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A new strategy for molecular modeling and receptor-based design of carborane containing compounds

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Abstract

Difficulties associated with computer-aided molecular design (CAMD) of carborane containing molecules have hampered drug development in boron neutron capture therapy (BNCT). A new approach of modeling and docking of carborane containing molecules with the readily available software packages HYPERCHEM, SYBYL and FLEXX is described. This new method is intended as a guide for boron chemists interested in using CAMD of carborane containing agents for medical applications such as BNCT.

Keywords: Computer-aided molecular design; Carborane; Estrogen receptor; Retinoic acid receptor; Scoring function; Docking

1. Introduction

The design and synthesis of agents for boron neutron capture therapy (BNCT) has focused predominantly on using the hydrophobic carborane cluster [1–4] as the boron moiety because of its high boron content, stability, and chemically modifiable properties [5–9]. Similar to the use of fullerenes (C_{60}) in the design of drugs [10,11], carborane clusters have recently attracted substantial interest as pharmacophores in non-BNCT related drug design [1–3]. Also, Hawthorne and coworkers [12] and Endo et al. [13] recently reported the synthesis of dodecamethyl-*p*-carborane. This structure possesses dimensions closely resembling those of fullerene [12] and may, therefore, also have potential as a pharmacophore for use in BNCT and other pharmaceutical applications [13].

The possibility to use carborane clusters as replacements for the hydrophobic portions of, e.g. estradiol [3], retinoic acid [2], TNF-α modulators [4], and teleocidin [1] has been extensively explored [1–4]. Some of these carboranyl analogues [1–4] interacted effectively with receptor enzymes and exhibited equal or even higher biological activity compared with their endogenous counterparts. Most of these carborane constructs were easily synthesized with few reaction steps, thus, providing feasible synthetic routes to biologically active carboranyl analogs of estradiol, retinoic acid, and teleocidin.

So far, carborane-based drug design utilizing computer-aided molecular design (CAMD) has been applied only in relatively few cases [1–4]. This is mainly due to the complex structures of carboranes with sixfold coordinated carbon and boron atoms. In addition, CAMD of molecules containing boron atoms is not supported by most commercially available software packages because they do not provide the required empirical potential energy functions for the boron atom in default settings [14]. Endo et al. were the first to describe SBDD strategies for the synthesis of carboranyl derivatives of estradiol [3], retinoic acid [2], and teleocidin [1] were using a software package called ADAM [1–3,15]. However, this docking program is not

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readily accessible to scientist interested in CAMD of carboranyl derivatives [2,3].

In this paper, a general strategy for modeling and docking of carborane containing derivatives using HYPERCHEM 5.1 (Hypercube, Inc.), SYBYL 6.8 (Tripos, Inc.) and FLEXX (Tripos, Inc.) is described. This strategy is intended as a guide for synthetic boron chemists interested in using CAMD of carborane containing agents for medical applications. The data obtained from our modeling studies are compared with the ealier report using carboranyl derivatives of estradiol and retinoic acid and the respective estrogen- and retinoic acid receptor proteins [2,3]. We have also addressed the general value of CAMD at the example of our modeling studies.

2. General modeling and docking strategies

The human estrogen receptor protein (hERαLBD) [16] and the human γ-retinoic acid receptor protein (hRARγLBD) [17] were obtained from the protein data bank [Research Collaboratory for Structural Bioinformatics (RCSB) (http://www.rcsb.org/pdb)] as PDB files entitled 1ERE (3.1 Å structure resolution) and 2LBD (2.0 Å structure resolution), respectively. The ligands **1**–**16** [2,3], shown in Fig. 1, were used for docking.

HYPERCHEM 5.1 (Hypercube, Inc., Waterloo, Ont., Canada) and SYBYL 6.8 (Tripos, Inc., St. Louis, MO) were used for modeling. Estradiol (**1**) and retinoic acid (**2**) were built and minimized using SYBYL. The atomic point charges were calculated using the Gasteiger–Hückel method. The molecules were minimized using the Maximin2 minimizer and the TRIPOS force field/parameters until an energy gradient of 0.005 kcal mol^{-1} was reached.

o-, *m*-, and *p*-Carboranes (Fig. 2) and the caboranyl estradiol and retenoid derivatives **3**–**16** (Fig. 1) were constructed on the HYPERCHEM platform and were minimized by the semi-empirical AM1 method to an energy gradient of 0.005 kcal mol^{-1}. The molecules were saved as SYBYL-readable files in PDB format. The atom type assignments of HYPERCHEM and SYBYL are not identical and use different symbols for the same atom type. Thus, a SYBYL compatible form of the molecules was generated using the Built/Edit option in SYBYL. The atomic point charges of *o*-, *m*-, and *p*-carboranes as well as compounds **3**–**16** were calculated using the MOPAC interface of SYBYL applying the semi-empirical AM1 method. Compounds **3**–**16** were formatted for docking by changing the atom type of boron 'B' to carbon 'C.3'.

