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Imitation and modification of bioactive lead structures via integration of boron clusters*

Sven Stadlbauer[1], René Frank[1], Matthias Scholz[1], Solveig Boehnke[1], Verena M. Ahrens[2], Annette G. Beck-Sickinger[2], and Evamarie Hey-Hawkins[1,‡]

[1]Institute of Inorganic Chemistry, Universität Leipzig, Johannisallee 29, D-04103 Leipzig, Germany; [2]Institute of Biochemistry, Universität Leipzig, Brüderstraße 34, D-04103 Leipzig, Germany

Abstract: In medicinal chemistry, carbaboranes can be employed either as boron carriers for boron neutron capture therapy (BNCT) or as scaffolds for radiodiagnostic or therapeutic agents. We have developed a suitable synthesis employing the phosphoramidite method to connect *meta*-carbaboranyl bis-phosphonites with the 6'-OH group of isopropylidene-protected galactose, followed by oxidation or sulfurization to give the corresponding bis-phosphonates. Deprotection yielded water-soluble compounds. The corresponding disodium salts exhibit especially low cytotoxicity. Preliminary results on the in vivo toxicity and biodistribution of two compounds in mice indicated a lack of selectivity for the cotton rat lung (CRL) tumor chosen for the experiment. For the incorporation of carbaboranes into breast tumor-selective modified neuropeptide Y, [F^7, P^{34}]-NPY, a synthesis of a carbaborane-modified lysine derivative was developed. Linkage of the lysine to the boron cluster was achieved by using a propionic acid spacer. Incorporation of the amino acid derivatives into NPY and [F^7, P^{34}]-NPY by solid-phase peptide synthesis was successful. Preliminary studies showed that the receptor binding affinity and signal transduction of the boron-modified peptides were very well retained.

Asborin, the carbaborane analogue of aspirin, is a rather weak inhibitor of cyclooxygenase-1 (COX-1) and COX-2, but a highly potent aldo/keto reductase 1A1 (AKR1A1) inhibitor. Modification either at the carboxyl group or at the chlorophenyl ring in indomethacin with *ortho*- and *meta*-carbaboranyl derivatives gave active derivatives only for the *ortho*-carbaborane directly attached to the carboxyl group, while the corresponding adamantyl and *meta*-carbaboranyl derivatives were inactive.

Keywords: asborin; boron neutron capture therapy (BNCT); carbaboranes; carboranes; cyclooxygenase (COX) inhibitors; indomethacin derivatives; nonsteroidal anti-inflammatory drugs (NSAIDs); neuropeptide Y (NPY)-carbaborane conjugates; pharmacophores; phosphonates; tumor selectivity.

INTRODUCTION

Since the discovery of dicarba-*closo*-dodecarboranes(12) ($C_2B_{10}H_{12}$, carbaboranes) in 1963, various applications [1] have been found in catalysis [2], materials design [3], and medicine [4]. In medicinal

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‡Corresponding author: Tel.: +49-341-9736151; Fax: +49-341-9739319; E-mail: hey@rz.uni-leipzig.de

chemistry, carbaboranes are preferably used for the design of boron neutron capture therapy (BNCT) agents. BNCT is a cancer treatment based on the reaction $^{10}B(n,\alpha)^{7}Li$ acting only locally on the dimensions of a cell diameter [4,5]. The breakthrough in BNCT has not been achieved yet, and only a very few non-carbaborane compounds, such as L-4-(dihydroxyboryl)phenylalanine (BPA) and sodium mercapto-undecahydro-*closo*-dodecaborate (BSH) are used in clinical treatments [6–8]. The rationale behind the BNCT approach is the use of carbaboranes as multiple boron carriers. Connection of the cluster to a tumor-targeting vector is a common principle in the design of BNCT agents and is aimed to improve their tumor-to-blood ratio to at least 5:1, the prerequisite for therapeutic application [4,9].

