**1**).<sup>18)</sup> In addition, the cyano group of **5** was suggested to interact with Gln725 and Arg766 in the PR-LBD, which also interact with 3-carbonyl group of progesterone (**1**).<sup>18)</sup> On the other hand, compound **7** having an *m*-carborane core exhibited bidirectional PR ligand activity, namely, it showed PR-antagonistic activity in the low concentration range, and PR-agonistic activity in the high concentration range.<sup>20)</sup> Compound **8** having a 3-trifluoromethyl substituent on the phenyl group showed only antagonistic activity.<sup>20)</sup> These results indicate that the mode of PR ligand activity is affected by the nature and position of the polar functional group on the phenyl group. Therefore, it is important to investigate the characteristics of a variety of polar functional groups of PR ligands.

The pentafluorosulfanyl (SF<sub>5</sub>) group is known as a “super trifluoromethyl group,” because it possesses larger volume, stronger electronegativity, and higher lipophilicity than the trifluoromethyl group.<sup>28–30)</sup> Because of its unique combination of high polarity and lipophilicity, together with chemical stability, it is attracting considerable interest in the field of medicinal chemistry.<sup>29–31)</sup> Indeed, many investigations involving the replacement of the trifluoromethyl group in bioactive

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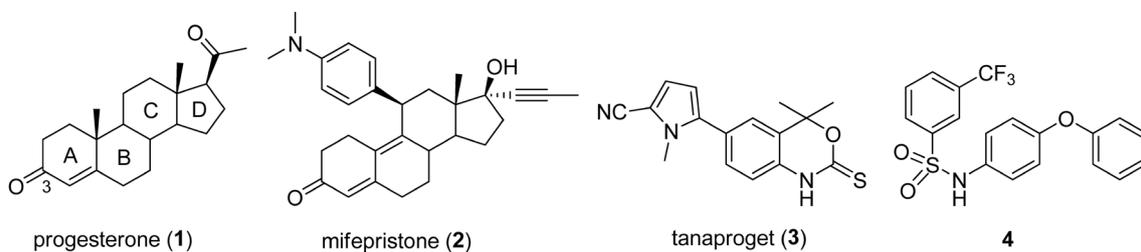


Fig. 1. Progesterone 1 and Synthetic PR Ligands 2–4

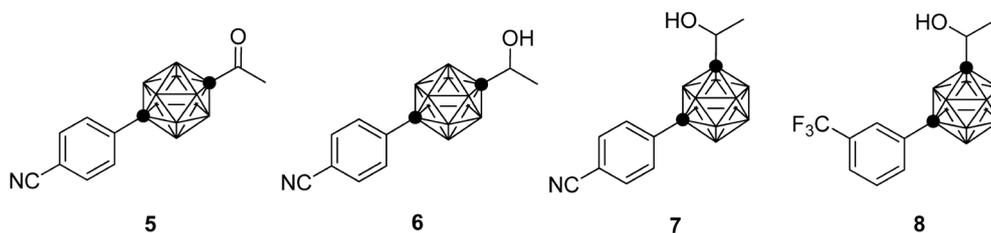
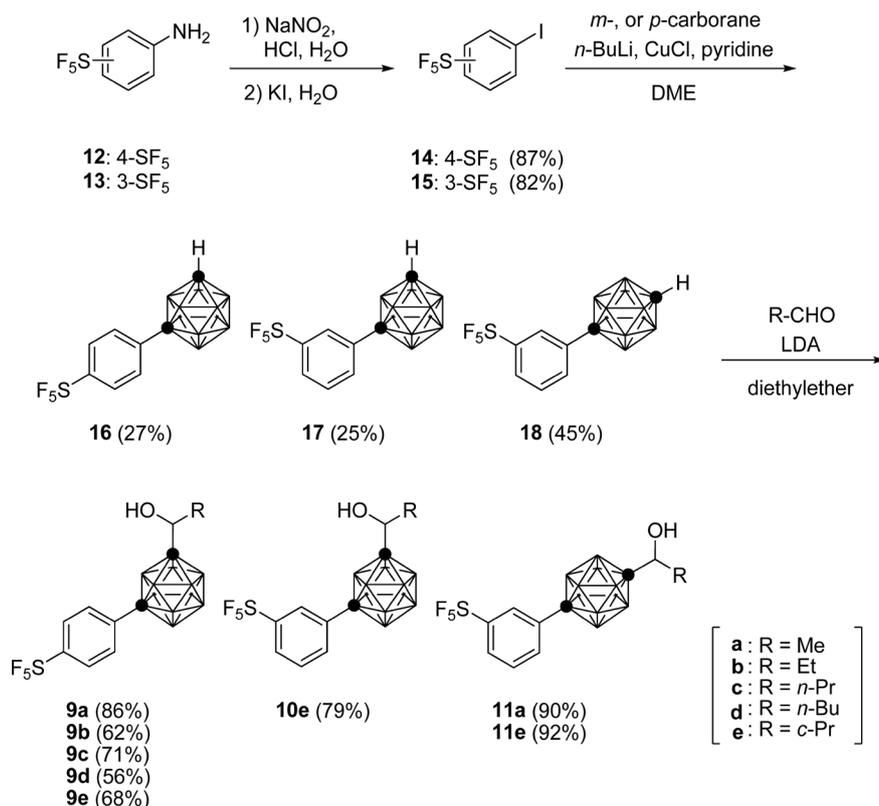


