European Journal of Medicinal Chemistry 84 (2014) 264–277

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

# Design and synthesis of nonsteroidal progesterone receptor antagonists based on *C,C′*-diphenylcarborane scaffold as a hydrophobic pharmacophore

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ARTICLE INFO

*Article history:*
Received 24 April 2014
Received in revised form
8 July 2014
Accepted 10 July 2014
Available online 10 July 2014

*Keywords:*
Carborane
Progesterone receptor (PR)
Hydrophobic pharmacophore
Scaffold

ABSTRACT

The progesterone receptor (PR) plays important roles in multiple physiological processes, including female reproduction. Here, we report the synthesis of nonsteroidal PR antagonists containing a boron cluster as the hydrophobic core. We found that 1,7-diphenyl-*meta*-carborane was the preferred substructure among the three carborane isomers. Compound **39** was the most potent PR antagonist ($IC_{50}$: 29 nM). Compound **41** also exhibited potent activity ($IC_{50}$: 93 nM), and did not bind to androgen receptor, glucocorticoid receptor or mineralocorticoid receptor. These compounds may be useful for investigating potential clinical applications of PR modulators.



## 1. Introduction

Progesterone receptor (PR) is a member of the nuclear receptor superfamily of ligand-inducible transcription factors [1] and has roles in multiple physiological processes, including female reproduction. The endogenous PR ligand progesterone (P4, **1**) is involved in regulation of uterine cell proliferation/differentiation, implantation, ovulation, and mammary gland growth/differentiation [2–5]. Various synthetic PR agonists have been developed and are used clinically for contraception, hormone replacement therapy to reduce estrogen-mediated endometrial cancer risk, and treatment of gynecological disorders [6–8]. The PR agonists currently in clinical use have a steroidal skeleton, but this is associated with various side effects due to cross-binding affinity for other nuclear steroid receptors, including androgen receptor (AR), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR). Therefore, several nonsteroidal PR agonists have been developed in order to minimize such side effects [9]. Tanaproget (**2**) is one of the most investigated nonsteroidal PR agonists [10], and clinical application is expected in due course. On the other hand, little work has been done on potential clinical applications of PR antagonists. Mifepristone (RU-486: **3**) is a representative PR antagonist with a steroidal skeleton, and is used to induce abortion in some European countries [11]. The results of investigation of **3** suggested that PR antagonists might be effective not only as contraceptive agents, but also in the treatment of endometriosis [12], uterine leiomyoma [13], and breast cancer [14,15]. Thus, development of potent and selective nonsteroidal PR antagonists is required for detailed investigation of the pharmaceutical potential of PR modulation. Several nonsteroidal PR antagonists, such as **4a** and **5a**, have been developed based on the structure of **2** [16,17]. However, it was revealed that quite small modifications of these compounds can cause switching of agonistic/antagonistic activity of the compounds. For example, modification of the carbonyl group of **4a** to a thiocarbonyl group yielded agonist **4b** [18]. Modification of the hydrophobic part of **5a** to **5b** also dramatically changed the activity [17]. We recently developed coumarin derivatives, such as **6**, as novel nonsteroidal PR antagonists [19]. However, the pharmacophore of these coumarin derivatives is common to that of tanaproget (**2**) and other derivatives (Fig. 1).

On the basis of these considerations, we planned to develop novel nonsteroidal PR antagonists based on novel nonsteroidal scaffold structures. For this purpose, we focused on carboranes, which are icosahedral boron clusters. Carboranes (dicarba-*closo*-

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http://dx.doi.org/10.1016/j.ejmech.2014.07.034
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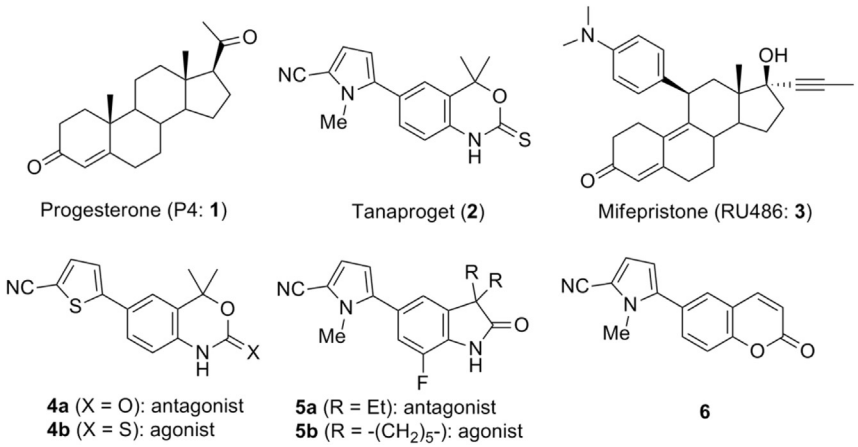



**Fig. 1.** Structures of PR endogenous ligand P4 (**1**) and synthesized agonists and antagonists.

dodecaboranes; Fig. 2) are polyhedral carbon-containing boron clusters that have a bulky spherical structure [20,21]. There are three isomeric carboranes, differing in the position of the two carbon atoms. They all exhibit high hydrophobicity, as well as having high thermal and chemical stability. We have already applied the carborane cage as a hydrophobic structural moiety for nuclear receptor ligands, and developed novel carborane-based ligands for vitamin D receptor (VDR) [22,23], androgen receptor (AR) [24,25], and estrogen receptor (ER) [26,27]. These carborane-based nonsteroidal ligands are advantageous for separation of pleiotropic receptor functions, as well as having excellent chemical stability. Herein, we describe the development of non-secosteroidal PR antagonists based on a carborane scaffold.

## 2. Chemistry

### 2.1. Molecular design

Our previous work on nuclear receptor ligands bearing a carborane cage as a hydrophobic pharmacophore demonstrated that the *C*-phenylcarborane framework functions as an effective alternative structure to a steroidal skeleton [24–27]. We also established that *C*-cyanophenylcarborane is a privileged structure for AR antagonists [24], and this finding suggested that the *C*-cyanophenylcarborane substructure might also be useful for development of ligands for other nuclear receptors specific for 3-ketosteroids, including PR. Therefore, we chose the *C*-cyanophenylcarborane framework as a core structure for nonsteroidal PR antagonists.

In the ligand-dependent activation of nuclear receptors, agonists induce a drastic conformational change of the receptors to the active form, including folding of the helix (12th helix, H12 in PR) at the terminal of the ligand-binding domain (LBD) of the receptors [28,29]. Full antagonism toward nuclear receptors can be obtained by inhibiting the folding of H12, and therefore introduction of a bulky substituent into a ligand to inhibit formation of the active conformation of the receptor is an effective design approach for nuclear receptor antagonists [30]. Structurally, the steroidal PR antagonist mifepristone (**3**) has an aryl substituent at the 11β-position in addition to the standard steroidal skeleton. X-ray analysis suggested that the aryl substituent at 11β-position would disturb the proper folding of H12 of PR, and this is considered to be the reason for the antagonistic activity of **3** toward PR [31].

Based on these considerations, we designed folding inhibitor-type nonsteroidal PR antagonists using cyanophenylcarborane as the core structure and an aryl group corresponding to the 11β-phenyl group of **3**. Two substituents can be introduced on the two carbon atoms of each carborane isomer, so we investigated three different diphenylcarborane scaffolds, namely 1,2-diphenyl-*o*-carborane, 1,7-diphenyl-*m*-carborane, and 1,12-diphenyl-*p*-carborane structure. As a bulky substituent corresponding to the 11β-phenyl group of **3**, we chose a substituted phenyl group.

### 2.2. Synthesis

Scheme 1 shows the synthesis of 1,2-diphenyl-*o*-carborane derivatives. Copper (I)-mediated Ullmann-type coupling using *C*-lithiated *o*-carborane and 4-iodobenzonitrile gave 1-(4-cyanophenyl)-*o*-carborane (**10**) [32], and $S_NAr$ reaction using the sodium salt of **10** and 4-fluoronitrobenzene afforded compound **11** with the 1,2-diphenyl-*o*-carborane core structure. Catalytic hydrogenation of the nitro group using Pd-carbon under a hydrogen atmosphere afforded amine **12**. Methylation of amine **12** with iodomethane gave monomethyl derivative **13** and dimethyl derivative **14**. Acylation or sulfonylation of **12** gave the corresponding amide or sulfonamide. Carbamate **17** was also prepared from amine **12** by using chloroformate. *N*-Methylated derivatives **19**–**22** were prepared by methylation of **15**–**18**, respectively.

Scheme 2 shows the synthesis of 1,7-diphenyl-*m*-carborane derivatives. Ullmann-type coupling using *C*-lithiated *m*-carborane and iodobenzene gave 1-phenyl-*m*-carborane **23**, and further Ullmann-type coupling using 4-iodobenzonitrile afforded compound **24** bearing the 1,7-diphenyl-*m*-carborane core structure. Nitration with mixed acid gave 4′-nitrated product **26** as a major product together with 3′-nitrated compound **25**. After separation of the isomers, reduction of the nitro group of each compound under a hydrogen atmosphere afforded amines **27** and **28**, respectively. Acetylation or methanesulfonylation of 3′-amino derivative **27** gave amide **29** and sulfonamide **30**. *N*-Methylation of **29** and **30** gave **31**

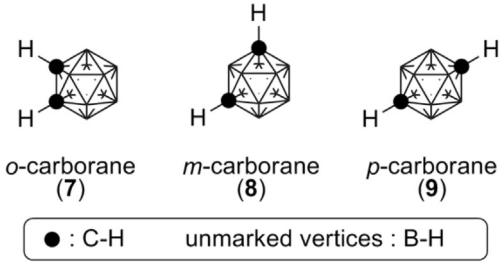
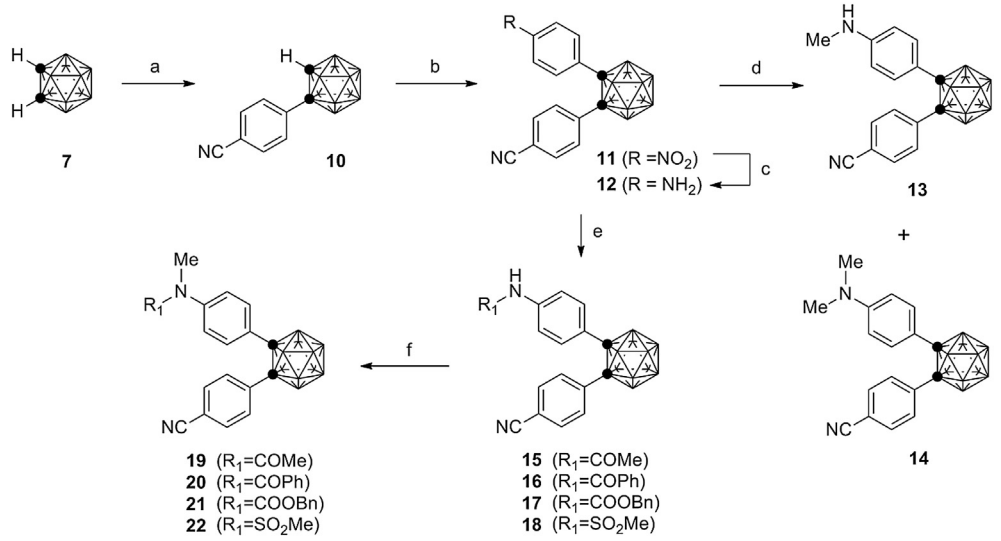
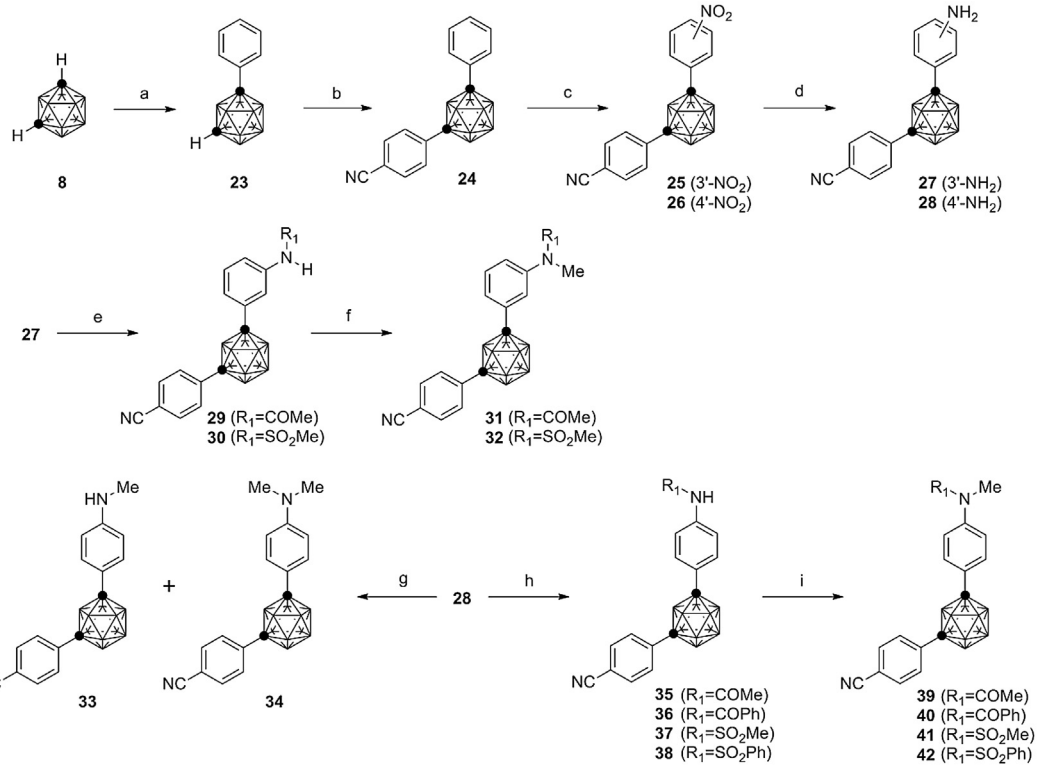



**Fig. 2.** Structures of carboranes.




**Scheme 1.** Synthesis of 1,2-diphenyl-*o*-carborane derivatives. Reagents and conditions: (a) *n*-BuLi, CuCl, DME, 0 °C, then 4-iodobenzonitrile, pyridine, 80 °C, 49%; (b) NaH, 4-fluoronitrobenzene, DME, 80 °C, 51%; (c) $Pd(OH)_2/C$, $H_2$, EtOH-THF, rt, 64%; (d) MeI, DMF, rt, 20% (**13**), 53% (**14**); (e) acyl chloride, solvent, 85%–98%; (f) NaH, MeI, DMF, rt, 85%-quant.