Docking of ligands **1**–**16** to the active sites of the receptor proteins was performed using FLEXX (Tripos, Inc., St. Louis, MO). The active sites of the receptor proteins were generated at a radius of 6.5 Å centered on the X-ray geometry of the native ligand in the protein–ligand complex [18]. Docking produced 30 possible docked conformations for each of the ligands **1**–**16** and the Cscore™ program of SYBYL scored each

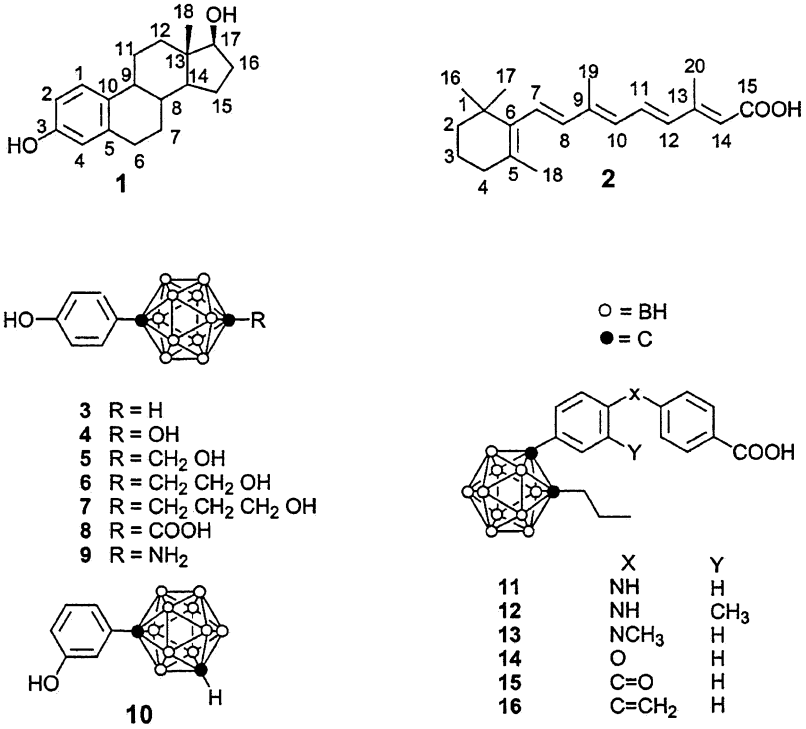

Fig. 1. Structures of ligands **1**–**16**.

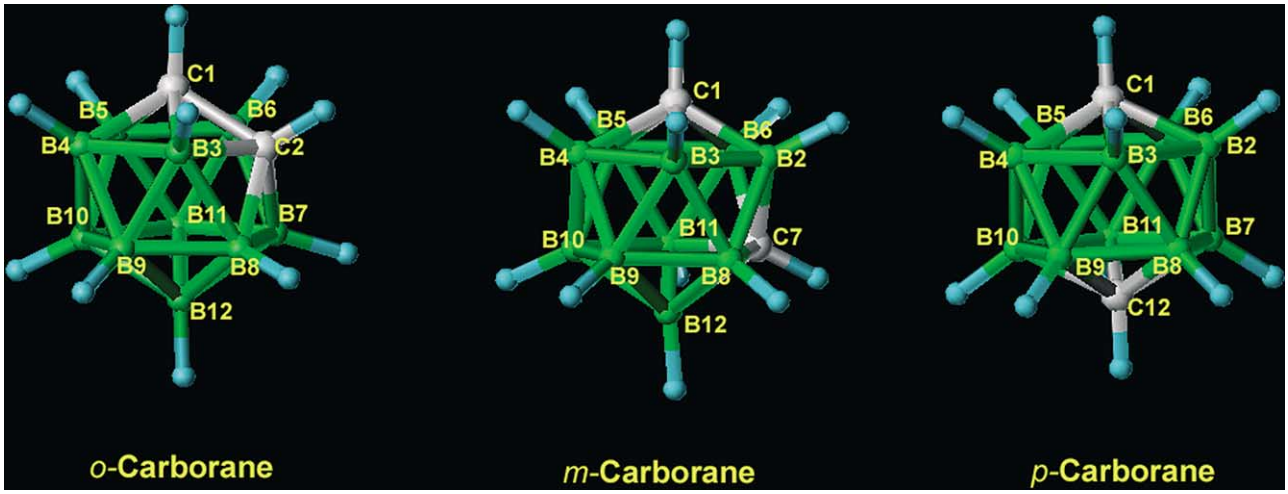

Fig. 2. Structures of *o*-, *m*-, and *p*-carboranes optimized by the semi-empirical AM1 method.