Fig. 2. Carborane-Based Non-steroidal PR Antagonists

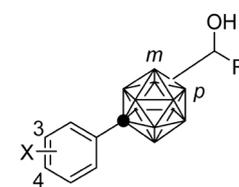
Chart 1. Synthesis of Pentafluorosulfonyl (SF<sub>5</sub>)-Containing Carborane Derivatives 9–11

molecules with a SF<sub>5</sub> group have been reported.<sup>32–34</sup> The SF<sub>5</sub> group has five fluorine atoms in a pyramidal structure, and might interact in a distinctive way with proteins. Therefore, in this work, we investigated the utility of the SF<sub>5</sub> group as the polar functional group of PR ligands.

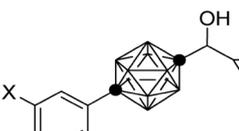
The phenyl carborane derivatives 5–8 were used as the lead compounds because the substituent on their phenyl group would act as the key polar functional group to bind PR-LBD. Based on the structures of 5–8, we designed the *m*- and *p*-carborane derivatives 9–11 having a SF<sub>5</sub> group on the phenyl

group. Synthesis of 9–11 is illustrated in Chart 1. Sandmeyer iodination of 4- or 3-pentafluorosulfonylanilines (12 and 13) afforded iodobenzenes 14 and 15, respectively. Ullmann-type coupling of *m*- or *p*-carborane with 14 and 15 gave phenylcarborane derivatives 16–18. The unsubstituted carbon atom of the carboranes of 16–18 was lithiated with lithium diisopropylamide and then reacted with several aldehydes, affording the corresponding secondary alcohols 9, 10, and 11 as racemic mixtures.

The PR-ligand activities of 9–11 were evaluated by means

Table 1. PR-Antagonistic Activity of SF<sub>5</sub>-Containing Carborane Derivatives


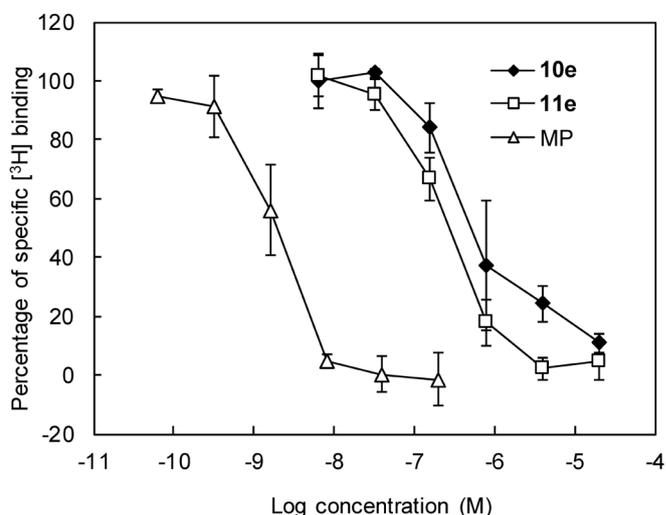
Compound	Carborane	X	R	IC <sub>50</sub> (μM)
9a	<i>m</i>	4-SF <sub>5</sub>	Me	1.9 ± 0.07
9b	<i>m</i>	4-SF <sub>5</sub>	Et	2.9 ± 0.23
9c	<i>m</i>	4-SF <sub>5</sub>	<i>n</i> -Pr	3.1 ± 0.26
9d	<i>m</i>	4-SF <sub>5</sub>	<i>n</i> -Bu	4.3 ± 0.11
9e	<i>m</i>	4-SF <sub>5</sub>	Cyclopropyl	2.9 ± 0.10
10e	<i>m</i>	3-SF <sub>5</sub>	Cyclopropyl	1.7 ± 0.18
11a	<i>p</i>	3-SF <sub>5</sub>	Me	0.37 ± 0.027
11e	<i>p</i>	3-SF <sub>5</sub>	Cyclopropyl	0.42 ± 0.054