**Scheme 2.** Synthesis of 1,7-diphenyl-*m*-carborane derivatives. Reagents and conditions: (a) *n*-BuLi, CuCl, DME, 0 °C, then iodobenzene, pyridine, 80 °C, 66%; (b) *n*-BuLi, CuCl, DME, 0 °C, then 4-iodobenzonitrile, pyridine, 80 °C, 68%; (c) $HNO_3$, $H_2SO_4$, $CH_2Cl_2$, rt, 27% (**15**), 69% (**16**); (d) (for **27**) Pd/C, $H_2$, MeOH, rt, 74%; (for **28**) $Pd(OH)_2/C$, $H_2$, EtOH-THF, rt, 64%; (e) acetyl chloride, pyridine, $CH_2Cl_2$, rt, 78% (for **29**); methanesulfonyl chloride, pyridine, $CH_2Cl_2$, rt, 70% (for **30**); (f) NaH, MeI, DMF, rt, 65% (for **31**), 66% (for **32**); (g) MeI, DMF, rt, 17% (**33**), 22% (**34**); (e) acyl chloride, base, solvent, 33%–94%; (f) NaH, MeI, DMF, rt, 63%-quant.

and **32**, respectively. As for the 4′-substituted compounds, methylation of amine **28** with iodomethane gave monomethyl derivative **33** and dimethyl derivative **34**. Acylation or sulfonylation of **28** gave amides or sulfonamides (**35**–**38**), respectively. *N*-Methylated derivatives of amide and sulfonamide were also prepared by methylation of **39**–**42**.

1,12-Diphenyl-*p*-carborane derivatives were also synthesized in a similar manner to that used for preparation of *m*-carborane derivatives. Ullmann-type coupling using *C*-lithiated *p*-carborane and iodobenzene gave 1-phenyl-*p*-carborane (**43**), and further Ullmann-type coupling using 4-iodobenzonitrile afforded compound **44** bearing the 1,12-diphenyl-*p*-carborane core structure. Nitration with mixed acid gave 4′-nitrated product **45** as a mixture with 3′-nitrated minor product (ca: 4:1). Reduction of the nitro group of the isomeric mixture under a hydrogen atmosphere afforded amine **46** together with the 3′-amino isomer (ca: 3:1).

Acetylation or methanesulfonylation of **46** gave acetoamide **47** or sulfonamide **48**, respectively. The 3′-isomer was separated in this step. *N*-Methylated acetoamide **49** and sulfonamide **50** were prepared by methylation with iodomethane (Scheme 3).

## 3. Results

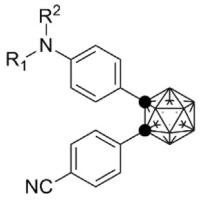
### 3.1. PR antagonistic activity

PR-agonistic and -antagonistic activities of synthesized compounds were evaluated by means of alkaline phosphatase assay using T-47D human breast carcinoma cell line, in which alkaline phosphatase expression is regulated by PR [33]. None of the synthesized carborane derivatives exhibited activity alone (data not shown), i.e., they did not act as PR agonists. PR-antagonistic activity was examined in the presence of 1 nM P4 (**1**), and the $IC_{50}$ values were calculated (Tables 1–3).

Several 1,2-diphenyl-*o*-carborane derivatives exhibited moderate PR-antagonistic activity (Table 1). Compound **14** bearing a dimethylamino group, which corresponds to the substituent of mifepristone (**3**), exhibited PR-antagonistic activity with the $IC_{50}$ value of 3.5 μM, and acetoamide **15** exhibited the most potent antagonistic activity among the 1,2-diphenyl-*o*-carborane derivatives with the $IC_{50}$ value of 2.2 μM. *N*-Methylation of amide derivatives resulted in decreased activity.

In contrast to the *o*-carborane derivatives, the 1,7-diphenyl-*m*-carborane derivatives exhibited potent PR-antagonistic activity (Table 2). Many of the tested *m*-carborane derivatives exhibited submicromolar $IC_{50}$ values. Among the 4′-substituted derivatives, amine derivatives **33** and **34** exhibited significant PR-antagonistic activity, while amide and sulfonamide derivatives **33**–**38** exhibited potent activity. Secondary acetoamide **35**, secondary methanesulfonamide **37** exhibited potent activity, with $IC_{50}$ values around 0.1 μM. Further, *N*-methylation of these amide and sulfonamide derivatives increased their potency, and *N*-methylacetoamide **39** exhibited the most potent activity with the $IC_{50}$ value of 29 nM. Though the 3′-substituted compounds **29**–**32** also exhibited potent PR-antagonistic activity, their potency was somewhat lower than that of the corresponding 4′-substituted compounds. We also determined binding affinity of the *m*-carborane derivatives using human PR-LBD and [$^3$H]-labeled P4 (**1**). Binding affinity to PR-LBD was roughly correlated with the PR antagonistic activity evaluated by T-47D alkaline phosphatase assay. 4-Substituted *N*-Acetyl and *N*-methanesulfonyl derivatives **35**, **37**, **39** and **41** exhibited potent binding affinity (binding $IC_{50}$ < 0.1 μM), and benzoyl and benzenesulfonyl derivatives exhibited lower affinity than that of the corresponding acetoamide or methanesulfonamide. These results suggested that the potent PR-antagonistic activity of acetyl and methanesulfonyl derivatives in T-47D alkaline phosphatase assay was indeed mediated by binding of the compound with PR.

**Table 1**
PR-antagonistic activity of 1,2-diphenyl-*o*-carborane derivatives in T-47D alkaline phosphatase assay.[a]



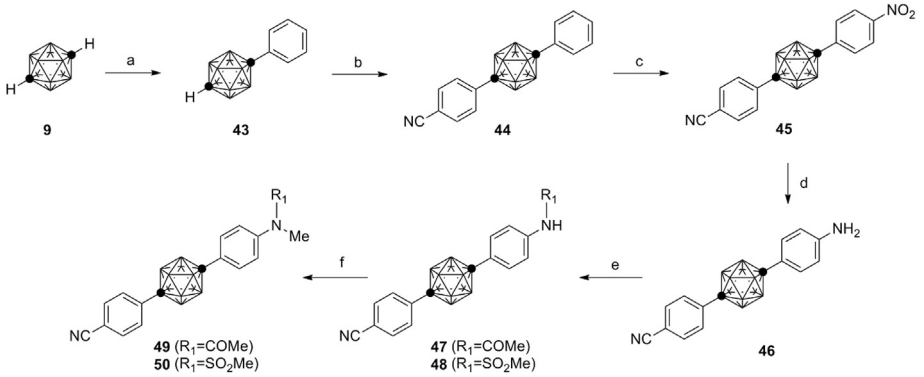

| Compd | $R^1$ | $R^2$ | T-47D $IC_{50}$ (μM)[a] |
|---|---|---|---|
| **13** | Me | H | 3.9 ± 0.32 |
| **14** | Me | Me | 3.5 ± 0.43 |
| **15** | COMe | H | 2.2 ± 0.20 |
| **16** | COPh | H | >10 |
| **17** | COOBn | H | >10 |
| **18** | $SO_2Me$ | H | >10 |
| **19** | COMe | Me | >10 |
| **20** | COPh | Me | >10 |
| **21** | COOBn | Me | 6.5 ± 0.43 |
| **22** | $SO_2Me$ | Me | >10 |

[a] Expression of alkaline phosphatase was induced with 1 nM progesterone.

Next, we examined the biological activity of 1,12-diphenyl-*p*-carborane derivatives bearing an acetyl or a methanesulfonyl moiety (Table 3). Secondary acetoamide **47** and sulfonamide **48** did not exhibit PR-antagonistic activity. Tertiary amide **49** and sulfonamide **50** exhibited PR-antagonistic activity with submicromolar $IC_{50}$ values (0.56 μM and 0.65 μM, respectively), though their potencies were lower than those of the corresponding 1,7-diphenyl-*m*-carborane derivatives **39** and **41** (0.029 μM and 0.093 μM, respectively).

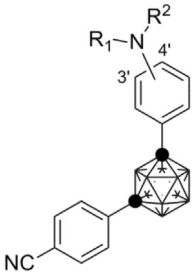
### 3.2. Binding affinity toward other steroid hormone receptors

To investigate selectivity of the synthesized PR antagonists, we examined the binding affinity of the most potent compound **39** and related sulfonamide **41** toward other 3-ketosteroid hormone nuclear receptors; androgen receptor (AR), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR). The binding affinities




**Scheme 3.** Synthesis of 1,12-diphenyl-*p*-carborane derivatives. Reagents and conditions: (a) *n*-BuLi, CuCl, DME, 0 °C, then iodobenzene, pyridine, 80 °C, 51%; (b) *n*-BuLi, CuCl, DME, 0 °C, then 4-iodobenzonitrile, pyridine, 80 °C, 76%; (c) $HNO_3$, $H_2SO_4$, $CH_2Cl_2$, rt, 52%; (d) $Pd(OH)_2/C$, $H_2$, EtOH-THF, rt, 66%; (e) acetyl chloride, pyridine, $CH_2Cl_2$, rt, 65% (for **47**); methanesulfonyl chloride, pyridine, $CH_2Cl_2$, rt, 77% (for **48**); (f) NaH, MeI, DMF, rt, 71% (for **49**), 50% (for **50**).

**Table 2**
PR-antagonistic activity of 1,7-diphenyl-*m*-carborane derivatives in T-47D alkaline phosphatase assay and PR binding affinity using hPR-LBD.




| Compd | Substituent | | | T-47D $IC_{50}$ (μM)[a] | Binding $IC_{50}$ (μM)[b] |
|---|---|---|---|---|---|
| | Position | $R^1$ | $R^2$ | | |
| **29** | 3′ | COMe | H | 0.098 ± 0.018 | 0.067 |
| **30** | | $SO_2Me$ | H | 0.27 ± 0.018 | 0.079 |
| **31** | | COMe | Me | 0.049 ± 0.003 | 0.11 |
| **32** | | $SO_2Me$ | Me | 0.34 ± 0.031 | 7.1 |
| **33** | 4′ | Me | H | 0.28 ± 0.047 | 0.34 |
| **34** | | Me | Me | 0.61 ± 0.077 | 25 |
| **35** | | COMe | H | 0.067 ± 0.008 | 0.022 |
| **36** | | COPh | H | 0.20 ± 0.019 | 6.6 |
| **37** | | $SO_2Me$ | H | 0.13 ± 0.038 | 0.043 |
| **38** | | $SO_2Ph$ | H | 0.43 ± 0.12 | 0.095 |
| **39** | | COMe | Me | 0.029 ± 0.005 | 0.042 |
| **40** | | COPh | Me | 0.24 ± 0.062 | 2.1 |
| **41** | | $SO_2Me$ | Me | 0.093 ± 0.034 | 0.087 |
| **42** | | $SO_2Ph$ | Me | 1.3 ± 0.36 | 1.4 |

[a] Expression of alkaline phosphatase was induced with 1 nM progesterone.
[b] The concentration of [$^3$H]progesterone was 4 nM.

were evaluated using the receptor ligand-binding domains and radiolabelled ligands (Table 4). Compound **39** exhibited moderate binding affinities toward AR and GR, though these affinities were quite low in comparison with that towards PR. In contrast to **39**, compound **41** bearing tertiary sulfonamide in place of acetoamide of **39** did not exhibit binding affinity toward AR, GR, or MR. These results suggest that the 1,7-diphenyl-*m*-carborane core structure is a versatile scaffold for development of PR antagonists, and also that simple structural modification by introducing substituents might effectively enhance the PR selectivity. The potent and selective nonsteroidal PR antagonists **39** and **41** are expected to be useful in the process of developing clinical applications of PR antagonists.