Parallel to utilization as boron carriers, carbaboranes were found to be excellent scaffolds for diagnostic and therapeutic labeling [10]. BNCT has been comprehensively summarized, and the medicinal potential of carbaboranes has also been reviewed [9–14]. The first BNCT agents were reported about 50 years ago [15], but the investigation of carbaboranes as pharmacophores is more recent [16–18]. The most promising approach to studying carbaborane moieties in pharmaceuticals is the integration of the cluster into a drug with known pharmacological profile. Since the aromatic cluster has a reported diameter of about 5.3 Å, it is just a little larger than a rotating phenyl group (ca. 4.7 Å) [4]. The phenyl-mimetic geometry and aromaticity were already applied in the synthesis of carbaborane analogues of known drugs [17,19].

Here, both approaches—the development of selective carbaborane derivatives as potential BNCT agents and the use of carbaboranes as pharmacophores—are presented.

CARBABORANES AS POTENTIAL BNCT AGENTS

To date, the treatment of malignant tumors is always accompanied by extremely negative side effects. One potentially useful approach for selective destruction of tumor cells is BNCT, a powerful form of radiotherapy involving preferential incorporation of ^{10}B-containing compounds into tumor cells, followed by irradiation of the tumor with nonhazardous thermal neutrons. The latter enter into a nuclear reaction with the ^{10}B isotope, which has a natural abundance of ca. 19.9 % and a remarkable capability of capturing thermal neutrons with a capture cross-section of ca. 3800 barn [20,21].

$$^{10}_{5}B + ^{1}_{0}n \rightarrow ^{11}_{5}B^{*} \rightarrow ^{7}_{3}Li + ^{4}_{2}He$$

The high-energy fission products that are formed, ^{7}Li and ^{4}He particles, allow selective destruction of the tumor cells without affecting the surrounding healthy tissue. Their pathway of action is restricted to the range of ca. 10 μm, which coincides with the diameter of a human cell. Both the intracellular production of cytotoxic particles and their limited area of action are the major advantages of BNCT compared to classical chemotherapeutic methods [20]. However, high and selective accumulation in tumor cells is one important requirement for a BNCT agent [4,20,21]. For successful treatment, a concentration of 30 μg ^{10}B per gram tumor must be achieved.

To date, an increasing number of boron compounds have been synthesized [4,12,20,21], but among them only the *para*-dihydroxy-[^{10}B]-boryl-phenylalanine-fructose complex (BPA-Fr) and [^{10}B]-mercaptoundecahydrododecaborate(2–) (BSH) have been studied in clinical trials [22,23]. In the past two decades, mostly compact, boron-rich moieties, e.g., dodecahydrododecaborate(2–) ($B_{12}H_{12}^{2-}$) and carbaboranes ($C_2B_{10}H_{12}$), have been functionalized and investigated as boron-delivering agents. The main problems to date are the availability of boron compounds that exhibit the necessary water solubility and low toxicity in high concentrations and the targeted delivery of ^{10}B into the tumor cells [9].

We have therefore devised efficient syntheses for novel boron compounds which provide a combined tumor-targeting system:

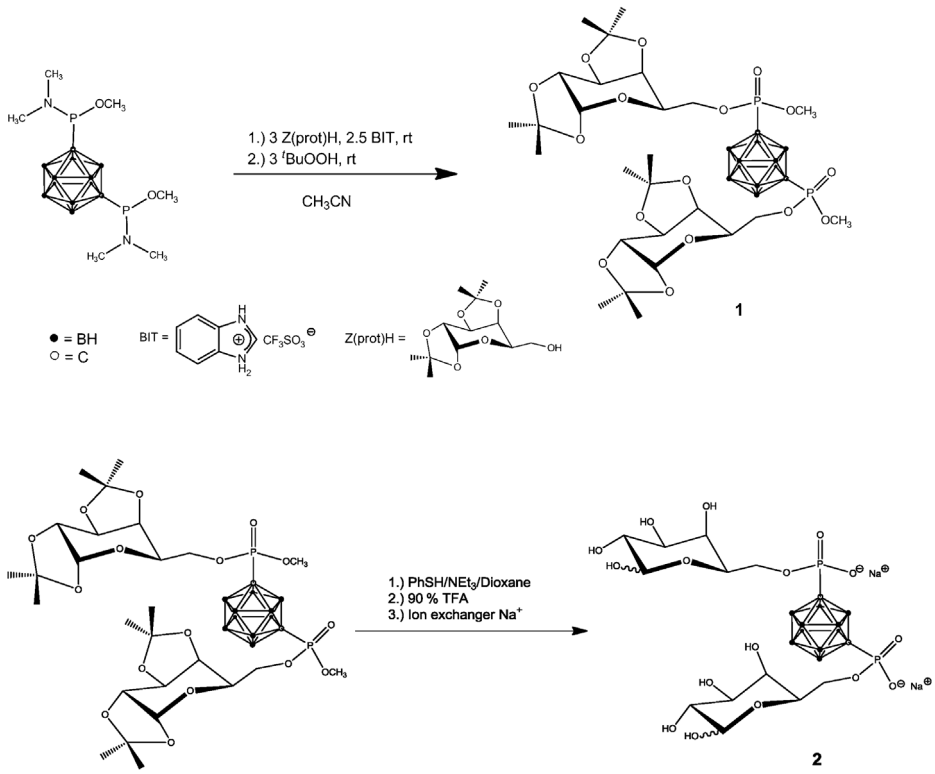
- use of phosphonato groups as phosphate mimics and galactosyl groups for binding to lectins at the surface of a tumor cell [24], and

- carbaborane-containing amino acids for incorporation into modified NPY to selectively target breast cancer cells.

Carbaboranyl glycophosphonates

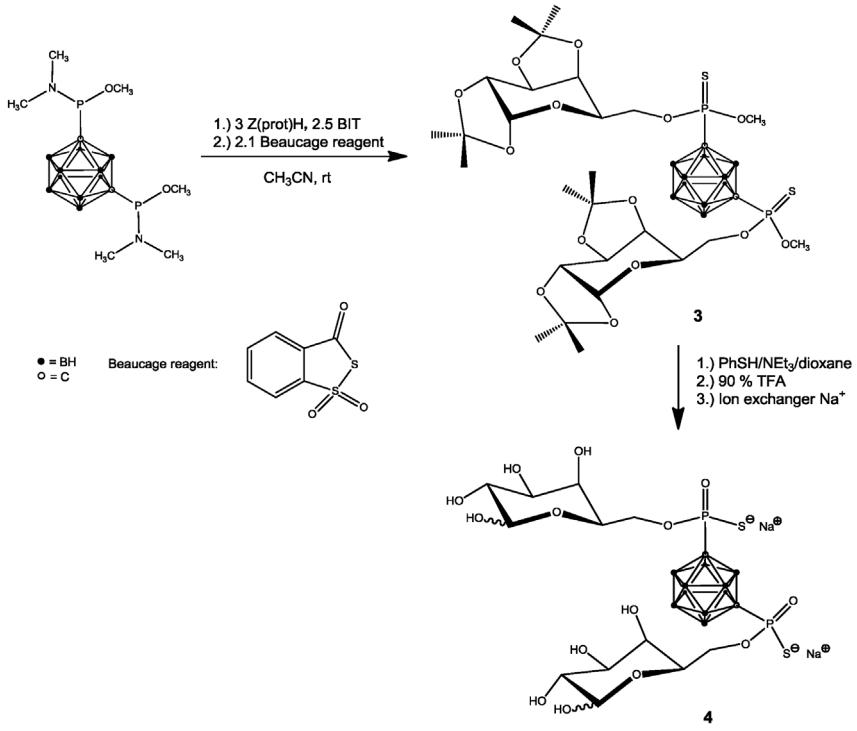
The synthesis of and bioactivity studies on the first phosphorus-containing boron cluster compounds bearing phosphate and pyrophosphate moieties were reported by Kaczmarczyk and Bechtold in 1975 [25]. However, these compounds turned out to be highly toxic. Interestingly, some simple carbaboranyl bis-phosphonates exhibit high tumor selectivity and can be used in the treatment of calcifying tumors [26]. Oligomeric phosphate diesters that contain *closo*- or *nido*-carbaboranes show high accumulation in tumor tissue in BALB/c mice bearing EMT6 tumors [27]. However, comprehensive biological assessments of boron-containing phosphonates as potential tumor-targeting agents in BNCT are still rare [28].