Table 2. PR-Antagonistic Activity of *p*-Carborane Derivatives Having Different Functional Groups


Compound	X	IC <sub>50</sub> (μM)
11e	SF <sub>5</sub>	0.42 ± 0.054
19	CN	0.045 ± 0.005
20	NO <sub>2</sub>	0.051 ± 0.004
21	CF <sub>3</sub>	0.35 ± 0.054

of alkaline phosphatase assay using the T-47D human breast cancer cell line, in which alkaline phosphatase expression is regulated by PR. The PR-agonistic activity was evaluated in terms of the increase ratio of alkaline phosphatase activity in the presence of test compound alone, while the PR-antagonistic activity was evaluated in terms of inhibition of coexisting progesterone (1 nM)-induced alkaline phosphatase activity by the test compound.

All of the synthesized SF<sub>5</sub>-containing carborane derivatives exhibited PR-antagonistic activity (Table 1). None of the test compounds exhibited PR-agonistic activity. Although compound **7** bearing a *p*-cyanophenyl moiety showed bidirectional PR ligand activity (antagonistic activity at low concentration, and agonistic activity at high concentration), compounds **9a–e** having the same skeletal structure as **7** did not act as PR agonists even in the high concentration range. This result indicates that the mode of PR ligand activity can be changed depending upon the nature of the polar functional group on the phenyl group. The antagonistic activity of **9a–e** having an *m*-carborane core and a 4-pentafluorosulfonylphenyl group was moderate (IC<sub>50</sub> approx. 2–4 μM), and the length of the alkyl chain (R group) of the secondary alcohol did not greatly affect the potency. The potency of **10e** (IC<sub>50</sub> = 1.7 μM) having a 3-pentafluorosulfonylphenyl group on *m*-carborane was similar to that of **9a–e**. On the other hand, **11a** (IC<sub>50</sub> = 0.37 μM) and **11e** (IC<sub>50</sub> = 0.42 μM) having a *p*-carborane and a 3-SF<sub>5</sub> group, exhibited about 10-fold higher antagonistic activities

Fig. 3. Competitive Binding Assay of the SF<sub>5</sub>-Containing Carborane Derivatives

The concentration of [<sup>3</sup>H]progesterone was 4 nM. Mifepristone (MP) was used as the positive control.

than the corresponding *m*-carborane derivatives **9** and **10**.

To evaluate the effect of polar functional groups, we synthesized compounds **19**, **20**, and **21**, having different polar functional groups on the same skeletal structure of **11e**, according to our previous report,<sup>18)</sup> and examined their PR-antagonistic activities (Table 2). Among them, **19** with a cyano group and **20** with a nitro group showed potent PR-antagonistic activity. Compound **11e** with a SF<sub>5</sub> group and **21** with a trifluoromethyl group showed relatively low PR-antagonistic activity compared to **19** and **20**. These results suggest that functional groups having π electron system such as nitro and cyano group could interact more strongly with PR-LBD than functional groups having multiple fluorine atoms. Compounds **11e** and **21** showed comparable antagonistic activity, while SF<sub>5</sub> group is stronger electron-withdrawing than trifluoromethyl group,<sup>35)</sup> which suggests that the electron density of the phenyl ring of the carborane derivatives would not be important for the interaction with PR-LBD, and that the multiple fluorines of SF<sub>5</sub> and trifluoromethyl group might play similar function in PR-LBD.

Finally, we examined the PR-binding affinity of selected compounds **10e**, and **11e** (Fig. 3). The binding affinities were evaluated by means of competitive binding assay using the PR-LBD and [1,2,6,7-<sup>3</sup>H]progesterone. Both **10e** and **11e** bound to the PR-LBD at submicro- to micromolar concentrations. Compound **11e** that exhibited higher PR-antagonistic activity than **10e** showed higher binding affinity to the PR-LBD than **10e**. These results suggest that the PR-antagonistic activity of these compounds evaluated by T-47D alkaline phosphatase assay was mediated by binding of the compounds to PR.

We designed and synthesized a series of carborane-based PR antagonists having a pentafluorosulfonyl group as the polar functional group. All of the synthesized compounds **9–11** exhibited PR-antagonistic activity, and in particular, the *p*-carborane derivatives **11** showed potent antagonistic activities at submicromolar concentration. The results suggest that the pentafluorosulfonyl group is an effective polar functional group that can interact with the PR-LBD as an alternative to the 3-carbonyl group of progesterone. Although the antago-

nistic activities of SF<sub>5</sub>-containing carborane derivatives **9–11** were lower than that of **19** or **20** having a cyano group or a nitro group, respectively, further structural optimization might increase the activity. The carborane structure and pentafluorosulfanyl group may prove to be valuable building blocks for the design of ligands not only for PR, but also for other nuclear receptors.