### 3.3. Docking simulation

In order to estimate the binding mode of *m*-carborane derivatives, docking simulation using the co-crystal structure of human PR LBD with mifepristone (**3**) (PDB ID: 2W8Y) [31] was performed. Fig. 4 shows the docking model of compound **39** with PR-LBD as superimposition of co-crystal structure of **3**. In the calculated structure, cyano group of **39** interacts with Gln725 and Arg766; these residues are interacting with 3-carbonyl group of **3**. The carborane moiety of **39** binds at hydrophobic region of the PR LBD, where the CD ring of **3** is located. The acetamidophenyl group of compound **39** is oriented in direction different from that of 11β-phenyl group of **3**, interacting with side chain of Met909 in H12. Formation of hydrogen-bonding between acetamide and the receptor was not observed. This study suggested that the *m*-carborane derivatives function as PR antagonist in the designed manner as illustrated in Fig. 3, whereas the second phenyl group destabilize the active folding of H12 in different manner from that of **3**.

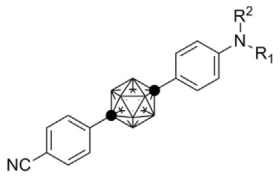
## 4. Discussion

Several nonsteroidal PR antagonists that are considered to have potential clinical utility have been developed, though all have a similar backbone or pharmacophore. Tanaproget (**2**) and its derivatives show potent PR ligand activities, but their agonist–antagonistic activities are strongly substituent-dependent. In this study, we designed novel nonsteroidal PR ligand candidates based on the structure of the steroidal PR antagonist mifepristone (**3**). We focused on two key structural parts of **3**, that is, the cyclohexenone ring as significant group for PR binding, and the dimethylaminophenyl group at the 11-position as a critical component for antagonistic activity. We arranged two aromatic rings corresponding to these key structures on a carborane moiety as a hydrophobic core structure. As shown in Schemes 1–3, it is straightforward to construct *C*,*C*′-diarylcarboranes with different orientation and distance between two aromatic rings by using the three isomeric carboranes. In other words, carboranes are useful building blocks that can be used to arrange two or more substituents in well-defined, distinct spatial positions.

The PR-dependent alkaline phosphatase assay revealed that none of the carborane derivatives examined exhibited PR-agonistic activity, though some of them showed potent PR-antagonistic activity. Among the three types of carborane derivatives, 1,7-diphenyl-*m*-carborane derivatives exhibited significant PR-antagonistic activity, while 1,2-diphenyl-*o*-carborane derivatives and 1,12-diphenyl-*p*-carborane derivatives exhibited no or lower PR antagonistic activity. These results suggested that the 1,7-diphenyl-*m*-carborane core structure is a versatile scaffold for PR full antagonists.

We previously showed that the cyanophenylcarborane moiety can function as an alternative structure to 3-ketosteroids such as testosterone [24], and thus we considered that the second phenyl ring of the 1,7-diphenyl-*m*-carborane derivatives (i.e., the 4-acetoaminophenyl group of **39**) functionally corresponds to the 11β-phenyl group of the steroidal PR antagonist **3**, serving to disturb the proper folding of H12 of PR. Docking simulation using co-crystal structure of PR LBD and compound **39** supported the concept of compound design. Since the overall molecular structure of 1,7-diphenyl-*m*-carborane derivatives is considerably different from that of **3**, our results suggest that the ligand-binding pocket of PR can accept a variety of compounds having different frameworks, at least as antagonists. Docking study suggested the difference in location of phenyl groups of **3** and *m*-carborane derivative **39** that interfere the folding of H12, and this was a possible reason why the acetyl and methanesulfonyl derivatives were more potent than the *N*,*N*-dimethyl derivative **34**. Though the *N*,*N*-dimethyl functionality is of relevance for the high activity of **3**, structure–activity relationship of 1,7-diphenyl-*m*-carborane derivatives as for phenyl substituents could be different from that of steroidal compounds. Compounds bearing an acetoamide group (**35**, **39**) or a methanesulfonamide group (**37**, **41**) exhibited potent antagonistic activity, whereas benzoyl derivatives (**36**, **40**) or benzensulfonyl derivatives (**38**, **42**) exhibited comparatively weak activity. *N*-Methylated compounds **37** and **41** were more potent than the parent compounds **35** and **39**, respectively. X-ray crystallographic analysis of the PR-LBD complex with **3** revealed that the 11β-substituent of **3** interacts with the hydrophobic pocket lined by four hydrophobic amino acid residues (Gly722, Trp755, Met759 and Met909), and also that slight steric interference between the 11β-substituent and Met909 side chain could disturb the active folding of PR H12 [31]. It is speculated that increasing the hydrophobicity by introduction of a methyl group at the 4′-substiuent of *m*-carborane derivatives increases the PR-antagonistic activity, and also that a benzoyl or benzenesulfonyl group is too large to be

**Table 3**
PR-antagonistic activity of 1,12-diphenyl-*p*-carborane derivatives in T47D alkaline phosphatase assay.




| Compd | $R^1$ | $R^2$ | T-47D $IC_{50}$ (μM)[a] |
|---|---|---|---|
| **47** | COMe | H | >10 |
| **48** | $SO_2Me$ | H | >10 |
| **49** | COMe | Me | 0.56 ± 0.032 |
| **50** | $SO_2Me$ | Me | 0.65 ± 0.010 |

[a] Expression of alkaline phosphatase was induced with 1 nM progesterone.

**Table 4**
Binding affinity of compounds **39** and **41** toward 3-ketosteroid nuclear receptors.

| Compd | PR | AR | GR | MR |
|---|---|---|---|---|
| | $IC_{50}$ (μM)[a] | $IC_{50}$ (μM)[b] | $IC_{50}$ (μM)[c] | $IC_{50}$ (μM)[d] |
| **39** | 0.042 | 4.5 | 2.9 | N.D[e] |
| **41** | 0.087 | N.D[e] | N.D[e] | N.D[e] |

[a] The concentration of [$^3$H]progesterone was 4 nM.
[b] The concentration of [$^3$H]DHT was 4 nM.
[c] The concentration of [$^3$H]dexamethasone was 1 nM.
[d] The concentration of [$^3$H]aldosterone was 2 nM.
[e] No detectable binding was observed.

compatible with the slight steric interference required for antagonistic activity. Our present results indicate that the substituent on the phenyl group has a critical role in binding to PR and in PR-antagonist activity.

## 5. Conclusion

We designed and synthesized three series of *C,C′*-diphenylcarborane derivatives as candidate nonsteroidal PR antagonists. Biological evaluation revealed that, among the three diphenylcarborane frameworks, the 1,7-diphenyl-*m*-carborane core structure functions as a versatile scaffold for PR antagonists. Structural development and structure–activity relationship studies suggested that one of the aryl groups of 1,7-diphenyl-*m*-carborane derivatives is critical for PR antagonism, serving to inhibit the active folding of PR in a manner slightly different to the 11β-substituent of **3**. The most potent compound **39** exhibited potent PR-antagonistic activity and high binding affinity for PR, and the related compound **41** also exhibited potent activity with high selectivity for PR over AR, GR and MR. The present results are expected to contribute to clinical development of PR antagonists.

## 6. Experimental

### 6.1. Chemistry

All reagents were purchased from Sigma–Aldrich Chemical Co., Tokyo Kasei Kogyo Co., Wako Pure Chemical Industries, and Kanto Chemical Co., INC. NMR spectra were recorded on Bruker AVANCE

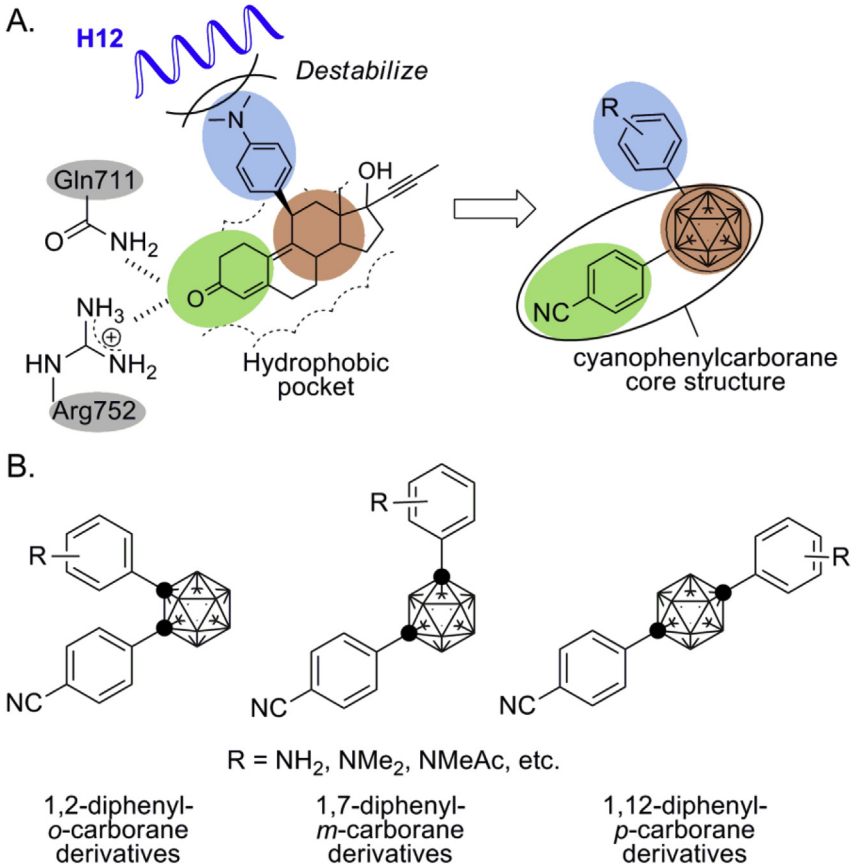



**Fig. 3.** Design of novel PR antagonists based on carboranes. A) Design scheme for cyanophenylcarborane-based folding inhibitor-type PR antagonists. B) Structures of the three designed series of *C,C′*-diphenylcarborane derivatives.

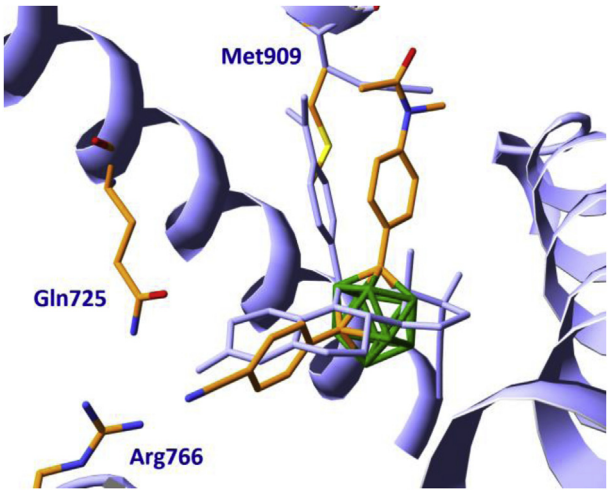



**Fig. 4.** Docking model of *m*-carborane derivative **39** with hPR-LBD by a docking program AutoDock [34]. Superimposition of PR LBD binding to mifepristone (**3**) (blue) and docking model of **39** (orange) is displayed.

400 or AVANCE 500 spectrometers. Chemical shifts are reported in ppm as $\delta$ values from tetramethylsilane. Data are reported as follows; chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q quartet; br, broad; m, multiplet), coupling constants (Hz), integration. Mass Spectra were collected on Bruker Daltonics microTOF-2focus or JEOL AX505H in the positive and negative ion modes. Melting points were obtained on a Yanagimoto micro melting point apparatus without correction. The purity of compounds was determined by elemental analysis or HPLC analysis confirming ≥95% purity (see Supporting Information).

### 6.1.1. Preparation of compounds

*6.1.1.1. 1-(4-Cyanophenyl)-1,2-dicarba-closo-dodecaborane (**10**).* Under argon atmosphere, *n*-butyllithium (1.65 mol/L in *n*-hexane, 13.9 mL, 22.9 mmol) was added dropwise to a solution of *o*-carborane (3.00 g, 20.8 mmol) in dimethoxyethane (20 mL) at 0 °C. The reaction mixture was stirred for 30 min, then copper (I) chloride (2.68 g, 27.0 mmol) was added to the reaction vessel and stirred at room temperature. After 1 h, pyridine (7 mL) and 4-iodobenzonitrile (5.24 g, 22.9 mmol) was added and stirred at 80 °C for overnight. The reaction mixture was cooled at room temperature then diluted with diethyl ether, filtered through Celite. The mixture was washed with 5% aqueous solution of sodium thiosulfate, 2 M hydrochloric acid, water and brine then dried with sodium sulfate and evaporated. The crude product was purified by flush silica gel column chromatography (eluent: *n*-hexane/$CH_2Cl_2$, 2:1) and 2.49 g of **10** (10.1 mmol, 49%) was obtained. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.66 (d, 2H, $J$ = 8.9 Hz), 7.61 (d, 2H, $J$ = 8.8 Hz), 3.97 (br s, 1H), 2.91–1.75 (m, 10H).