We have employed glycosyl substituents to reduce the toxicity and increase the water solubility of compounds containing hydrophobic carbaborane cages [29–31] as well as to increase the biological availability by using existing transportation systems [32]. The galactosylation of the *meta*-carbaborane 1,7-{$P(NMe_2)(OMe)$}$_2C_2B_{10}H_{10}$, catalyzed by benzimidazolium triflate (BIT) at room temperature, followed by oxidation with *tert*-butyl hydroperoxide (TBHP) in situ resulted in formation of bis-phosphonate **1**, which was obtained as a mixture of four diastereomers. Deprotection of the galactosyl and phosphonato groups and conversion to the sodium salt gave highly water-soluble compound **2** (910 g/L water; Scheme 1) [31].



Scheme 1 Galactosylation of 1,7-{$P(NMe_2)(OMe)$}$_2C_2B_{10}H_{10}$, followed by oxidation and deprotection of the galactosyl and phosphonato groups of **1** to give **2**.

For improved in vivo stability toward phosphatases and phosphonate esterases, the corresponding bis-phosphonothioate **4** was prepared according to this method using 3*H*-1,2-benzodithiol-3-one-1,1-dioxide, the so-called Beaucage reagent (Scheme 2). The water solubility of 830 g/L is slightly lower than that of **2**.



Scheme 2 Synthesis of bis-phosphonothioate **4**.

The biological activity of **2** and **4** was tested on the tumor cell line HeLa by employing the resazurin assay. Compounds **2** and **4** do not show cytotoxicity up to a concentration of 20 mM and are thus far less toxic than the boron compounds that are presently employed in BNCT, e.g., sodium mercaptoundecahydrododecaborane (BSH, IC_{50} 3.9 mM) [33], and this makes them interesting candidates for BNCT. As compounds **2** and **4** exhibit low cytotoxicity they are suitable for studies on tumor selectivity. Preliminary in vivo toxicity studies in Swiss mice were carried out in collaboration with Prof. Gabel, Universität Bremen, Germany, on the bis-phosphonothioate **4** as a representative example. For these studies, four female BALB/c mice with a cotton rat lung (CRL) tumor were subjected to intraperitoneal treatment at a dosage of 100 mg/kg boron. The mice were euthanized after certain periods of time, and then frozen thin sections were produced and subjected to neutron capture radiography (NCR). The results showed high concentrations of the compound in the kidneys, liver, and colon, and only low concentration in the tumor. Within 2 h the compound was excreted through the colon. In conclusion, this compound showed a lack of selectivity for this tumor type.

We are, therefore, now focusing on different glycosides, such as mannose [34], and different connectivities with the phosphorus atom, e.g., via the anomeric position, to achieve higher selectivity.

Carbaborane conjugates with neuropeptide Y

The targeted delivery of ^{10}B into the tumor cells still represents one of the major problems to be solved in BNCT. Numerous molecules with high affinity and selectivity for tumor cells were studied as selective carriers into cancer cells. Peptides that have been proposed as carrier systems are somatostatin (SST), epidermal growth factor (EGF), neurotensin, substance P, gastrin-releasing peptide (GRP), insulin-like growth factor (IGF) [35], alpha-melanocyte stimulating hormone (α-MSH), cholecystokinin (CCK), vascoactive intestinal peptide (VIP), bombesin (BN), and NPY [36]. NPY is a member of the pancreatic polypeptide family and is composed of 36 amino acid residues. It is one of the most abundant neuropeptides in the brain [37], binds to four Y-receptor subtypes (Y_1, Y_2, Y_4, and Y_5) in nanomolar concentration and even triggers receptor internalization [38]. The signal transduction of Y-receptors follows a G protein-coupled (GPC) receptor cascade [39,40].