## Experimental

**General** SF<sub>5</sub>-containing anilines **12** and **13** were supplied from UBE Industries, LTD., Japan. Other reagents were purchased from Sigma-Aldrich (U.S.A.), Tokyo Chemical Industry (Japan), Wako Pure Chemical Industries, Ltd. (Japan), and Kanto Chemicals (Japan) and were used without further purification. NMR spectra were recorded on Bruker AVANCE 400 or Bruker AVANCE 500 spectrometers. Chemical shifts for NMR are reported as parts of per million (ppm) relative to chloroform (7.27 ppm for <sup>1</sup>H-NMR and 77.23 ppm for <sup>13</sup>C-NMR) and benzotrifluoride (–63.72 ppm for <sup>19</sup>F-NMR) as an external standard. Coupling patterns are denoted as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), triplet (t), quartet (q), quintet (quin), multiplet (m), broad singlet (brs), and broad multiplet (brm). MS were collected on a Bruker Daltonics microTOF-2focus spectrometer in the negative ion mode. Melting points were obtained on a Yanagimoto micro melting point apparatus without correction. Elemental analyses were carried out by using Yanaco MT-6 CHNCORDER spectrometer.

**General Procedure for Synthesis of 14 or 15** A cold solution of NaNO<sub>2</sub> (102 mg, 1.48 mmol) in water (2.5 mL) was added slowly to a solution of **12** or **13** (306 mg, 1.40 mmol) in conc. HCl (1.5 mL) and ice (2.5 g). The mixture was stirred at 0°C for 2 min and then added slowly to a solution of KI (220 mg, 1.33 mmol) in water (20 mL) at 0°C. The resulting mixture was stirred for 30 min on ice and then allowed to warm to r.t. for 1 h, and the product was extracted with dichloromethane. The organic layer was washed with saturated aqueous NaHCO<sub>3</sub> solution, dried over sodium sulfate, and concentrated. Purification by silica gel column chromatography (eluent: *n*-hexane) gave iodinated products **14** or **15**.

### 3-Iodophenylsulfur Pentafluoride (**14**)

Colorless oil (87% yield): <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 8.09 (t, *J* = 2.0 Hz, 1 H), 7.86 (d, *J* = 8.0 Hz, 1 H), 7.75 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.22 (dd, *J* = 8.8, 8.0 Hz, 1 H); <sup>19</sup>F-NMR (376 MHz, CDCl<sub>3</sub>) δ: 82.81 (quin, *J* = 150.1 Hz, 1 F), 62.53 (d, *J* = 150.1 Hz, 4 F).

### 4-Iodophenylsulfur Pentafluoride (**15**)

Colorless solid (82% yield): <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.82 (d, *J* = 7.2 Hz, 2 H), 7.49 (d, *J* = 7.2 Hz, 2 H); <sup>19</sup>F-NMR (376 MHz, CDCl<sub>3</sub>) δ: 83.21 (quin, *J* = 150.3 Hz, 1 F), 62.55 (d, *J* = 150.1 Hz, 4 F).

**General Procedure for Synthesis of 16–18** A solution of *n*-butyllithium in *n*-hexane (2.67 M, 0.8 mL, 2.14 mmol) was added to a solution of *m*- or *p*-carborane (211 mg, 1.46 mmol) in 1,2-dimethoxyethane (10 mL) at 0°C under an Ar atmosphere, and the mixture was stirred at 0°C for 30 min. Copper (I) chloride (162 mg, 1.64 mmol) was added to the reaction mixture at room temperature. After 1 h, pyridine (1.5 mL) and pentafluorosulfanylated iodobenzene **14** or **15** (500 mg, 1.51 mmol) were added, and the mixture was stirred at 80°C

for 20 h. After cooling, the reaction mixture was diluted with ethyl acetate, and insoluble materials were filtered off through celite. The filtrate was washed successively with 5% sodium thiosulfate, 2 M hydrochloric acid, and brine, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (eluent: *n*-hexane) to give the products **16–18**.