*6.1.1.2. 1-(4-Cyanophenyl)-2-(4-nitrophenyl)-1,2-dicarba-closo-dodecaborane (**11**).* Under argon atmosphere, sodium hydride (60% in oil, 25 mg, 0.61 mmol) was added to a solution of **10** (100 mg, 0.41 mmol) in DMF (4 mL) and stirred at 0 °C. After 10 min, 4-fluoronitrobenzene (52 μL, 0.49 mmol) was added to the reaction mixture and stirred at 0 °C. After 1 h, the reaction was quenched with saturated aqueous solution of ammonium chloride and diluted with ethyl acetate. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. The crude product was purified by flush silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 10:1) and 77.5 mg of **11** (0.21 mmol, 51%) was obtained. The compound was recrystallized from $CH_2Cl_2$/*n*-hexane. Yellow needle; mp: 179.2–180.0 °C; $^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 8.11 (d, 2H, $J$ = 9.1 Hz), 7.93 (d, 2H, $J$ = 9.0 Hz), 7.86 (d, 2H, $J$ = 8.8 Hz), 7.70 (d, 2H, $J$ = 8.8 Hz), 3.41–1.72 (m, 10H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 150.05, 136.62, 134.95, 133.50, 133.26, 132.63, 124.54, 118.00, 115.58, 84.85, 84.37.

*6.1.1.3. 1-(4-Aminophenyl)-2-(4-cyanophenyl)-1,2-dicarba-closo-dodecaborane (**12**).* Compound **11** (50 mg, 0.14 mmol) was dissolved in ethanol (1 mL) and THF (0.5 mL), and palladium hydroxide on carbon (5 mg) was suspended in the solution and stirred under hydrogen atmosphere. After 3 h, the reaction mixture was filtered through Celite and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 5:1) and 28.8 mg of **12** (0.09 mmol, 64%) was obtained. The compound was recrystallized from $CH_2Cl_2$/*n*-hexane. Pale yellow needle; mp: 198.2–199.9 °C; $^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 7.79 (d, 2H, $J$ = 8.7 Hz), 7.69 (d, 2H, $J$ = 8.8 Hz), 7.23 (d, 2H, $J$ = 8.8 Hz), 6.46 (d, 2H, $J$ = 8.8 Hz), 5.11 (br s, 2H), 3.40–1.62 (m, 10H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 151.83, 136.20, 133.06, 132.88, 132.73, 118.21, 118.03, 114.96, 114.20, 89.91, 85.27.

*6.1.1.4. 1-(4-Cyanophenyl)-2-(4-methylaminophenyl)-1,2-dicarba-closo-dodecaborane (**13**) and 1-(4-cyanophenyl)-2-(4-dimethylaminophenyl)-1,2-dicarba-closo-dodecaborane (**14**).* Under argon atmosphere, iodomethane (94 μL, 1.53 mmol) was added to a solution of **12** (100 mg, 0.30 mmol) in DMF (3 mL) at 0 °C and stirred at 40 °C. After 2 days, the solvent was removed under reduced pressure then the residue was diluted with ethyl acetate. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. The crude product was purified by flush silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 5:1) and 22.0 mg of **13** (0.06 mmol, 20%) and 57.3 mg (0.16 mmol, 53%) of **14** was obtained. The compounds were recrystallized from $CH_2Cl_2$/*n*-hexane. **13**; Yellow block; mp: 146.3–148.0 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.55 (d, 2H, $J$ = 8.6 Hz), 7.45 (d, 2H, $J$ = 8.7 Hz), 7.18 (d, 2H, $J$ = 8.9 Hz), 6.28 (d, 2H, $J$ = 8.8 Hz), 3.91 (br s, 1H), 3.20–1.79 (m, 10H), 2.76 (d, 3H, $J$ = 5.0 Hz); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 152.62, 136.25, 133.06, 132.81, 132.72, 118.21, 117.48, 114.94, 111.83, 90.16, 85.38, 39.84: **14**; Yellow needle; mp: 181.0–182.3 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.56 (d, 2H, $J$ = 8.8 Hz), 7.45 (d, 2H, $J$ = 8.8 Hz), 7.21 (d, 2H, $J$ = 9.1 Hz), 6.37 (d, 2H, $J$ = 9.1 Hz), 3.29–1.68 (m, 10H), 2.91 (s, 6H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 152.48, 136.23, 133.08, 132.72, 132.61, 118.20, 117.27, 114.96, 111.85, 89.88, 85.40, 39.86.

*6.1.1.5. 1-(4-Acetamidophenyl)-2-(4-cyanophenyl)-1,2-dicarba-closo-dodecaborane (**15**).* Under argon atmosphere, acetyl chloride (24 μL, 0.34 mmol) was added to a solution of **12** (100 mg, 0.30 mmol) in pyridine (3 mL) at 0 °C and stirred at room temperature. After 30 min, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with 2 M hydrochloric acid and brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 1:1) and 108 mg of **15** (0.28 mmol, 93%) was obtained. The compound was recrystallized from $CH_2Cl_2$/*n*-hexane. Yellow needle; $^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 9.26 (br s, 1H), 7.82 (d, 2H, $J$ = 8.8 Hz), 7.69 (d, 2H, $J$ = 8.8 Hz), 7.52 (d, 2H, $J$ = 9.4 Hz), 7.49 (d, 2H, $J$ = 9.4 Hz), 3.19–1.96 (m, 10H), 2.03 (s, 3H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 169.31, 142.72, 135.64, 133.17, 132.67, 132.34, 124.77, 119.09, 118.09, 115.08, 87.34, 84.80, 24.28.

*6.1.1.6. 1-(4-Benzoylaminophenyl)-2-(4-cyanophenyl)-1,2-dicarba-closo-dodecaborane (**16**).* Under argon atmosphere, triethylamine (30 μL, 0.22 mmol) and benzoyl chloride (20 μL, 0.22 mmol) was added to a solution of **12** (66.7 mg, 0.20 mmol) in $CH_2Cl_2$ (1 mL) at

0 °C and stirred at room temperature. After 30 min, the reaction was quenched with water and diluted with $CH_2Cl_2$. The organic layer was washed with 2 M hydrochloric acid and brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 3:1) and 74.1 mg of **16** (0.17 mmol, 85%) was obtained. The compound was recrystallized from $CH_2Cl_2$/*n*-hexane. White powder; mp: 250.7–252.3 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.81 (dd, 2H, $J$ = 7.9, 1.4 Hz), 7.73 (br s, 1H), 7.57 (d, 2H, $J$ = 8.8 Hz), 7.57–7.55 (m, 1H), 7.49 (dd, 2H, $J$ = 7.8, 7.6 Hz), 7.49 (d, 2H, $J$ = 9.2 Hz), 7.47 (d, 2H, $J$ = 8.1 Hz), 7.42 (d, 2H, $J$ = 9.0 Hz), 3.62–1.82 (m, 10H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 165.72, 140.15, 135.32, 134.30, 132.42, 132.11, 131.56, 131.37, 129.00, 127.03, 125.75, 119.33, 117.53, 114.34, 85.42, 83.09.

*6.1.1.7. 1-(4-Benzyloxycarbonylaminophenyl)-2-(4-cyanophenyl)-1,2-dicarba-closo-dodecaborane (**17**).* Under argon atmosphere, sodium hydrogen carbonate (28.3 mg, 0.34 mmol) was added to a solution of **12** (100 mg, 0.30 mmol) in THF (2 mL) then benzyl chloroformate (48 μL, 0.34 mmol) was added dropwise to the reaction and stirred at 0 °C. After 3 h, benzyl chloroformate (48 μL, 0.34 mmol) was added dropwise to the reaction and stirred at 0 °C. After 1 h, the reaction mixture was heated to room temperature. After 14 h, benzyl chloroformate (excess) was added dropwise to the reaction. After 6 h, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 3:1 to 4:1) and 137 mg of **17** (0.29 mmol, 98%) was obtained. The compound was recrystallized from $CH_2Cl_2$/*n*-hexane. White block; mp: 173.4–173.8 °C; $^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 8.93 (br s, 1H), 7.82 (d, 2H, $J$ = 8.6 Hz), 7.69 (d, 2H, $J$ = 8.6 Hz), 7.52 (d, 2H, $J$ = 8.9 Hz), 7.46 (d, 2H, $J$ = 9.0 Hz), 7.41–7.31 (m, 5H), 5.14 (s, 2H), 3.42–1.64 (m, 10H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 154.00, 142.65, 137.48, 135.73, 133.22, 132.71, 132.52, 129.31, 129.03, 128.98, 124.51, 118.41, 118.13, 115.16, 87.46, 84.89, 67.24.

*6.1.1.8. 1-(4-Cyanophenyl)-2-(4-methanesulfonylaminophenyl)-1,2-dicarba-closo-dodecaborane (**18**).* Under argon atmosphere, methanesulfonyl chloride (70 mg, 0.61 mmol) was added to a solution of **12** (100 mg, 0.30 mmol) in $CH_2Cl_2$ (3 mL) and pyridine (37 μL, 0.46 mmol) at 0 °C then stirred at room temperature. After 4 h, methanesulfonyl chloride (excess) was added to the reaction and stirred. After 17 h, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with 2 M hydrochloric acid and brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 2:1) and 113.0 mg of **18** (0.27 mmol, 90%) was obtained. The compound was recrystallized from ethyl acetate/*n*-hexane. White powder; mp: 252.7–253.7 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.56 (d, 2H, $J$ = 8.7 Hz), 7.48 (d, 2H, $J$ = 8.8 Hz), 7.39 (d, 2H, $J$ = 8.9 Hz), 6.97 (d, 2H, $J$ = 8.9 Hz), 6.52 (br s, 1H), 3.27–1.86 (m, 10H), 3.01 (s, 3H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 141.93, 135.55, 133.16, 132.96, 132.61, 125.56, 118.99, 118.05, 115.13, 86.87, 84.74.

*6.1.1.9. 1-(4-Cyanophenyl)-2-{4-(N-methylacetamido)phenyl)}-1,2-dicarba-closo-dodecaborane (**19**).* Under argon atmosphere, sodium hydride (60% in oil, 7 mg, 0.16 mmol) was added to a solution of **15** (50 mg, 0.13 mmol) in DMF (1.5 mL) and stirred at 0 °C. Then iodomethane (41 μL, 0.67 mmol) was added to the reaction mixture at 0 °C and stirred at room temperature. After 30 min, the reaction was quenched with saturated aqueous solution of ammonium chloride and diluted with ethyl acetate. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 1:1) and 41.5 mg of **19** (0.11 mmol, 85%) was obtained. The compound was recrystallized from $CH_2Cl_2$/*n*-hexane. White block; mp: 187.2–188.2 °C; $^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 7.82 (d, 2H, $J$ = 8.8 Hz), 7.69 (d, 2H, $J$ = 8.8 Hz), 7.65 (d, 2H, $J$ = 8.8 Hz), 7.24 (d, 2H, $J$ = 8.8 Hz), 3.56–1.69 (m, 10H), 3.12 (s, 3H), 1.69 (br s, 3H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 148.02, 135.45, 133.18, 132.83, 132.68, 127.83, 118.05, 115.22, 86.22, 84.69, 54.97, 36.85, 22.42.

*6.1.1.10. 1-(4-Cyanophenyl)-2-{4-(N-methylbenzamido)phenyl)}-1,2-dicarba-closo-dodecaborane (**20**).* Under argon atmosphere, sodium hydride (60% in oil, 5 mg, 0.12 mmol) was added to a solution of **16** (44.9 mg, 0.10 mmol) in DMF (1 mL) and stirred at 0 °C. Then iodomethane (30 μL, 0.51 mmol) was added to the reaction mixture at 0 °C and stirred at room temperature. After 10 min, the reaction was quenched with saturated aqueous solution of ammonium chloride and diluted with ethyl acetate. The organic layer was washed with brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/$CH_2Cl_2$, 3:1 to ethyl acetate only) and 46.6 mg of **20** (0.10 mmol, quant.) was obtained. The compound was recrystallized from $CH_2Cl_2$/*n*-hexane. White plate; mp: 175.3–176.3 °C; $^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 7.49 (d, 2H, $J$ = 8.8 Hz), 7.43 (d, 2H, $J$ = 8.8 Hz), 7.36 (tt, 1H, $J$ = 6.8, 2.0 Hz), 7.27 (d, 2H, $J$ = 8.8 Hz), 7.14–7.01 (m. 4H), 6.85 (d, 2H, $J$ = 8.8 Hz), 3.74–1.65 (m, 10H), 3.40 (s, 3H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 170.37, 148.53, 137.03, 135.38, 133.33, 132.58, 132.44, 130.45, 129.29, 128.58, 128.11, 127.72, 118.34, 115.29, 86.29, 84.76, 37.88.