conformation. Cscore™ scoring functions include RMSD values [19], ChemScore [20], Dock_score [21], G_score [22], FLEXX_score [23], and PMF_score [24]. Among the 30 conformational solutions of ligands **1**–**16**, the ones with the best FLEXX_score (rank 1) were chosen as the optimal conformational poses [23] in all docking experiment. The rank 1-conformation showed better bonding interactions compared to ether solutions. SYBYL was used to generate dynamic hydrogen bonds between the best-docked conformational pose of a ligand and the amino acid residues in the active site of the protein. The same software package was used to visualize the binding mode of the docked protein–ligand complexes by generating a Connolly type MOLCAD surfaces for estradiol and retinoic acid with a probe sphere diameter of 1.4 Å based on the X-ray structures from the PDB files, 1ERE and 2LBD, respectively. The MOLCAD surfaces of estradiol and retinoic acid were superimposed on the best-docked conformations of ligands **3**–**10** and **11**–**16**, respectively, to visualize the binding of **3**–**16** within the active sites.

3. Results and discussion

3.1. Modeling strategies

CAMD of **3**–**16** using either Insight II or SYBYL and its associated docking program FLEXX was not successful because it requires force field parameterization of the boron atom, which is not provided by these software packages in default settings. This is a major drawback in applying computational chemistry as a predictive tool for synthetic chemists in BNCT drug development and related pharmaceutical areas. HYPERCHEM, however, provides a convenient way for generating and minimizing molecules containing boron atoms utilizing the Allow Ions option and geometry optimization with the semi-empirical AM1 method. Unfortunately, this software package does not provide any platform for docking operations. Thus, *o*-, *m*-, and *p*-carboranes as well as compounds **3**–**16** were successfully generated and minimized by the semi-empirical AM1 method within HYPERCHEM until an energy gradient of 0.005 kcal mol^{-1} was reached and saved as SYBYL-readable PDB files.

The PDB files generated by HYPERCHEM, however, were only partially readable by SYBYL. Certain bonds were missing in the carborane clusters displaying only fivefold coordinated carbon and boron atoms but the overall geometries of the carborane structures were conserved. Missing bonds were added using SYBYL and reconstructed cluster geometries were saved as 'mol2' files. The semi-empirical AM1 method available in the MOPAC interface of SYBYL was used to calculate the atomic point charges of *o*-, *m*-, and *p*-carboranes as well as in **3**–**16**. The structures of *o*-, *m*-, and *p*-carboranes that were obtained applying the described modeling strategy are depicted in Fig. 2. As expected, the geometries of *o*- and *m*-carboranes are slightly distorted, whereas *p*-carborane is a symmetrical icosahedron. The B–B, B–C, and C–C bond lengths and atomic point charges of *o*-, *m*-, and *p*-carboranes are summarized in Tables 1–3, along with previously reported theoretical and experimental values for these structures [25,26]. Bond length values calculated with the semi-empirical AM1 method of HYPERCHEM were comparable with those obtained from ab initio calculations at the Hartree-Fock/6-31G* level [26] and experimental electron diffraction data [25]. Good correlation was found between the bond length values of *o*-, *m*- and *p*-carboranes obtained from the semi-empirical AM1 method and experimental B–B, B–C, and C–C bond length values from X-ray crystallography experiments with bis(cyclotriveratrylene)-*o*-dicarbadodecaborane clathrate as well as hexamethylphosphoramide-*o*-car-

Table 1
Interatomic distances of the *o*-, *m*-, and *p*-carboranes optimized by the semi-empirical AM1 method