**1-(4-Pentafluoro-λ<sup>6</sup>-sulfanylphenyl)-1,7-dicarba-closo-dodecaborane (**16**)**

Yellow solid (27% yield): <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.68 (d, *J* = 7.2 Hz, 2 H), 7.53 (d, *J* = 6.8 Hz, 2 H), 3.12 (brs, 1 H), 3.5–1.5 (brm, 10 H); <sup>19</sup>F-NMR (376 MHz, CDCl<sub>3</sub>) δ: 83.41 (quin, *J* = 150.0 Hz, 1 F), 62.48 (d, *J* = 150.0 Hz, 4 F).

**1-(3-Pentafluoro-λ<sup>6</sup>-sulfanylphenyl)-1,7-dicarba-closo-dodecaborane (**17**)**

Colorless solid (25% yield): <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.81 (t, *J* = 2.0 Hz, 1 H), 7.71 (ddd, *J* = 8.0, 4.0, 0.8 Hz, 1 H), 7.59 (d, *J* = 8.8 Hz, 1 H), 7.39 (t, *J* = 8.0 Hz, 1 H), 3.13 (brs, 1 H), 4.0–1.5 (brm, 10 H); <sup>19</sup>F-NMR (376 MHz, CDCl<sub>3</sub>) δ: 83.13 (quin, *J* = 150.1 Hz, 1 F), 62.53 (d, *J* = 150.0 Hz, 4 F).

**1-(3-Pentafluoro-λ<sup>6</sup>-sulfanylphenyl)-1,12-dicarba-closo-dodecaborane (**18**)**

Colorless solid (45% yield): <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.62 (dt, *J* = 8.4, 2.0 Hz, 1 H), 7.59 (dd, *J* = 2.0, 1.6 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.30 (dd, *J* = 8.4, 8.0 Hz, 1 H), 2.85 (brs, 1 H), 3.5–1.5 (brm, 10 H); <sup>19</sup>F-NMR (376 MHz, CDCl<sub>3</sub>) δ: 83.10 (quin, *J* = 150.1 Hz, 1 F), 62.48 (d, *J* = 150.1 Hz, 4 F).

**General Procedure for Synthesis of 9–11** A solution of lithium diisopropylamide in a mixture of *n*-hexane and tetrahydrofuran (1.1 M, 0.14 mL, 0.16 mmol) was added to a solution of **16–18** (48 mg, 0.14 mmol) in THF (2 mL) at –78°C under an Ar atmosphere, and the mixture was stirred at –78°C for 20 min. The appropriate aldehyde (2.0–10 equiv.) was added to the reaction mixture at –78°C. The resulting mixture was stirred at –78°C for 1 h, then poured into saturated ammonium chloride, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate, 10/1) to give the racemic alcohols **9–11**.

**1-(4-Pentafluoro-λ<sup>6</sup>-sulfanylphenyl)-7-(1-hydroxyethyl)-1,7-dicarba-closo-dodecaborane (**9a**)**

Colorless oil (86% yield): <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.65 (d, *J* = 7.2 Hz, 2 H), 7.54 (d, *J* = 6.8 Hz, 2 H), 4.14–4.07 (m, 1 H), 3.5–1.5 (brm, 10 H), 1.89 (d, *J* = 4.8 Hz, 1 H), 1.34 (d, *J* = 5.2 Hz, 3 H); <sup>19</sup>F-NMR (376 MHz, CDCl<sub>3</sub>) δ: 83.10 (quin, *J* = 150.1 Hz, 1 F), 62.48 (d, *J* = 150.0 Hz, 4 F); high resolution (HR)MS electrospray ionization (ESI<sup>–</sup>) Calcd for C<sub>10</sub>H<sub>18</sub>B<sub>10</sub>F<sub>5</sub>OS [M–H]<sup>–</sup>: 391.1929. Found: 391.1937.

**1-(4-Pentafluoro-λ<sup>6</sup>-sulfanylphenyl)-7-(1-hydroxypropyl)-1,7-dicarba-closo-dodecaborane (**9b**)**

Colorless oil (62% yield): <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.66 (d, *J* = 7.2 Hz, 2 H), 7.53 (d, *J* = 6.8 Hz, 2 H), 3.76–3.72 (m, 1 H), 3.0–1.5 (brm, 10 H), 1.88 (d, *J* = 5.2 Hz, 1 H), 1.75–1.70 (m, 1 H), 1.43–1.37 (m, 1 H), 1.02 (t, *J* = 5.6 Hz, 3 H); <sup>19</sup>F-NMR (376 MHz, CDCl<sub>3</sub>) δ: 83.12 (quin, *J* = 150.2 Hz, 1 F), 62.49 (d, *J* = 150.1 Hz, 4 F); HRMS (ESI<sup>–</sup>) Calcd for C<sub>11</sub>H<sub>20</sub>B<sub>10</sub>F<sub>5</sub>OS [M–H]<sup>–</sup>: 405.2086. Found: 405.2094.