*6.1.1.11. 1-{4-(Benzyloxycarbonyl)(methyl)aminophenyl}-2-(4-cyanophenyl)-1,2-dicarba-closo-dodecaborane (**21**).* Under argon atmosphere, sodium hydride (60% in oil, 13 mg, 0.36 mmol) and iodomethane (68 μL, 1.12 mmol) was added to a solution of **17** (100 mg, 0.21 mmol) in DMF (3 mL) and stirred at 0 °C. After 3 h, the reaction was quenched with saturated aqueous solution of ammonium chloride and diluted with ethyl acetate. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/$CH_2Cl_2$, 1:1) and 111.3 mg of **21** (0.23 mmol, quant.) was obtained. The compound was recrystallized from $CH_2Cl_2$/*n*-hexane. White plate; mp: 158.1–158.9 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.52 (d, 2H, $J$ = 8.7 Hz), 7.39 (d, 2H, $J$ = 8.7 Hz), 7.40–7.27 (m, 5H), 7.36 (d, 2H, $J$ = 9.1 Hz), 7.12 (d, 2H, $J$ = 8.8 Hz), 5.14 (s, 2H), 3.25 (s, 3H), 3.12–1.63 (m, 10H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 155.15, 146.71, 137.63, 135.69, 133.20, 132.65, 131.97, 129.31, 128.87, 128.69, 127.00, 125.28, 118.10, 115.20, 86.70, 84.78, 67.97, 37.05.

*6.1.1.12. 1-(4-Cyanophenyl)-2-{4-(N-methylmethylsulfonamido)phenyl)}-1,2-dicarba-closo-dodecaborane (**22**).* Under argon atmosphere, sodium hydride (60% in oil, 7.3 mg, 0.18 mmol) and iodomethane (50 μL, 0.76 mmol) was added to a solution of **18** (63 mg, 0.15 mmol) in DMF (2 mL) at 0 °C and stirred at room temperature. After 4 h, iodomethane (excess) was added to the reaction mixture and stirred at room temperature. After 13 h, the reaction was quenched with saturated aqueous solution of ammonium chloride and diluted with ethyl acetate. The organic layer was washed with brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 2:1) and 60.9 mg of **22** (0.14 mmol, 93%) was obtained. The compound was recrystallized from $CH_2Cl_2$/*n*-hexane. White needle; mp: 196.6–197.2 °C; $^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 7.81 (d, 2H, $J$ = 8.7 Hz), 7.69 (d, 2H, $J$ = 8.8 Hz), 7.60 (d,

2H, $J = 8.9$ Hz), 7.34 (d, 2H, $J = 8.9$ Hz), 3.34–1.96 (m, 10H), 3.24 (s, 3H), 2.81 (s, 3H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 143.99, 134.96, 131.96, 131.31, 131.21, 127.91, 124.13, 117.27, 114.21, 84.39, 82.86, 37.17, 35.68.

*6.1.1.13. 1-Phenyl-1,7-dicarba-closo-dodecaborane (**23**).* Under argon atmosphere, *n*-butyllithium (1.65 mol/L in *n*-hexane, 13.8 mL, 22.9 mmol) was added dropwise to a solution of *m*-carborane (3.00 g, 20.8 mmol) in dimethoxyethane (20 mL) at 0 °C. The reaction mixture was stirred for 30 min, then copper (I) chloride (2.68 g, 27.0 mmol) was added to the reaction vessel and stirred at room temperature. After 1 h, pyridine (7 mL) and iodobenzene (2.0 mL, 18.4 mmol) was added and stirred at 85 °C. After 3 h, the reaction mixture was cooled at room temperature then diluted with diethyl ether, filtered through Celite. The mixture was washed with 5% aqueous solution of sodium thiosulfate, 2 M hydrochloric acid, water and brine then dried with sodium sulfate and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane only and *n*-hexane/ethyl acetate 20:1) and 3.03 g of **23** (13.7 mmol, 66%) was obtained. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.43 (dd, 2H, $J = 8.2$, 1.9 Hz), 7.30–7.25 (m, 3H), 3.77–1.67 (m, 10H), 3.07 (br s, 1H).

*6.1.1.14. 1-(4-Cyanophenyl)-7-phenyl-1,7-dicarba-closo-dodecaborane (**24**).* Under argon atmosphere, *n*-butyllithium (1.65 mol/L in *n*-hexane, 9.15 mL, 15.1 mmol) was added dropwise to a solution of **23** (3.03 g, 13.7 mmol) in dimethoxyethane (14 mL) at 0 °C. The reaction mixture was stirred for 30 min, then copper (I) chloride (1.76 g, 17.8 mmol) was added to the reaction vessel and stirred at room temperature. After 1 h, pyridine (5 mL) and 4-iodobenzonitrile (3.45 g, 15.1 mmol) was added and stirred at 85 °C. After 5 h, the reaction mixture was cooled at room temperature then diluted with diethyl ether, filtered through Celite. The mixture was washed with 5% aqueous solution of sodium thiosulfate, 2 M hydrochloric acid, water and brine then dried with sodium sulfate and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane only and *n*-hexane/acetone 50:1) and flush silica gel column chromatography (eluent: *n*-hexane/acetone 50:1 and 100:1) then 2.98 g of **24** (9.27 mmol, 68%) was obtained. $^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 7.81 (s, 4H), 7.58 (dd, 2H, $J = 8.0$, 1.4 Hz), 7.43–7.35 (m, 3H), 3.41–2.25 (m, 10H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 140.06, 134.85, 132.33, 129.11, 128.89, 128.65, 127.90, 118.08, 113.07, 78.45, 76.58.

*6.1.1.15. 1-(4-Cyanophenyl)-7-(3-nitrophenyl)-1,7-dicarba-closo-dodecaborane (**25**) and 1-(4-cyanophenyl)-7-(4-nitrophenyl)-1,7-dicarba-closo-dodecaborane (**26**).* A mixture of nitric acid (12 mL) and sulfuric acid (48 mL) was added dropwise to a solution of **24** (2.76 g, 8.59 mmol) in $CH_2Cl_2$ (90 mL) at 0 °C and stirred at room temperature. After 30 min, the reaction mixture was quenched with iced water and diluted with $CH_2Cl_2$. The organic layer was washed with saturated aqueous solution of sodium hydrogen carbonate and brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 15:1) and 854.9 mg of **25** (2.33 mmol, 27%) and 2.17 g of **26** (5.92 mmol, 69%) were obtained. **25**; $^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 8.34 (dd, 1H, $J = 2.0$, 1.8 Hz), 8.21 (ddd, 1H, $J = 8.2$, 2.2, 0.9 Hz), 7.79 (ddd, 1H, $J = 8.0$, 2.0, 0.9 Hz), 7.60 (s, 4H), 7.50 (dd, 1H, $J = 8.1$, 8.1 Hz), 3.47–1.76 (m, 10H): **26** was recrystallized from $CH_2Cl_2$/*n*-hexane. **26**; White powder; mp: 189.1–189.6 °C; $^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 8.24 (d, 2H, $J = 9.1$ Hz), 7.91 (d, 2H, $J = 9.1$ Hz), 7.82 (s, 4H), 3.44–1.53 (m, 10H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 148.42, 140.73, 138.98, 132.59, 129.38, 128.91, 123.70, 117.49, 113.24, 77.47, 77.00.

*6.1.1.16. 1-(3-Aminophenyl)-7-(4-cyanophenyl)-1,7-dicarba-closo-dodecaborane (**27**).* Compound **25** (120 mg, 0.33 mmol) was hydrogenerated in ethyl acetate (0.5 mL) and methanol (0.3 mL) with 10% palladium on carbon (12 mg) under atmospheric pressure of $H_2$. The mixture was stirred at room temperature for 3 h. After removal of catalyst by filtration, the filtrate was concentrated and gave to **27** (80 mg, 74%) as white solid. The compound **27** was recrystallized from *n*-hexane/$CHCl_3$: mp: 153–155 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.58 (br s, 4H), 7.04 (t, 1H, $J = 8.0$ Hz), 6.82 (ddd, 1H, $J = 7.5$ Hz, 2.0 Hz, 0.5 Hz), 6.74 (t, 1H, $J = 2.0$ Hz), 6.61 (ddd, 1H, $J = 7.5$ Hz, 2.0 Hz, 0.5H z), 3.5–2.0 (br m, 10H); $^{13}$C NMR(500 MHz, $CDCl_3$) $\delta$ 146.5, 140.1, 135.9, 132.3, 129.5, 128.9, 118.1, 115.6, 114.6, 113.0.

*6.1.1.17. 1-(4-Aminophenyl)-7-(4-cyanophenyl)-1,7-dicarba-closo-dodecaborane (**28**).* Compound **26** (50 mg, 0.15 mmol) was dissolved in methanol (1.5 mL) and THF (1 mL). Palladium hydroxide on carbon (5 mg) was suspended in the solution and stirred under hydrogen atmosphere. After 1.5 h, the reaction mixture was filtered through Celite and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 5:1) and 29.0 mg of **28** (0.09 mmol, 60%) was obtained. The compound was recrystallized from $CH_2Cl_2$/*n*-hexane. Yellow plate; mp: 160.7–162.0 °C; $^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 7.79 (s, 4H), 7.21 (d, 2H, $J = 8.7$ Hz), 6.59 (d, 2H, $J = 8.7$ Hz), 4.93 (br s, 2H), 4.06–1.71 (m, 10H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 150.34, 140.49, 133.36, 129.78, 129.32, 123.07, 118.48, 114.44, 113.77, 80.92, 77.26.

*6.1.1.18. 1-(3-Acetamidophenyl)-7-(4-cyanophenyl)-1,7-dicarba-closo-dodecaborane (**29**).* Acetyl chloride (9 μL, 0.13 mmol) was added to a solution of **27** (40 mg, 0.12 mmol) in $CH_2Cl_2$ (0.5 mL) and pyridine (10 μL, 0.13 mmol) under Ar at 0 °C. The mixture was stirred at room temperature for 1 h. Then the reaction was quenched with water and extracted by $CH_2Cl_2$, The organic layer was washed with 2 M HCl, 2 M NaOH, and brine, dried over $Na_2SO_4$, filtered and concentrated. Purification by silica gel column chromatography (*n*-hexane/ethyl acetate, 2:1) gave **29** (35 mg, 78%) as a yellow solid. Compound **29** was recrystallized with *n*-hexane and ethyl acetate. mp: 202–204 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.7 (br s, 1H), 7. 58 (br s, 4H), 7.45 (d, 1H, $J = 7.5$ Hz), 7.21 (m, 3H), 2.18 (s, 3H), 3.5–2.0 (br m, 10H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 168.5, 140.0, 138.2, 135.8, 132.4, 129.4, 129.0, 123.8, 120.4, 118.1, 113.1, 24.8.

*6.1.1.19. 1-(4-Cyanophenyl)-7-(3-methylsulfonamidophenyl)-1,7-dicarba-closo-dodecaborane (**30**).* Methanesulfonyl chloride (10 μL, 0.13 mmol) was added to a solution of **27** (40 mg, 0.12 mmol) in $CH_2Cl_2$ (0.5 mL) and pyridine (10 μL, 0.13 mmol) under Ar at 0 °C. The mixture was stirred at room temperature for 1.5 h. Then the reaction was quenched with water and extracted by $CH_2Cl_2$, washed with 2 M HCl, 2 M NaOH, and brine, dried over $Na_2SO_4$, filtered and concentrated. Purified by silica gel column chromatography (*n*-hexane/ethyl acetate, 2:1) gave **30** (34 mg, 70%) as a white solid. **30** was recrystallized with *n*-hexane and ethyl acetate. 208–210 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.58 (s, 4H), 7.29(m, 3H), 7.18 (m, 1H), 6.37 (br s, 1H), 3.03 (s, 3H), 3.5–2.0 (br m, 10H); $^{13}$C NMR(125 MHz, $CDCl_3$) $\delta$ 139.7, 137.1, 136.7, 132.4, 130.1, 128.9, 124.7, 120.7, 119.9, 118.0, 113.2, 39.9.

*6.1.1.20. 1-(3-N-Methylacetamidophenyl)-7-(4-cyanophenyl)-1,7-dicarba-closo-dodecaborane (**31**).* NaH (8 mg, 0.21 mmol) was added to a solution of **29** (27 mg, 0.07 mmol) in DMF (0.5 mL) under Ar at 0 °C. Then iodomethane (13 μL, 0.21 mmol) was added to the mixture and stirring was continued at room temperature for 12 h. Then the reaction was quenched with water and extracted by ethyl acetate, washed with aqueous $NH_4Cl$, and brine, dried over $Na_2SO_4$,

filtered and concentrated. Purification by silica gel column chromatography (*n*-hexane/ethyl acetate, 2:1) gave **31** (18 mg, 65%) as a white solid. mp: 152–155 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ7.59 (s, 4H), δ 7.43 (br d, 1H, $J$ = 7.5 Hz), 7. 35(t, 1H, $J$ = 8.0 Hz), 7.27 (br s, 1H), 7.17 (br d, $J$ = 8.0 Hz, 1H), 3.25 (s, 3H), 3.2–2.0 (br m, 10H), 1.85(s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 170.0, 144.9, 139.7, 136.7, 132.4, 130.0, 128.9, 127.6, 127.1, 126.8, 118.0, 113.2, 37.3, 22.6.