Bond type in *o*-, *m*- and *p*-carboranes[a]	AM1			Ab initio calculations[b]			Electron diffraction[c]
	o-Carborane (Å)	*m*-Carborane (Å)	*p*-Carborane (Å)	*o*-Carborane (Å)	*m*-Carborane (Å)	*p*-Carborane (Å)	*o*-Carborane (Å)
C(1)–B(3)	1.71	1.67	1.69	1.71	1.69	1.70	1.62
C(1)–B(4)	1.68	1.71	1.70	1.69	1.71	1.70	1.62
B(3)–B(4)	1.78	1.76	1.79	1.78	1.76	1.79	1.84
B(5)–B(6)	1.79	1.77	1.79	1.78	1.78	1.79	–
B(4)–B(9)	1.76	1.78	1.74	1.78	1.79	1.77	–
B(6)–B(10)	1.74	1.77	1.74	1.77	1.79	1.77	1.70
B(6)–B(11)	1.79	1.76	1.74	1.78	1.77	1.77	–
C(1)–B(2)	–	1.68	1.70	–	1.69	1.70	–
B(2)–B(3)	–	1.81	1.70	–	1.81	1.79	–
B(2)–B(6)	–	1.76	1.79	–	1.76	1.79	–
C(1)–C(2)	1.65	–	–	1.60	–	–	1.53
C(2)–B(3)	1.70	–	–	1.71	–	–	1.79
C(2)–B(6)	1.71	–	–	1.71	–	–	1.71
B(3)–B(7)	1.78	–	1.75	1.78	–	1.77	1.78
B(7)–B(8)	1.77	–	1.78	1.79	–	1.79	1.85
B(7)–B(12)	1.76	–	–	1.78	–	–	–
B(3)–C(7)	–	1.67	–	–	1.69	–	–
C(7)–B(8)	–	1.72	–	–	1.71	–	–
B(7)–C(12)	–	–	1.71	–	–	1.70	–

[a] The atom numbers correspond to the numbers of *o*-, *m*-, and *p*-carboranes in Fig. 2.
[b] Data from ab initio calculations of *o*-, *m*-, and *p*-carboranes (Hartree-Fock/6-31G*) were taken from Ref. [26].
[c] Electron diffraction data of *o*-carborane were taken from Ref. [28].

Table 2
Mean interatomic distances of *o*-, *m*- and *p*-carboranes

	AM1 (Å)	Ab initio calculations[a] (Å)	Experimental values[b] (Å)
B–B	1.74–1.81	1.74–1.81	1.76–1.78
B–C	1.67–1.72	1.69–1.71	1.69–1.71
C–C	1.65	1.60	1.62

[a] Data from ab initio calculations of *o*-, *m*-, and *p*-carborane (Hartree-Fock/6-31G*) were taken from Ref. [26].
[b] Data of X-ray structures of bis(cyclotriveratrylene)-*o*-dicarbadodecaborane clathrate as well as of hexamethylphosphoramide-*o*-carborane and its *m*- and *p*-carboranyl derivatives were taken from Refs. [27,28].

borane and its *m*- and *p*-carboranyl derivatives (Table 2) [27,28]. Charges on the boron atoms in *o*-, *m*-, and *p*-carboranes, calculated with the semi-empirical AM1 methods, using either the MOPAC interface of SYBYL or HYPERCHEM, ranged from 0.002 to −0.09 while those on the carbon atoms varied from −0.316 to −0.378 (Table 3). These values are slightly less negative than those obtained from ab initio Hartree-Fock/6-31G* calculations [26]. Variations in reported charge distribution within carboranes, however, are, in general, rather significant and seem to depend strongly on the computational method [26].

3.2. Docking strategies

The popular docking program FLEXX was chosen because of its capacity to rapidly dock flexible ligands into the binding sites of proteins and its versatile ranking and scoring applications.

Docking of **3**–**16** into the active sites of the respective receptor proteins with FLEXX, however, could only be carried out with a simple but effective modification, which circumvents the fact that this program does not contains the empirical potential energy functions for the boron atom [29]. Thus, all boron atoms 'B' in ligands **3**–**16** were changed to carbon atoms 'C.3' using the Built/Edit option in SYBYL. The geometries, bond lengths, bond angles, dihedral angles, and atomic point charges of the structures, obtained from semi-empirical AM1 calculations, did not change during this operation.

3.2.1. Estrogen receptor ligands

The estrogen receptor protein (hERαLBD) contains six ligand binding domains [16]. Each domain contains one receptor site and the amino acid residues, sequences, and active sites are conserved in all domains. In order to simplify the docking process, five of the six domains of the estrogen receptor protein [30–32] were truncated

Table 3
Mulliken charges on the atoms of *o*-, *m*-, and *p*-carboranes optimized by the semi-empirical AM1 method

Atom type[a]	AM1			Ab initio calculations[b]		
	o-Carborane	*m*-Carborane	*p*-Carborane	*o*-Carborane	*m*-Carborane	*p*-Carborane
C1	−0.32	−0.38	−0.37	−0.51	−0.62	−0.63
C2	−0.32	–	–	−0.51	–	–
C7	–	−0.38	–	–	−0.62	–
C12	–	–	−0.37	–	–	–0.63
B2	–	−0.04	−0.04	–	0.07	−0.02
B3	0.00	0.00	−0.04	0.05	0.07	−0.02
B4	−0.02	−0.00	−0.04	−0.03	−0.02	−0.02
B5	−0.03	−0.02	−0.04	−0.03	−0.03	−0.02
B6	0.00	−0.02	−0.04	−0.05	−0.02	−0.02
B7	−0.07	–	−0.04	−0.03	–	−0.02
B8	−0.07	−0.03	−0.04	−0.09	−0.02	−0.02
B9	−0.08	−0.02	−0.04	−0.11	−0.09	−0.02
B10	−0.03	−0.09	−0.04	−0.09	−0.09	−0.02
B11	−0.03	−0.08	−0.04	−0.03	−0.02	−0.02
B12	−0.06	−0.03	–	−0.11	−0.03	–
H on C	0.17	0.16	0.16	0.24	0.23	0.23
H on B	0.06–0.07	0.06–0.08	0.08	0.01–0.03	0.02–0.04	0.03