**1-(4-Pentafluoro-λ<sup>6</sup>-sulfanylphenyl)-7-(1-hydroxybutyl)-1,7-dicarba-closo-dodecaborane (**9c**)**

Colorless oil (71% yield): <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ:

7.66 (d,  $J = 7.2$  Hz, 2 H), 7.53 (d,  $J = 8.0$  Hz, 2 H), 3.85–3.82 (m, 1H), 3.0–1.5 (brm, 10 H), 1.86 (d,  $J = 4.8$  Hz, 1 H), 1.61–1.57 (m, 1 H), 1.42–1.35 (m, 3 H), 0.92 (t,  $J = 5.8$  Hz, 3 H);  $^{19}\text{F}$ -NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$ : 83.12 (quin,  $J = 150.1$  Hz, 1 F), 62.49 (d,  $J = 150.8$  Hz, 4 F); HRMS (ESI $^-$ ) Calcd for  $\text{C}_{12}\text{H}_{22}\text{B}_{10}\text{F}_5\text{OS}$  [M-H] $^-$ : 419.2242. Found: 419.2250.

1-(4-Pentafluoro- $\lambda^6$ -sulfanylphenyl)-7-(1-hydroxypentyl)-1,7-dicarba-*closo*-dodecaborane (**9d**)

Colorless oil (56% yield):  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.65 (d,  $J = 7.2$  Hz, 2 H), 7.53 (d,  $J = 7.2$  Hz, 2 H), 3.84–3.82 (m, 1 H), 3.0–1.5 (brm, 10 H), 1.87 (d,  $J = 4.8$ , 1 H), 1.67–1.62 (m, 1 H), 1.43–1.32 (m, 5 H), 0.92 (t,  $J = 5.8$ , 3 H);  $^{19}\text{F}$ -NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$ : 83.16 (quin,  $J = 150.3$  Hz, 1 F), 64.30 (d,  $J = 150.0$  Hz, 4 F); HRMS (ESI $^-$ ) Calcd for  $\text{C}_{13}\text{H}_{25}\text{B}_{10}\text{F}_5\text{OS}$  [M-H] $^-$ : 433.2399. Found: 433.2407.

1-(4-Pentafluoro- $\lambda^6$ -sulfanylphenyl)-7-(1-cyclopropyl-1-hydroxymethyl)-1,7-dicarba-*closo*-dodecaborane (**9e**)

Colorless oil (68% yield):  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.67 (d,  $J = 7.2$  Hz, 2 H), 7.55 (d,  $J = 7.2$  Hz, 2 H), 3.20 (q,  $J = 3.5$  Hz, 1 H), 3.0–1.5 (brm, 10 H), 1.93 (d,  $J = 3.6$  Hz, 1 H), 1.28–0.98 (m, 1 H), 0.73–0.60 (m, 2 H), 0.45–0.38 (m, 2 H);  $^{19}\text{F}$ -NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$ : 83.12 (quin,  $J = 149.8$  Hz, 1 F), 62.49 (d,  $J = 150.1$  Hz, 4 F); HRMS (ESI $^-$ ) Calcd for  $\text{C}_{12}\text{H}_{20}\text{B}_{10}\text{F}_5\text{OS}$  [M-H] $^-$ : 417.2086. Found: 417.2094.

1-(3-Pentafluoro- $\lambda^6$ -sulfanylphenyl)-7-(1-cyclopropyl-1-hydroxymethyl)-1,7-dicarba-*closo*-dodecaborane (**10e**)

Colorless oil (79% yield):  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.82 (dd,  $J = 2.0$ , 1.6 Hz, 1 H), 7.71 (ddd,  $J = 8.4$ , 2.4, 1.2 Hz, 1 H), 7.61 (d,  $J = 8.8$  Hz, 1 H), 7.39 (dd,  $J = 8.4$ , 7.6 Hz, 1 H), 3.20 (q,  $J = 4.4$  Hz, 1 H), 3.0–1.5 (brm, 10 H), 1.95 (d,  $J = 4.8$  Hz, 1 H), 1.04–0.97 (m, 1 H), 0.74–0.63 (m, 2 H), 0.54–0.48 (m, 2 H);  $^{13}\text{C}$ -NMR (126 MHz, methanol- $d_4$ )  $\delta$ : 155.0 (quin,  $J = 17.6$  Hz), 138.2, 132.7, 130.8, 127.8 (quin,  $J = 4.5$  Hz), 126.4 (quin,  $J = 4.8$  Hz), 85.4, 77.1, 76.8, 19.0, 5.47, 4.03;  $^{19}\text{F}$ -NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$ : 81.64 (quin,  $J = 148.0$  Hz, 1 F), 60.83 (d,  $J = 147.9$  Hz, 4 F); HRMS (ESI $^-$ ) Calcd for  $\text{C}_{12}\text{H}_{20}\text{B}_{10}\text{F}_5\text{OS}$  [M-H] $^-$ : 417.2086. Found: 417.2090.