*6.1.1.21. 1-(3-N-Methylmethylsulfonamidophenyl)-7-(4-cyanophenyl)-1,7-dicarba-closo-dodecaborane (**32**).* NaH (7 mg, 0.18 mmol) was added to a solution of **30** (25 mg, 0.06 mmol) in DMF (0.3 mL) under Ar at 0 °C, then iodomethane (11 μL, 0.18 mmol) was added to the mixture and stirring was continued at room temperature for 4 h. The reaction was quenched with water and extracted by $CHCl_3$, washed with aqueous $NH_4Cl$ and brine, dried over $Na_2SO_4$, filtered and concentrated. Purification by silica gel column chromatography (*n*-hexane/ethyl acetate, 4:1) gave **32** (17 mg, 66%) as a yellow solid. **32** was recrystallized with *n*-hexane and ethyl acetate. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 4H), 7.49(br s, 1H), 7.38 (m, 1H), 7.31 (m, 2H), 3.32 (s, 3H), 2.83 (s, 3H), 3.2–2.0 (br m, 10H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 141.8, 139.8, 136.1, 132.4, 129.5, 128.9, 126.6, 126.3, 126.0, 118.0, 113.2, 38.3, 35.5.

*6.1.1.22. 1-(4-Cyanophenyl)-7-(4-methylaminophenyl)-1,7-dicarba-closo-dodecaborane (**33**) and 1-(4-cyanophenyl)-7-(4-dimethylaminophenyl)-1,7-dicarba-closo-dodecaborane (**34**).* Under argon atmosphere, iodomethane (56 μL, 0.92 mmol) was added to a solution of **28** (60 mg, 0.18 mmol) in DMF (2 mL) at 0 °C and stirred at room temperature. After 2 days, the reaction mixture was quenched with water and diluted with ethyl acetate. The organic layer was washed with brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 20:1) and 12.2 mg of **33** (0.03 mmol, 17%) and 16.3 mg (0.04 mmol, 22%) of **34** was obtained. The compounds were recrystallized from $CH_2Cl_2$/*n*-hexane. **33**; White solid; mp: 143.9–145.0 °C; $^1$H NMR (400 MHz, Acetone-$d_6$) δ 7.79 (s, 4H), 7.26 (d, 2H, $J$ = 8.8 Hz), 6.52 (d, 2H, $J$ = 8.8 Hz), 5.27 (br s, 1H), 4.08–1.61 (m, 10H), 2.77 (d, 3H, $J$ = 5.2 Hz); $^{13}$C NMR (125 MHz, Acetone-$d_6$) δ 151.54, 140.58, 133.38, 129.82, 129.31, 122.63, 118.50, 113.85, 112.18, 81.08, 77.34, 60.53; Anal. Calcd. for C16H22B10N2·1/4$H_2O$: C, 54.14; H, 6.39; N, 7.89. Found C, 54.19; H, 6.28, N; 7.90: **34**; Yellow needle; Mp: 202.2–203.2 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 4H), 7.33 (d, 2H, $J$ = 9.1 Hz), 6.65 (d, 2H, $J$ = 9.1 Hz), 3.20–1.47 (m, 10H), 2.95 (s, 6H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) δ 151.80, 140.55, 133.39, 129.82, 129.19, 122.59, 118.49, 113.87, 112.49, 80.43, 77.40, 40.21.

*6.1.1.23. 1-(4-Acetamidophenyl)-7-(4-cyanophenyl)-1,7-dicarba-closo-dodecaborane (**35**).* Under argon atmosphere, acetyl chloride (14 μL, 0.20 mmol) was added to a solution of **28** (60 mg, 0.18 mmol) in pyridine (2 mL) at 0 °C and stirred at room temperature. After 10 min, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with 2 M hydrochloric acid and brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 1:1) and 59.8 mg of **35** (0.16 mmol, 89%) was obtained. The compound was recrystallized from $CH_2Cl_2$/*n*-hexane. White plate; mp: 211.5–212.0 °C; $^1$H NMR (400 MHz, Acetone-$d_6$) δ 8.80 (br s, 1H), 7.81 (s, 4H), 7.55 (d, 2H, $J$ = 8.9 Hz), 7.30 (d, 2H, $J$ = 8.9 Hz), 3.32–1.50 (m, 10H), 3.04 (s, 3H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) δ 169.17, 141.36, 140.25, 133.41, 129.78, 129.04, 119.56, 118.47, 118.46, 113.88, 79.72, 77.66, 24.30.

*6.1.1.24. 1-(4-Benzoylaminophenyl)-27-(4-cyanophenyl)-1,7-dicarba-closo-dodecaborane (**36**).* Under argon atmosphere, benzoyl chloride (23 μL, 0.20 mmol) was added to a solution of **28** (60 mg, 0.18 mmol) in pyridine (2 mL) at 0 °C and stirred at room temperature. After 2 h, benzoyl chloride (23 μL, 0.20 mmol) and $CH_2Cl_2$ (6 mL) was added to the reaction mixture and stirred at room temperature. After 14 h, the reaction was quenched with water and diluted with $CH_2Cl_2$. The organic layer was washed with 2 M hydrochloric acid and brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 2:1) and 76.3 mg of **36** (0.17 mmol, 94%) was obtained. The compound was recrystallized from $CH_2Cl_2$/*n*-hexane. White plate; mp: 200.8–201.5 °C; $^1$H NMR (400 MHz, Acetone-$d_6$) δ 9.67 (br s, 1H), 7.98 (d, 2H, $J$ = 8.5 Hz), 7.86 (d, 2H, $J$ = 8.8 Hz), 7.82 (s, 4H), 7.59–7.50 (m, 5H), 3.39–1.58 (m, 10H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) δ 166.50, 141.38, 140.34, 135.95, 133.44, 132.58, 130.45, 129.85, 129.34, 129.09, 128.39, 120.68, 118.48, 113.97, 79.79, 77.79.

*6.1.1.25. 1-(4-Cyanophenyl)-7-(4-methanesulfonylaminophenyl)-1,7-dicarba-closo-dodecaborane (**37**).* Under argon atmosphere, methanesulfonyl chloride (70 mg, 0.61 mmol) was added to a solution of **28** (100 mg, 0.30 mmol) in $CH_2Cl_2$ (3 mL) and pyridine (37 μL, 0.46 mmol) at 0 °C then stirred at room temperature. After 1 h, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with 2 M hydrochloric acid and brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 2:1). The crude product was washed with saturated aqueous solution of sodium hydrogen carbonate, dried with sodium sulfate, and evaporated. 103.5 mg of **37** (0.25 mmol, 83%) was obtained. Yellow needle; mp: 238.0–239.0 °C; $^1$H NMR (400 MHz, Acetone-$d_6$) δ 8.80 (br s, 1H), 7.81 (s, 4H), 7.55 (d, 2H, $J$ = 8.9 Hz), 7.30 (d, 2H, $J$ = 8.9 Hz), 3.40–1.42 (m, 10H), 3.04 (s, 3H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) δ 140.52, 140.22, 133.40, 130.75, 129.77, 129.75, 119.90, 118.43, 113.95, 79.38, 77.81, 60.51, 39.83.

*6.1.1.26. 1-(4-Benzenesulfonamidophenyl)-7-(4-cyanophenyl)-1,7-dicarba-closo-dodecaborane (**38**).* Under argon atmosphere, benzenesulfonyl chloride (20 μL, 0.23 mmol) was added to a solution of **28** (60 mg, 0.18 mmol) in $CH_2Cl_2$ (2 mL) and triethylamine (50 μL, 0.37 mmol) at 0 °C then stirred at room temperature. After 12 h, benzenesulfonyl chloride (excess) was added to the reaction and stirred at room temperature. After 25 h, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with 2 M hydrochloric acid and brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/$CH_2Cl_2$ 5:1) and 30.8 mg of **38** (0.06 mmol, 33%) was obtained. Colorless block; mp:195.0–196.0 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, 2H, $J$ = 8.7 Hz), 7.58 (m, 5H), 7.48 (t, 2H, $J$ = 7.5 Hz), 7.32 (d, 2H, $J$ = 7.5 Hz), 6.95 (d, 2H, $J$ = 8.9 Hz), 6.52 (s, 1H), 3.2–1.7 (br m, 10H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 139.88, 139.13, 137.44, 133.49, 132.34, 131.46, 129.39, 129.00, 128.84, 127.29, 120.20, 118.05, 113.08, 78.01, 76.65.

*6.1.1.27. 1-(4-Cyanophenyl)-7-{4-(N-methylacetamido)phenyl)}-1,7-dicarba-closo-dodecaborane (**39**).* Under argon atmosphere, sodium hydride (60% in oil, 3.6 mg, 0.09 mmol) was added to a solution of **35** (29.1 mg, 0.08 mmol) in DMF (1 mL) and stirred at 0 °C. Then iodomethane (24 μL, 0.39 mmol) was added to the reaction mixture at 0 °C and stirred at room temperature. After 5 h, the reaction was quenched with saturated aqueous solution of ammonium chloride and diluted with ethyl acetate. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography and 20.1 mg of **39** (0.05 mmol, 63%) was obtained. The compound was recrystallized from $CH_2Cl_2$/*n*-hexane. White powder; mp:

162.1–162.8 °C; $^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 7.81 (s, 4H), 7.64 (d, 2H, $J$ = 8.4 Hz), 7.34 (d, 2H, $J$ = 8.7 Hz), 3.42–1.65 (m, 10H), 3.20 (br s, 3H), 1.82 (br s, 3H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 169.43, 146.68, 140.07, 134.17, 133.42, 129.77, 128.20, 118.42, 113.94, 78.99, 77.91, 36.86, 36.77, 22.50.

*6.1.1.28. 1-(4-Cyanophenyl)-7-{4-(N-methylbenzamido)phenyl)}-1,7-dicarba-closo-dodecaborane (**40**).* Under argon atmosphere, sodium hydride (60% in oil, 5 mg, 0.13 mmol) was added to a solution of **36** (41 mg, 0.09 mmol) in DMF (1 mL) and stirred at 0 °C. Then iodomethane (29 μL, 0.47 mmol) was added to the reaction mixture at 0 °C and stirred at room temperature. After 1 h, the reaction was quenched with saturated aqueous solution of ammonium chloride and diluted with ethyl acetate. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 1:1) and 49.5 mg of **40** (0.11 mmol, quant.) was obtained. mp: 175.3–176.3 °C; $^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 7.79 (s, 4H), 7.46 (d, 2H, $J$ = 8.8 Hz), 7.31 (tt, 1H, $J$ = 7.5, 1.4 Hz), 7.30 (d, 2H, $J$ = 7.0 Hz), 7.23 (dd, 2H, $J$ = 7.8, 7.4 Hz), 7.16 (d, 2H, $J$ = 8.8 Hz), 4.19–1.50 (m, 10H), 3.41 (s, 3H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 170.44, 147.05, 140.15, 137.27, 133.42, 133.03, 130.50, 129.80, 129.39, 129.30, 128.61, 127.74, 118.43, 114.00, 79.11, 77.89, 38.18.

*6.1.1.29. 1-(4-Cyanophenyl)-7-(4-N-methylmethylsulfonamidophenyl)-1,7-dicarba-closo-dodecaborane (**41**).* Under argon atmosphere, sodium hydride (60% in oil, 5 mg, 0.13 mmol) was added to a solution of **37** (50 mg, 0.11 mmol) in DMF (1 mL) and stirred at 0 °C. Then iodomethane (32 μL, 0.53 mmol) was added to the reaction mixture at 0 °C and stirred at room temperature. After 10 min, the reaction was quenched with saturated aqueous solution of ammonium chloride and diluted with ethyl acetate. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/$CH_2Cl_2$ 1:1) and 44.7 mg of **41** (0.10 mmol, 91%) was obtained. The compound was recrystallized from $CH_2Cl_2$/*n*-hexane. White needle; mp: 171.1–171.6 °C; $^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 7.81 (s, 4H), 7.60 (d, 2H, $J$ = 8.9 Hz), 7.45 (d, 2H, $J$ = 8.8 Hz), 3.48–1.54 (m, 10H), 3.33 (s, 3H), 2.91 (s, 3H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 143.94, 140.10, 133.43, 129.78, 129.31, 126.54, 118.43, 113.94, 79.00, 77.91, 37.85, 35.43.