[a] The atom numbers correspond to the numbers of *o*-, *m*- and *p*-carboranes in Fig. 2.
[b] Data from ab initio calculations of *o*-, *m*-, and *p*-carboranes (Hartree-Fock/6-31G*) were taken from Ref. [26].

using SYBYL and the resulting monomeric ligand binding domain was used for docking of ligands **3**–**10**. The minimized structure of estradiol (**1**) was docked first with the estrogen receptor site and the structure of the resulting protein–ligand complex was compared with that of the X-ray crystallograpically determined structure of the same complex. The X-ray structure showed hydrogen bonding interactions of the hydroxyl groups at positions 3 and 17 of estradiol with the amino group of the arginine residue (R394) and the imino group of the histidine residue (H524), respectively. FLEXX docking of estradiol produced 30 possible solutions. The optimal conformational pose corresponded to the highest FLEXX_score value (rank 1) and the lowest RMSD value (0.80 Å). The docked estradiol–estrogen receptor protein complex reproduced the native binding interactions as shown in Fig. 2A. The RMSD value of ≤ 2 Å for the docked ligand–protein structure also suggests that estradiol was appropriately docked within the active site of the estrogen receptor [19]. Both visual inspection of MOLCAD surface and RMSD value confirmed the validity of our docking strategy using a truncated monomeric form of the estrogen receptor protein and its applicability to the carboranyl estradiol derivatives **3**–**10**.

FLEXX docking of ligands **3**–**10** was carried out using the Run One ligand option of FLEXX producing 30 conformations for each ligand, which were ranked based on their positioning and interactions within the active site by FLEXX_score along with other Cscore™ scoring functions. The structures of optimal conformational poses of ligands **3**–**10** (Table 4) within the active site of the estrogen receptor and the superimposed MOLCAD surface of the X-ray geometry of estradiol were visually examined for binding interactions. All poses of the ligands **3**–**10** fitted within the MOLCAD surface area of the X-ray geometry of estradiol as demonstrated in compounds **1**, **5**, **3** and **10** (Fig. 3A–D). The poses of these ligands showed hydrogen bonding between either the carboranyl hydroxyl- (**5**–**7**), carboxylic- (**8**) or amino group (**9**) and the imino group of histidine residue (H524) while the phenolic hydroxyl group in these structures interacted with either the amino group of the arginine residue (R394) (**3**–**5**, **7**, and **8**) or the carboxylic function of the glutamate residue (E353) (**9** and **10**). The bulky carborane clusters of ligands **3**–**10** were positioned in the active site similarly to the decahydronaphthalene portion of estradiol and showed hydrophobic interactions with the isobutyl group of the leucine residues (L384 and L428) as shown in Fig. 3B and C. Unlike ligand **3**, structure **10** formed a hydrogen bond via its phenolic *meta*-hydroxyl group with the carboxylic function of glutamic acid (E353).

Various scoring values of ligands **3**–**10** are listed in Table 4 in comparison with the estrogenic activity of these compounds, in order to evaluate the effectiveness of the Cscore™ scoring functions for the estrogen receptor protein–ligand complexes. Among the Cscore™ scoring functions, FLEXX_score [23] (based on empirical functions), PMF_score [24] (based on statistical ligand-receptor atom-pair interaction potentials), D_score [21] (based on both electrostatic and hydrophobic contributions to the binding energy), and ChemScore [20] (based on a diverse training set of 82

Table 4
Cscore™ scoring values for complexes of the estrogen receptor with optimal conformational poses of ligands **1**, **3**–**10**

Ligand bonds	RMSD (Å)	FLEXX	G_score	PMF_score	D_score	ChemScore	Hydrogen	Biological activity[a]	Interaction energy[b] (Kcal)
1	0.80	−19	−229	−46	−117	−40	E353, R394, H524	× × ×	−54.67
3	3.49	−16	−157	−34	−163	−37	R394	× ×	−45.88
4	3.60	−16	−153	−37	−164	−36	R394	× × × ×	−47.76
5	5.94	−19	−164	−42	−208	−39	R394,H524	× × × ×	−51.60
6	7.43	−18	−186	−41	−220	−41	G521	× × ×	–
7	3.59	−17	−204	−34	−206	−43	R394, H524, G521	× ×	–
8	3.48	−17	−183	−49	−217	−39	R394, H524	× ×	–
9	3.62	−18	−177	−36	−175	−36	E353, H524, G521	× × × ×	–
10	4.80	−14	−199	−27	−153	−35	E353	×	−45.34