1-(3-Pentafluoro- $\lambda^6$ -sulfanylphenyl)-12-(1-hydroxyethyl)-1,12-dicarba-*closo*-dodecaborane (**11a**)

Colorless oil (90% yield):  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.63 (ddd,  $J = 8.0$ , 2.0, 0.8 Hz, 1 H), 7.59 (t,  $J = 2.0$  Hz, 1 H), 7.38 (d,  $J = 8.0$  Hz, 1 H), 7.30 (dd,  $J = 8.0$ , 7.2 Hz, 1 H), 3.77 (m, 1 H), 3.5–1.5 (br, m, 10 H), 1.65 (d,  $J = 6$  Hz, 1 H), 1.13 (d,  $J = 6.4$  Hz, 1 H);  $^{13}\text{C}$ -NMR (126 MHz, methanol- $d_4$ )  $\delta$ : 154.9 (quin,  $J = 17.4$  Hz), 138.9, 132.0, 130.5, 127.5 (quin,  $J = 4.5$  Hz), 125.8 (quin,  $J = 4.7$  Hz), 90.2, 82.6, 69.9, 23.6;  $^{19}\text{F}$ -NMR (376 MHz, methanol- $d_4$ )  $\delta$ : 81.74 (quin,  $J = 148.0$  Hz, 1 F), 60.78 (d,  $J = 148.0$  Hz, 4 F); HRMS (ESI $^-$ ) Calcd for  $\text{C}_{10}\text{H}_{18}\text{B}_{10}\text{F}_5\text{OS}$  [M-H] $^-$ : 391.1929. Found: 391.1938.

1-(3-Pentafluoro- $\lambda^6$ -sulfanylphenyl)-12-(1-cyclopropyl-1-hydroxymethyl)-1,12-dicarba-*closo*-dodecaborane (**11e**)

Colorless oil (92% yield):  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.63–7.60 (m, 2 H), 7.39 (d,  $J = 6.4$  Hz, 1 H), 7.30 (dd,  $J = 6.8$ , 6.0 Hz, 1 H), 2.88 (q,  $J = 3.5$  Hz, 1 H), 3.5–1.5 (br, m, 10 H), 1.69 (d,  $J = 4.0$  Hz, 1 H), 0.83–0.76 (m, 1 H), 0.64–0.51 (m, 2 H), 0.34–0.25 (m, 2 H); HRMS (ESI $^-$ ) Calcd for  $\text{C}_{12}\text{H}_{20}\text{B}_{10}\text{F}_5\text{OS}$  [M-H] $^-$ : 417.2086. Found: 417.2087.

1-(3-Cyanophenyl)-12-(1-cyclopropyl-1-hydroxymethyl)-1,12-dicarba-*closo*-dodecaborane (**19**)

Colorless solid: mp 145–147°C;  $^1\text{H}$ -NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.52 (m, 2 H), 7.45 (t,  $J = 1.6$  Hz, 1 H), 7.31 (t,  $J = 7.6$  Hz, 1

H), 2.9–1.6 (brm, 10 H), 2.88 (dd,  $J = 8.3$ , 1.2 Hz, 1 H), 1.70 (s, 1 H), 0.83–0.76 (m, 1 H), 0.60–0.59 (m, 2 H), 0.34–0.25 (m, 2 H);  $^{13}\text{C}$ -NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$ : 137.9, 132.0, 131.7, 131.0, 129.2, 118.3, 112.7, 87.0, 81.5, 17.9, 4.8, 3.2; HRMS (ESI $^-$ ) Calcd for  $\text{C}_{14}\text{H}_{22}\text{B}_{10}\text{F}_3\text{O}_3$  [M+HCOO] $^-$ : 362.2530. Found: 362.2534.