*6.1.1.30. 1-(4-Cyanophenyl)-7-(4-N-methylbenzenesulfonamidophenyl)-1,7-dicarba-closo-dodecaborane (**42**).* Sodium hydride (60% in oil, 3 mg, 0.08 mmol) was washed with *n*-hexane and added DMF (1 mL). The reaction vessel was displaced argon atmosphere then added **38** (30 mg, 0.06 mmol) in DMF (1 mL) and iodomethane (19 μL, 0.32 mmol) at 0 °C and stirred at room temperature. After 1 h, the reaction was quenched with saturated aqueous solution of ammonium chloride and diluted with ethyl acetate. The organic layer was washed with brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 4:1) and 22.7 mg of **42** (0.05 mmol, 83%) was obtained. The compound was recrystallized from $CH_2Cl_2$/*n*-hexane. White powder; mp: 59.1–60.2 °C; $^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 7.81 (s, 4H), 7.22–7.68 (m, 1H), 7.60–7.56 (m, 4H), 7.54 (d, 2H, $J$ = 8.8 Hz), 7.17 (d, 2H, $J$ = 8.9 Hz), 3.37–1.58 (m, 10H), 3.20 (s, 3H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 143.55, 140.10, 137.37, 134.05, 133.80, 133.44, 129.95, 129.79, 129.12, 128.42, 126.86, 118.43, 113.95, 79.00, 77.91, 38.07.

*6.1.1.31. 1-Phenyl-1,12-dicarba-closo-dodecaborane (**43**).* Under argon atmosphere, *n*-butyllithium (1.65 mol/L in *n*-hexane, 2.77 mL, 4.57 mmol) was added dropwise to a solution of *p*-carborane (0.60 g, 4.16 mmol) in dimethoxyethane (3.6 mL) at 0 °C. The reaction mixture was warmed to room temperature for 30 min, then copper (I) chloride (535.1 mg, 5.40 mmol) was added to the reaction vessel. After the reaction mixture was stirred for 1 h, pyridine (2.3 mL) and iodobenzene (50 mL, 14.60 mmol) was added and stirred at 80 °C. After 3 h, the reaction mixture was cooled at room temperature then diluted with diethyl ether, filtered through Celite. The mixture was washed with 5% aqueous solution of sodium thiosulfate, 2 M hydrochloric acid, water and brine, dried with sodium sulfate and evaporated. 794 mg of **43** (mixture with 29% of iodobenzene and 8% of *p*-carborane, 2.12 mmol, 51% yield) was obtained. The crude product was recrystallized from *n*-hexane. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.24–7.15 (m, 5H), 3.14–1.65 (m, 10H), 2.90 (br s, 1H).

*6.1.1.32. 1-(4-Cyanophenyl)-12-phenyl-1,12-dicarba-closo-dodecaborane (**44**).* Under argon atmosphere, *n*-butyllithium (1.65 mol/L in *n*-hexane, 6.30 mL, 10.34 mmol) was added dropwise to a solution of **43** (included 29% of iodobenzene and 8% of *p*-carborane, 1.47 g, 4.18 mmol) in dimethoxyethane (4.3 mL) at 0 °C. The reaction mixture was warmed to room temperature for 30 min, then copper (I) chloride (1.03 g, 10.44 mmol) was added to the reaction vessel. After the reaction mixture was stirred for 1 h, pyridine (1.5 mL) and 4-iodobenzonitrile (2.87 g, 12.54 mmol) was added and stirred at 80 °C. After 15 h, the reaction mixture was cooled at room temperature then diluted with diethyl ether, filtered through Celite. The mixture was washed with 5% aqueous solution of sodium thiosulfate, 2 M hydrochloric acid, water and brine, dried with sodium sulfate and evaporated. The crude product was purified by flush silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 50:1) and 2.62 g of **44** (included 61% of *p*-iodobenzonitrile, 3.18 mmol, 76% yield) was obtained. The product was purified by preparative thin-layer chromatography (eluent: *n*-hexane/ethyl acetate 20:1) and recrystallized from *n*-hexane. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.50 (d, 2H, $J$ = 8.8 Hz), 7.36 (d, 2H, $J$ = 8.8 Hz), 7.25–7.17 (m, 5H), 3.24–2.06 (m, 10H).

*6.1.1.33. 1-(4-Cyanophenyl)-12-(4-nitrophenyl)-1,12-dicarba-closo-dodecaborane (**45**).* A mixture of nitric acid (0.4 mL) and sulfuric acid (1.6 mL) was added dropwise to a solution of **44** (included 61% of 4-iodobenzonitrile, 250.9 mg, 0.31 mmol) in $CH_2Cl_2$ (3 mL) and stirred at 0 °C. After 1 h, the reaction mixture was quenched with iced water and diluted with $CH_2Cl_2$. The organic layer was washed with saturated aqueous solution of sodium hydrogen carbonate, water and brine, dried with sodium sulfate, and evaporated. The crude product was purified by flush silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 50:1 to 25:1) and 79.1 mg of **45** (mixture with 23% of 3-nitrated isomer (0.05 mmol, 16%), 0.16 mmol, 52% yield). The compound was recrystallized from $CH_2Cl_2$/*n*-hexane. **45**; White block; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.06 (d, 2H, $J$ = 9.1 Hz), 7.51 (d, 2H, $J$ = 8.8 Hz), 7.41 (d, 2H, $J$ = 9.1 Hz), 7.35 (d, 2H, $J$ = 8.8 Hz), 3.28–2.05 (m, 10H).

*6.1.1.34. 1-(4-Aminophenyl)-12-(4-cyanophenyl)-1,12-dicarba-closo-dodecaborane (**46**).* Compound **45** (mixture with 13% of 3-isomer, 285.8 mg, 0.68 mmol) was dissolved in ethyl acetate (16 mL). Palladium on carbon (34.0 mg) was suspended in the solution and stirred under hydrogen atmosphere. After 4 h, the reaction mixture was filtered through Celite and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 5:1) and 161.9 mg of **46** (mixture with 30% of 3-$NH_2$ derivatives, 0.45 mmol, 66%) was obtained. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.49 (d, 2H, $J$ = 8.8 Hz), 7.35 (d, 2H, $J$ = 8.7 Hz), 6.99 (d, 2H, $J$ = 8.7 Hz), 6.46 (d, 2H, $J$ = 8.7 Hz), 3.68 (s, 2H), 3.5–1.5 (m, 10H).

*6.1.1.35. 1-(4-Acetamidophenyl)-12-(4-cyanophenyl)-1,12-dicarba-closo-dodecaborane (**47**).* Acetyl chloride (300 μL, 4.2 mmol) was added to a solution of **46** (mixture with 30% of 3-$NH_2$ derivatives, 56.7 mg, 0.17 mmol) in $CH_2Cl_2$ (3 mL) and pyridine (2 mL) at 0 °C and stirred at room temperature. After 1 h, the reaction was quenched with water and diluted with $CH_2Cl_2$. The organic layer was washed with 5% aqueous solution of potassium hydrogen sulfate, saturated aqueous solution of sodium hydrogen carbonate, water and brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 3:1, 1:1 to ethyl acetate only) and 42.4 mg of **47** (0.11 mmol, 65%) was obtained. The compound was washed with *n*-hexane, $CH_2Cl_2$ and methanol and recrystallized from ethyl acetate. White powder; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.02 (br s, 1H), 7.76 (d, 2H, $J = 8.7$ Hz), 7.46 (d, 2H, $J = 8.8$ Hz), 7.44 (d, 2H, $J = 8.7$ Hz), 7.16 (d, 2H, $J = 8.9$ Hz), 2.01 (s, 3H), 3.5–1.5 (m, 10H); HRMS(ESI−) Calcd. for $C_{17}H_{21}B_{10}N_2O$ $[M-H]^-$: 379.2584. Found 379.2588.

*6.1.1.36. 1-(4-Cyanophenyl)-12-(4-methylsulfonamidophenyl)-1,12-dicarba-closo-dodecaborane (**48**).* Methanesulfonyl chloride (40 μL, 0.52 mmol) was added to a solution of **46** (mixture with 30% of 3-$NH_2$ derivatives 81.0 mg, 0.17 mmol) in $CH_2Cl_2$ (3.5 mL) and pyridine (30 μL) at 0 °C and stirred at room temperature. After 2.5 h, the reaction was quenched with water and diluted with $CH_2Cl_2$. The organic layer was washed with 5% aqueous solution of potassium hydrogen sulfate, saturated aqueous solution of sodium hydrogen carbonate, water and brine, dried with sodium sulfate, and evaporated. The crude product was washed with ethyl acetate and 58.1 mg of **48** (0.14 mmol, 77%) was obtained. The compound was recrystallized from chloroform. White powder; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.50 (d, 2H, $J = 8.7$ Hz), 7.35 (d, 2H, $J = 8.7$ Hz), 7.21 (d, 2H, $J = 8.8$ Hz), 7.02 (d, 2H, $J = 8.8$ Hz), 6.26 (br s, 1H), 3.01 (s, 3H), 3.5–1.5 (m, 10H); HRMS(ESI-) Calcd. for $C_{16}H_{21}B_{10}N_2O_2S$ $[M-H]^-$: 415.2554. Found 415.2263.

*6.1.1.37. 1-(4-Cyanophenyl)-12-(4-N-methylacetamidophenyl)-1,12-dicarba-closo-dodecaborane (**49**).* Sodium hydride (60% in oil, 12.3 mg, 0.31 mmol) was added to a solution of **47** (65.8 mg, 0.17 mmol) in DMF (4.0 mL) and stirred at 0 °C. After 15 min, iodomethane (140 μL, 2.94 mmol) was added to the reaction mixture and stirred at room temperature. After 1.5 h, the reaction was quenched with saturated aqueous solution of ammonium chloride and diluted with ethyl acetate. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 2:1) and 46.6 mg of **49** (0.12 mmol, 71%) was obtained. The compound was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 2:1) and recrystallized from $CH_2Cl_2$/*n*-hexane. White powder; $^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 7.72 (d, 2H, $J = 8.8$ Hz), 7.54 (d, 2H, $J = 8.8$ Hz), 7.37 (d, 2H, $J = 8.6$ Hz), 7.25 (d, 2H, $J = 8.8$ Hz), 3.26–1.99 (m, 10H), 3.16 (br s, 3H), 1.79 (br s, 3H); HRMS(ESI+) Calcd. for $C_{18}H_{25}B_{10}N_2O$ $[M+H]^+$: 395.2897. Found 395.2892.

*6.1.1.38. 1-(4-Cyanophenyl)-12-(4-N-methyl-methylsulfonamidophenyl)-1,12-dicarba-closo-dodecaborane (**50**).* Sodium hydride (60% in oil, 2.5 mg, 0.06 mmol) was added to a solution of **48** (15.1 mg, 0.04 mmol) in DMF (0.5 mL) and stirred at 0 °C. After 15 min, iodomethane (40 μL, 0.84 mmol) was added to the reaction mixture and stirred at room temperature. After 2.5 h, the reaction was quenched with saturated aqueous solution of ammonium chloride and diluted with ethyl acetate. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. 10.4 mg of **50** (0.02 mmol, 50%) was obtained. The compound was recrystallized from $CH_2Cl_2$/*n*-hexane. Colorless plate; $^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 7.72 (d, 2H, $J = 8.8$ Hz), 7.53 (d, 2H, $J = 8.8$ Hz), 7.37 (d, 2H, $J = 9.1$ Hz), 7.32 (d, 2H, $J = 9.1$ Hz), 3.29 (s, 3H), 2.88 (s, 3H), 3.41–1.95 (m, 10H); HRMS(ESI+) Calcd. for $C_{17}H_{25}B_{10}N_2O_2S$ $[M+H]^+$: 431.2567. Found 431.2362.

### 6.2. Biological evaluation

#### 6.2.1. Alkaline phosphatase assay

T-47D breast-carcinoma cells were cultured in RPMI 1640 medium with 10% (v/v) fetal bovine serum and Penicillin-Streptomycin Mixed Solution. Cells were plated in 96-well plates at $1 \times 10^4$ cell/well and incubated overnight (37 °C, 5% $CO_2$ in air). After 24 h, cells were treated with fresh medium containing test compound in the presence or absence of progesterone (1 nM), and further incubated for 24 h. The medium was aspirated and the cells were fixed with 100 μL of 1.8% formalin (in PBS). The fixed cells were washed with PBS and 75 μL of assay buffer (1 mg/mL *p*-nitrophenol phosphate in diethanolamine water solution, pH 9.0, 2 mM $MgCl_2$) was added. The mixture was incubated at room temperature with shielding from light for 2 h, then the reaction was terminated by the addition of 100 μL of NaOH per each well. The absorbance at 405 nm was measured. All experiments were performed in triplicate or more.

#### 6.2.2. hPR binding assay

hPR-binding assay was performed using recombinant hPR-LBD purchased from Invitrogen. hPR-LBD was diluted with buffer (20 mM Tris–HCl, 300 mM NaCl, 1 mM EDTA, 5 mM DTT, pH 8.0) to 5 nM and 300 μL aliquots were incubated in the dark at 4 °C with 4 nM [1,2,6,7-$^3$H]progesterone (Perkin Elmer) and reference or test compounds (dissolved in 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 μL of Dextran T-70/γ-globulin-coated charcoal suspension was added to the ligand/protein mixtures (1% activated charcoal, 0.05% γ-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 g, and the radioactivity of the supernatant was measured in Ultima Gold scintillation cocktail (Perkin Elmer) by using a liquid scintillation counter. All experiments were performed in duplicate.