[a] Biological activity is defined as the capacity of the compound **1** and **3**–**10** to induce transcriptional activation of COS-1 cells and was estimated from results obtained by Endo et al. [3]. × × × ×, Very high; × × ×, High; × ×, Medium; ×, Low.
[b] Interaction energies between estrogen receptor protein and ligands **1** and **3**–**10**, generated by ADAM, were taken from Ref. [3].

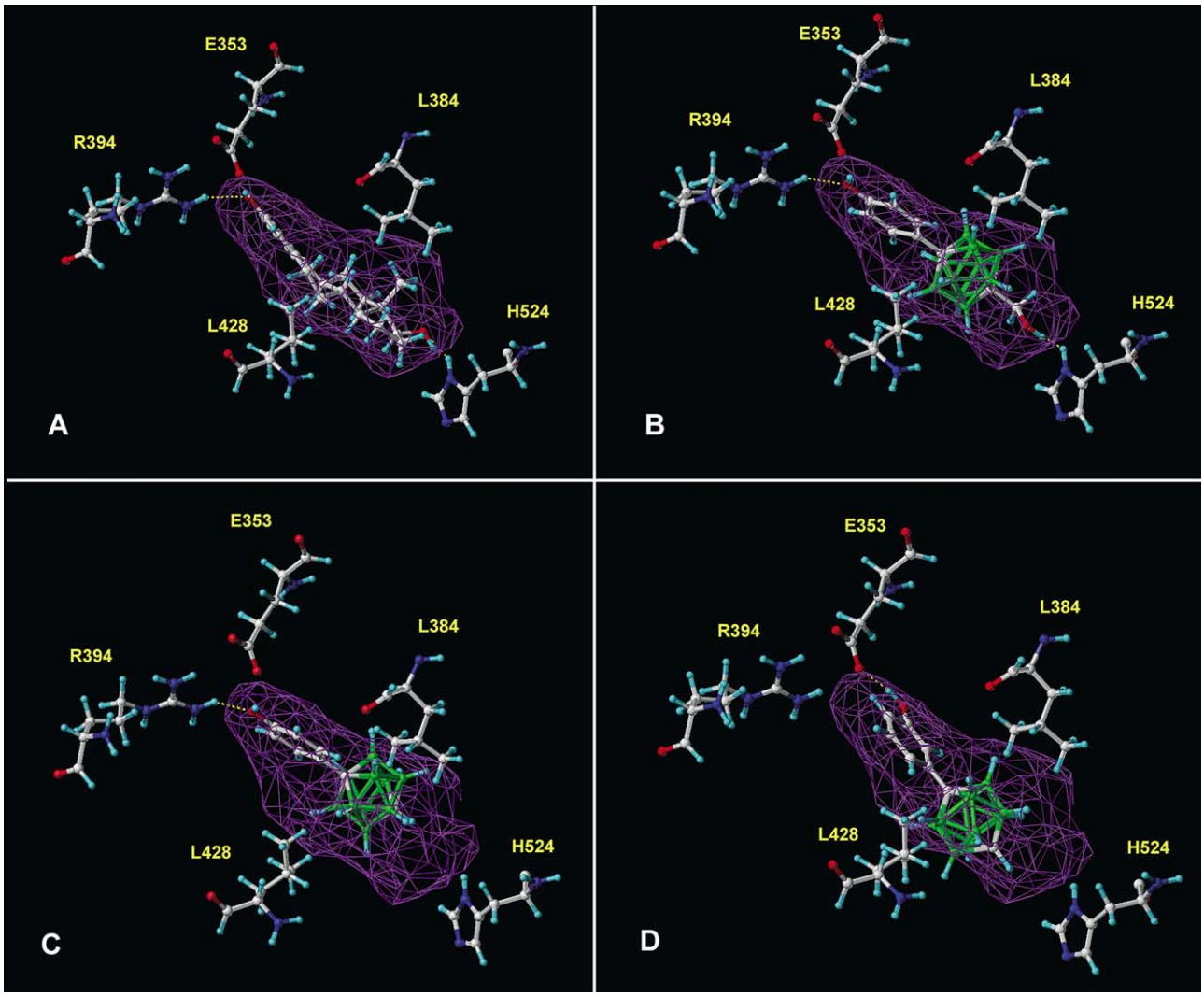

Fig. 3. Binding modes of the optimal conformational poses of ligands, **1** (3A), **5** (3B), **3** (3C), and **10** (3D) with the active site of the estrogen receptor. The yellow line represents hydrogen bond (≤ 3.3 Å). The pink grid represents the MOLCAD surface of X-ray geometry of estradiol.