1-(3-Nitrophenyl)-12-(1-cyclopropyl-1-hydroxymethyl)-1,12-dicarba-*closo*-dodecaborane (**20**)

Colorless solid:  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.09 (m, 2 H), 7.54 (ddd,  $J = 8.0$ , 3.2, 1.8 Hz, 1 H), 7.37 (t,  $J = 8.0$  Hz, 1 H), 3.3–2.3 (brm, 10 H), 2.87 (dd,  $J = 8.3$ , 5.3 Hz, 1 H), 1.68 (d,  $J = 5.0$  Hz, 1 H), 0.82–0.75 (m, 1 H), 0.64–0.54 (m, 2 H), 0.32–0.27 (m, 2 H);  $^{13}\text{C}$ -NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$ : 148.1, 138.4, 133.3, 129.3, 123.5, 122.5, 17.9, 5.0, 3.2. Anal Calcd for  $\text{C}_{12}\text{B}_{10}\text{H}_{21}\text{NO}_3$ : N, 4.18; C, 42.97; H, 6.31. Found: N, 4.08; C, 42.71; H, 6.15.

1-(3-Trifluoromethylphenyl)-12-(1-cyclopropyl-1-hydroxymethyl)-1,12-dicarba-*closo*-dodecaborane (**21**)

Colorless solid: mp 76–78°C;  $^1\text{H}$ -NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.48 (d,  $J = 7.7$  Hz, 1 H), 7.46 (s, 1 H), 7.41 (d,  $J = 8.4$  Hz, 1 H), 7.31 (d,  $J = 7.9$  Hz, 1 H), 3.3–2.3 (br, m, 10 H), 2.87 (dd,  $J = 8.3$ , 4.9 Hz, 1 H), 1.67 (d,  $J = 5.0$  Hz, 1 H), 0.83–0.75 (m, 1 H), 0.64–0.56 (m, 1 H), 0.55–0.49 (m, 1 H), 0.35–0.22 (m, 2 H);  $^{13}\text{C}$ -NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$ : 137.5, 130.8 (q,  $J = 31.5$ ), 130.8, 128.9, 125.5 (q,  $J = 3.8$ ), 124.2 (q,  $J = 3.8$ ), 123.9 (q,  $J = 273.4$ ), 86.8, 82.4, 17.9, 5.0, 3.3; HRMS (ESI $^-$ ) Calcd for  $\text{C}_{14}\text{H}_{22}\text{B}_{10}\text{F}_3\text{O}_3$  [M+HCOO] $^-$ : 405.2451. Found: 405.2451.

**Alkaline Phosphatase Assay Using T-47D Cells** T-47D breast-carcinoma cells were cultured in RPMI 1640 medium with 10% (v/v) fetal bovine serum. Cells were plated in 96-well plates at  $10^4$  cell/well and incubated overnight (37°C, 5%  $\text{CO}_2$  in air). The next day, the medium was replaced with fresh medium containing test compound, and incubation was continued for 24 h. Then, the medium was aspirated and the cells were fixed with 100  $\mu\text{L}$  of 1.8% formalin (in phosphate buffered saline (PBS)). The fixed cells were washed with PBS and 75  $\mu\text{L}$  of assay buffer (1 mg/mL *p*-nitrophenol phosphate in diethanolamine water solution, pH 9.0, 2 mM  $\text{MgCl}_2$ ) was added. The mixture was incubated at room temperature with shielding from light for 2 h, and then the reaction was terminated by the addition of 100  $\mu\text{L}$  of NaOH. The absorbance at 405 nm was measured.

**hPR-Binding Assay** hPR-Binding assay was performed using recombinant hPR-LBD purchased from Invitrogen (A15672). hPR-LBD was diluted with buffer (20 mM Tris-HCl, 300 mM NaCl, 1 mM EDTA, 5 mM DTT, pH 8.0) to 14  $\mu\text{g}/\text{mL}$  of total protein and 300  $\mu\text{L}$  aliquots were incubated in the dark at 4°C with 4 nM [ $1,2,6,7$ - $^3\text{H}$ ]progesterone (PerkinElmer, Inc., U.S.A.) and reference or test compounds (dissolved in dimethyl sulfoxide (DMSO); final concentration of DMSO was 3%). Nonspecific binding was assessed by addition of a 200-fold excess of nonradioactive progesterone. After 24 h, 30  $\mu\text{L}$  of Dextran T-70/c-globulin-coated charcoal suspension was added to the ligand/protein mixtures (1% activated charcoal, 0.05%  $\gamma$ -globulin, 0.05% Dextran 70, final concentrations) and incubated at 4°C for 5 min. The charcoal was removed by centrifugation for 5 min at  $1300 \times g$ , and the radioactivity of the supernatant was measured in Ultima Gold scintillation cocktail (PerkinElmer, Inc.) by using a liquid scintillation counter. All experiments were performed in duplicate.

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**Conflict of Interest** The authors declare no conflict of interest.

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