#### 6.2.3. hAR binding assay

A hAR-LBD expression plasmid vector which encodes GST-hARLBD (627-919 aa, EF domain) fusion protein under the lac promoter was transfected into *Escherichia 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 the optical density at 600 nm reached 0.6–0.7. 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). The 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. The 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 (Perkin Elmer, 4 nM final concentration) and reference or test compounds (dissolved in DMSO, final concentration of DMSO was 2%). Nonspecific binding was assessed by addition of a 200-fold excess of nonradioactive DHT. After 18 h, a Dextran 70/γ-

globulin-coated charcoal suspension was added to the ligand/protein mixture (1% activated charcoal, 0.05%γ-globulin, 0.05% Dextran, 70 final concentrations) 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 Ultima Gold scintillation cocktail (Perkin Elmer) by using a liquid scintillation counter. All experiments were performed in duplicate.

#### 6.2.4. hGR binding assay

hGR binding assays were performed at Perkin Elmer (US) using the methods described below. The hGR was diluted with binding buffer (50 mM $KH_2PO_4$ pH 7.4 with 10 mM sodium molybdate and 1 mM Ditiothreitol) to yield a final protein concentration of 1.25 nM in the assay tubes. The final incubation conditions were: [$^3$H] dexamethasone, $10^{-9}$ M; triamcinolone acetonide, $10^{-5}$ M (for non-specific binding determination only); test compounds, $10^{-7}$ to $10^{-5}$ M, 0.4% DMSO. After 18 h, the bound ligand was assayed by vacuum filtration onto glass fiber filters and radioactivity was counted in 50 μl of scintillation cocktail (Microscint-20). All experiments were performed in duplicate.

#### 6.2.5. rMR binding assay

rMR binding assays were also performed at Perkin Elmer (US) using the methods described below. The rMR was diluted with binding buffer (20 mM HEPES pH 7.4, 15 mM sodium molybdate, 1 mM Ditiothreitol, 10% glycerol and 1 mM EDTA). The concentration for the MR receptor tissue preparation is optimized for each tissue preparation and is expressed in original tissue wet weight/volume. For the assays in question it was 16.7 mg wet weight/ml in the final reaction. The final incubation conditions were: [$^3$H]aldosterone, $2 \times 10^{-9}$ M; spironolactone, $10^{-6}$ M (for non-specific binding determination only); test compounds, $10^{-7}$ to $10^{-5}$ M; 0.4% DMSO. After 18–20 h, the bound ligand was assayed by adsorption of unbound ligand onto dextran-coated charcoal, centrifugation of charcoal and unbound ligand, and removal of 200 μl of the supernatant. Unabsorbed radioactivity was counted in 6 mL of scintillation cocktail (Luma Safe). All experiments were performed in duplicate.

### 6.3. Molecular modeling

Structure of LBD of human PR was prepared from the Protein Data Bank accession 2W8Y chain A. The structure added for polar hydrogens, and partial atomic charges were assigned using AutoDockTools (ADT) [34]. Structures of ligand were optimized using MOPAC 2012 (Stewart J.J.P., Stewart Computational Chemistry, Colorado Springs, CO, USA, OpenMOPAC.net (2012)) with PM3 parameters and partial atomic charges of them were assigned using ADT. Molecular docking was performed using AutoDock 4.2 with Genetic Algorithm. Phe794 and Met909 were treated as flexible residues. Autodock parameter for boron atom Rii = 4.08 and εii = 0.180 were used.

## Acknowledgments

This work described in this paper was partially supported by Grants in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan (grant no. 25460146 to S.F.).

## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.07.034.

## References

[1] D.J. Mangelsdorf, C. Thummel, M. Beato, P. Herrlich, G. Schuetz, K. Umesono, B. Blumberg, P. Kastner, M. Mark, The nuclear receptor superfamily: the second decade, Cell 83 (1995) 835–839.
[2] A. Psychoyos, Hormonal control of ovo-implantation, Vitam. Horm. 31 (1973) 201–256.
[3] J.P. Lydon, F.J. Demayo, C.R. Funk, S.K. Mani, A.R. Hughes, C.A. Montgomery, G. Shyamala, O.M. Conneely, B.W. O'Malley, Mice lacking progesterone receptor exhibit pleiotropic reproductive abnormalities, Gene Dev. 9 (1995) 2266–2278.
[4] Z. Zhang, C. Funk, S.R. Glasser, J. Mulholland, Progesterone regulation of heparin-binding epidermal growth factor-like growth factor gene expression during sensitization and decidualization in the rat uterus: effects of the antiprogestin, ZK-98299, Endocrinology 135 (1994) 1256–1263.
[5] S.K. Mani, J.M.C. Allen, J.H. Clark, J.D. Blaustein, B.W. O'Malley, Convergent pathway for steroid hormone- and neurotransmitter induced rat sexual behavior, Science 265 (1994) 1246–1249.
[6] R.A. Edgren, F.M. Sturtevant, Potencies of oral contraceptives, Am. J. Obstet. Gynecol. 125 (1976) 1029–1038.
[7] D.J. Torgerson, S.E. Bell-Syer, Hormone replacement therapy and prevention nonvertebral fractures: a meta-analysis of randomized trials, J. Am. Med. Assoc. 285 (2001) 2891–2897.
[8] P. Vercellini, O. De Giorgi, S. Oldani, I. Cortesi, S. Panazza, P.G. Crosgnani, Depot medroxyprogesterone acetate versus an oral contraceptive combined with very-low-dose danazol for long-term treatment of pelvic pain associated with endometriosis, Am. J. Obstet. Gynecol. 175 (1996) 396–401.
[9] R.C. Winneker, A. Fensome, J.E. Wrobel, A. Zhang, P. Zhang, Nonsteroidal progesterone receptor modulators: structure activity relationships, Semin. Reprod. Med. 23 (2005) 46–57.
[10] A. Fensome, R. Bender, R. Chopra, J. Cohen, M.A. Collins, V. Hudak, K. Malakian, S. Lockhead, A. Olland, K. Svenson, E.A. Terefenko, R.J. Unwalla, J.M. Wilhelm, S. Wolfrom, Y. Zhu, Z. Zhang, P. Zhang, R.C. Winneker, J. Wrobel, Synthesis and structure-activity relationship of novel 6-aryl-1,4-dihydrobenzo[*d*][1,3]oxazine-2-thiones as progesterone receptor modulators leading to the potent and selective nonsteroidal progesterone receptor agonist tanaproget, J. Med. Chem. 48 (2005) 5092–5095.
[11] G. Teutsch, D. Philibert, History and perspectives of anti-progestins from the chemist's point of view, in: R.G. Edwards (Ed.), Human Reproduction, vol. 9 (1), Oxford University Press, Oxford, England, 1994, pp. 12–31.
[12] L.M. Kettel, A.A. Murphy, J.F. Mortola, J.H. Liu, A. Ulmann, S.S. Yen, Endocrine responses to long-term administration of the antiprogesterone RU486 in patients with pelvic endometriosis, Fertil. Steril. 56 (1991) 402–407.
[13] A.A. Murphy, L.M. Kettel, A.J. Morales, V.J. Roberts, S.S. Yen, Regression of uterine leiomyomata in response to the antiprogesterone RU486, J. Clin. Endocrinol. Metab. 76 (1993) 513–517.
[14] L.M. Kettel, Clinical applications of the antiprogestins, Clin. Obstet. Gynecol. 38 (1995) 921–934.
[15] N. Chabbert-Buffet, G. Meduri, P. Bouchard, I.M. Spitz, Selective progesterone receptor modulators and progesterone antagonists: mechanisms of action and clinical applications, Hum. Reprod. Update 11 (2005) 293–307.
[16] M.A. Collins, V. Hudak, R. Bender, A. Fensome, P. Zhang, L. Miller, R.C. Winneker, Z. Zhang, Y. Zhu, J. Cohen, R.J. Unwalla, J. Wrobel, Novel pyrrole-containing progesterone receptor modulators, Bioorg. Med. Chem. Lett. 14 (2004) 2185–2189.
[17] A. Fensome, W.R. Adams, A.L. Adams, T.J. Berrodin, J. Cohen, C. Huselton, A. Illenberger, J.C. Kern, V.A. Hudak, M.A. Marella, E.G. Melenski, C.C. McComas, C.A. Mugford, O.D. Slayden, M. Yudt, Z. Zhang, P. Zhang, Y. Zhu, R.C. Winneker, J.E. Wrobel, Design, synthesis, and SAR of new pyrrole-oxindole progesterone receptor modulators leading to 5-(7-fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile WAY-255348), J. Med. Chem. 51 (2008) 1861–1873.
[18] P. Zhang, E.A. Terefenko, A. Fensome, J. Wrobel, R. Winneker, Z. Zhang, Novel 6-aryl-1,4-dihydrobenzo[d][1,3]oxazine-2-thiones as potent, selective, and orally active nonsteroidal progesterone receptor agonists, Bioorg. Med. Chem. Lett. 13 (2003) 1313–1316.
[19] H. Sakai, T. Hirano, S. Mori, S. Fujii, H. Masuno, M. Kinoshita, H. Kagechika, A. Tanatani, 6-Arylcoumarins as novel non-steroidal type progesterone antagonists: an example with receptor binding-dependent fluorescence, J. Med. Chem. 54 (2011) 7055–7065.
[20] R.N. Grimes (Ed.), Carboranes, second ed., Academic Press, London, 2011.
[21] V.I. Bregadze, Dicarba-*closo*-dodecaboranes $C_2B_{10}H_{12}$ and their derivatives, Chem. Rev. 92 (1992) 209–223.
[22] S. Fujii, H. Masuno, Y. Taoda, A. Kano, A. Wongmayura, M. Nakabayashi, N. Ito, M. Shimizu, E. Kawachi, T. Hirano, Y. Endo, A. Tanatani, H. Kagechika, Boron cluster-based development of potent nonsecosteroidal vitamin D receptor ligands: direct observation of hydrophobic interaction between protein surface and carborane, J. Am. Chem. Soc. 133 (2011) 20933–20941.
[23] S. Fujii, A. Kano, C. Songkram, H. Masuno, Y. Taoda, E. Kawachi, T. Hirano, A. Tanatani, H. Kagechika, Synthesis and structure-activity relationship of *p*-carborane-based non-secosteroidal vitamin D analogs, Bioorg. Med. Chem. 22 (2014) 1227–1235.
[24] S. Fujii, T. Goto, K. Ohta, Y. Hashimoto, T. Suzuki, S. Ohta, Y. Endo, Potent androgen antagonists based on carborane as a hydrophobic core structure, J. Med. Chem. 48 (2005) 4654–4662.

[25] S. Fujii, Y. Hashimoto, T. Suzuki, S. Ohta, Y. Endo, A new class of androgen receptor antagonists bearing carborane in place of a steroidal skeleton, Bioorg. Med. Chem. Lett. 15 (2005) 227–230.
[26] Y. Endo, T. Iijima, Y. Yamakoshi, M. Yamaguchi, H. Fukasawa, K. Shudo, Potent estrogenic agonists bearing dicarba-*closo*-dodecaborane as a hydrophobic pharmacophore, J. Med. Chem. 42 (1999) 1501–1504.
[27] Y. Endo, T. Iijima, Y. Yamakoshi, H. Fukasawa, C. Miyaura, M. Inada, A. Kubo, A. Itai, Potent agonists based on carborane as a hydrophobic skeletal structure: a new medicinal application of boron clusters, Chem. Biol. 8 (2001) 341–355.
[28] S.P. Williams, P.B. Sigler, Atomic structure of progesterone complexed with its receptor, Nature 393 (1998) 392–396.
[29] D. Moras, H. Gronemeyer, The nuclear receptor ligand-binding domain: structure and function, Curr. Opin. Cell. Biol. 10 (1998) 384–391.
[30] T. Ishioka, A. Tanatani, K. Nagasawa, Y. Hashimoto, Anti-androgens with full antagonistic activity toward human prostate tumor LNCaP cells with mutated androgen receptor, Bioorg. Med. Chem. 13 (2003) 2655–2658.
[31] H.C.A. Raaijmakers, J.E. Versteegh, J.C.M. Uitdehaag, The X-ray structure of RU486 bound to the progesterone receptor in a destabilized agonistic conformation, J. Biol. Chem. 284 (2009) 19572–19579.
[32] R. Coult, M.A. Fox, W.R. Gill, P.L. Herbertson, J.A.H. MacBride, K. Wade, *C*-Arylation and *C*-heteroarylation of icosahedral carboranes via their copper(I) derivatives, J. Org. Chem. 462 (1993) 19–29.
[33] D.D. Lorenzo, A. Albertini, D. Zava, Progestin regulation of alkaline phosphatase in the human breast cancer cell line T-47D, Cancer Res. 51 (1991) 4470–4475.
[34] G.M. Morris, R. Huey, W. Lindstrom, M.F. Sanner, R.K. Belew, D.S. Goodsell, A.J. Olson, Autodock4 and AutoDockTools4: automated docking with selective receptor flexibility, J. Comput. Chem. 30 (2009) 2785–2791.