receptor–ligand complexes) produced values for ligands **3**–**10** that showed some correlation with the respective biological activities in as far as ligand **10**, having the lowest biological activity of all carboranyl estradiol derivatives, had also the lowest scoring values (Table 4). For G_score [22], which computes accurately scoring values for ligand–receptor complexes having many polar interactions, no obvious correlation between the scoring values for ligands **3**–**10** and respective biological activities could be observed. A possible explanation could be the presence of the carborane cluster in ligands **3**–**10**, which interacts strongly with the receptor in a hydrophobic fashion. Similar sub-optimal correlation of values from Cscore™ scoring functions with biological activities has been reported previously in different experimental/computational settings [19,33–35].

The optimal interaction of a docked ligand with a receptor protein is defined by RMSD values < 2 Å [19]. This value is based on the relative position of the same ligand in the corresponding ligand–protein X-ray structure [19]. Since the X-ray structures of the protein–ligand complexes of **3**–**10** were not available, we obtained the RMSD values for these ligands using the position of estradiol in the X-ray structure of its complex with estrogen as a reference. The RMSD values obtained in this way for the optimal conformational poses of ligands **3**–**10** ranged from 3.48 to 7.43 Å. Since all of these poses fitted adequately within the MOLCAD surface area of the X-ray geometry of estradiol, we theorize that RMSD values obtained in this fashion that are below ~ 7.5 Å may be indicative for properly docked ligands.

3.2.2. Retinoic acid receptor ligands

Retinoic acid (**2**) and its carboranyl derivatives **11**–**16** were modeled and, subsequently, docked into the active site of the γ-retinoic acid receptor protein as described for the modeling and docking of estradiol and its carboranyl derivatives with the estrogen receptor site. Detailed data of the docking results of ligands **2**, **11**–**16** along with respective biological activities [2] are summarized in Table 5. Hydrogen bonding interactions in the X-ray structure of the protein–retinoic acid complex were observed between the carboxylic function of retinoic acid and the hydroxyl group of the serine residue (S289) and the amino group of the arginine residue (R278). Docked retinoic acid (**2**) showed native binding interactions as indicated in Fig. 4A and its calculated RMSD value was 0.55 Å.

Only the carboranyl ligand **11**, having an RMSD value of 6.93 Å, fitted within the MOLCAD surface with all its structural elements and reproduced the native binding interactions of the X-ray geometry of the retinoic acid as well as an additional hydrogen bonding interaction between its imino group and the amido function of the leucine residue (L271), as shown in Fig. 4B. Ligands **12** and **13** did not fit into the active site of the retinoic acid receptor and for compounds **14**–**16**, FLEXX was not able to provide docking solutions. For compound **13**, with a computed RMSD value of 17.24 Å, the visual docking location in relation to the MOLCAD surface is shown in Fig. 4C. In case of receptor docked carboranyl retinoid ligands, RMSD values below ~ 7 Å may be indicative for proper docking.

4. Summary and conclusion

The combination of HYPERCHEM and SYBYL generated geometries of the *o*-, *m*-, and *p*-carboranes clusters resembled closely those obtained previously using different theoretical and experimental methods [25–27]. Receptor ligands **3**–**16** were modeled using the same strategy as applied for *o*-, *m*-, and *p*-carboranes. FLEXX docked the ligands **3**–**10** into the active site of the estrogen receptor within the MOLCAD surface and many of these ligands reproduced the native estradiol binding interactions. Similar results were obtained using the software package ADAM for docking compounds **3**–**5** and **10** into the active site of the estrogen receptor. In case of the estrogen receptor–ligand complexes, com-

Table 5
Cscore™ scoring values for complexes of the retinoic acid receptor active site with optimal conformational poses of ligands **2**, **11**–**16**

Ligand	RMSD (Å)	FLEXX	G_score	PMF_score	D_score	ChemScore	H-bonding with active site	Biological activity[a]
2	0.55	−32	−237	−60	−138	−53	R278, S289	× × × ×
11	6.93	−31	−328	−59	122	−65	R278, S289, L271	× × × ×
12	19.55	−6	−117	−23	151	−20	A	× × ×
13	17.24	−2	−133	−23	258	−20	A	×
14	ND							NA
15	ND							NA
16	ND							NA

[a] Biological activity is defined as the capacity of the compound **2** and **11**–**16** to induce differentiation in nitro blue tetrazolium positive HL-60 cells and was estimated from results obtained by Endo et al. [2]. × × × ×, Very high; × × ×, High; × ×, Medium; ×, Low; NA, not active; ND, no docking solution; A, no fit in active site and no hydrogen bonding interactions.

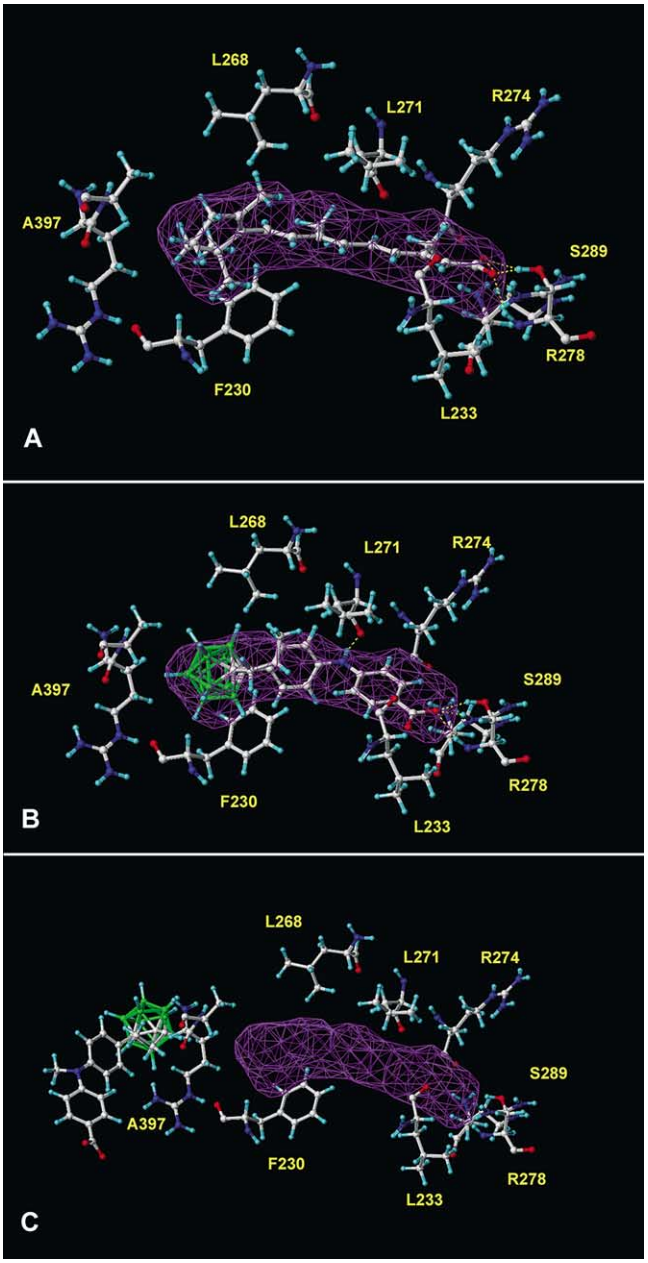

Fig. 4. Binding modes of the optimal conformational poses of ligands, **2** (4A), **11** (4B), and **13** (4C) with the active site of the γ-retinoic acid receptor. The yellow line represents hydrogen bond ($\leq$ 3.3 Å). The pink grid represents the MOLCAD surface of X-ray geometry of estradiol.

puted values from Cscore™ scoring functions, except G_score, showed some correlation with the biological activities.

Among the carboranyl retinoic acid derivatives **11**–**16**, only ligand **11** docked completely within the MOLCAD surface of the active site of the retinoic acid receptor and showed binding interactions identical to retinoic acid. For all docked γ-retinoic acid receptor-ligand complexes, a relative good correlation between Cscore™ values and the receptive biological activities was observed (Table 5). The poor overall docking performance of carboranyl retinoic acid derivatives may suggest that they were not good substrates for γ-retinoic acid receptor used in these experiments. Experimental biological activities of **11**–**16** obtained in previous studies indicate that these compounds are generally better substrates for the α- and β-retinoic acid receptors than γ-retinioc acid receptor [2].

Based on our studies, it appears that RMSD values, computed values from Cscore™ scoring functions, visual comparison between geometries of docked ligands and MOLCAD surfaces, and comparison between the binding interactions of docked ligands with those within ligand–receptor protein X-ray structures can be valuable tools for CAMD of carboranyl derivatives.

The lack of CAMD approaches involving carboranes is a major drawback in BNCT compound development. The described strategy for modeling molecules containing carborane clusters with the accessible software packages SYBYL, FLEXX, and HYPERCHEM should be of value for synthetic chemists involved in BNCT compound development.

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