Reubi et al. found a selective over-expression of Y_1-receptor subtypes for more than 90 % of the breast tumors and for 100 % of all metastatic tumors, and an alteration of the receptor subtype expression from Y_2-receptors in healthy breast tissue to Y_1-receptors in affected tissue [41]. Beck-Sickinger et al. developed a modified neuropeptide Y, [F^7, P^{34}]-NPY, that was shown to preferentially bind to the human Y_1-receptor compared to other Y-receptor subtypes with a high tolerance towards modifications [42]. Therefore, we considered [F^7, P^{34}]-NPY as a potent selective carrier for ^{10}B into breast tumor cells.

ortho-Carbaboranyl propionic acid was synthesized and linked to the ε-amino group of N_α-Fmoc protected L-lysine (Fig. 1). The compound was characterized by NMR, IR, and MS studies. The carbaborane-modified amino acid was incorporated at the 4-position of NPY and [F^7, P^{34}]-NPY by an optimized solid-phase peptide synthesis using Fmoc protection followed by manual coupling (last four amino acid residues). Binding studies and inositol trisphosphate (IP) accumulation assays confirmed nanomolar affinity and activity of the modified analogues despite the large carbaborane cluster. Internalization studies revealed excellent and receptor subtype-specific uptake of the conjugates into respective cells. Therefore, these compounds are very promising for future in vivo studies [43].

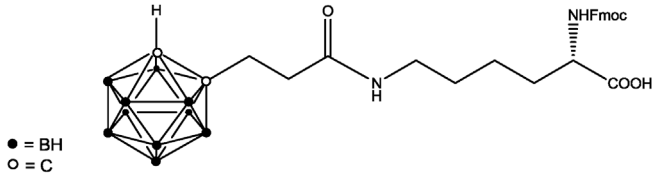


Fig. 1 Carbaborane-modified L-lysine derivative.

CARBABORANES AS PHARMACOPHORES

In medicinal chemistry, carbaboranes have been used almost exclusively as boron carriers for BNCT. Recent developments extended the carrier approach and use carbaboranes as scaffolds for radiodiagnostic or therapeutic agents. The most promising approach to studying carbaborane moieties in pharmaceuticals is integration of the cluster into a drug with known pharmacological profile. The phenyl analogy was already applied in the synthesis of carbaborane analogues of tamoxifen [44] and trimethoprim (TMP) [45]. Carbaborane-modified flufenamic acid and diflunisal, two nonsteroidal anti-inflammatory drugs (NSAIDs), were also reported [46]. We have now extended this concept to other cyclooxygenase (COX) inhibitors.

Aspirin is one of the smallest members of the NSAID family. These compounds are structurally very diverse, but all of them are capable of inhibiting COX enzymes. These enzymes catalyze the conversion of arachidonic acid to prostaglandin H_2 (PGH_2), the key compound in the prostanoid system. COX itself exists as different isoforms, of which COX-1 and COX-2 are the best scrutinized [47]. The

pharmacological action of aspirin is unique among the NSAIDs, since it modifies the enzymes covalently by acetylating an active-site serine residue [48]. When the serine residue is acetylated, PGH_2 cannot be formed and the synthesis of all further prostaglandins, prostacyclins, and thromboxanes is blocked.

We have modified aspirin by replacing the phenyl ring with a three-dimensional carbaborane cluster (Fig. 2). Asborin, the carbaborane analogue of aspirin, has a highly hydrophobic cluster framework and hydrophilic carboxyl group and is remarkably amphiphilic: It dissolves in water and nonpolar organic solvents. The pharmacological behavior of asborin was studied [49]. COX inhibition was studied with an enzyme-linked immunosorbent assay (ELISA)-based COX inhibitor screening assay with the free enzymes of COX-1 and COX-2. At an asborin concentration of 500 μM, COX-1 is about 50 % inhibited and COX-2 to the lesser extent of 28 %. Thus, asborin inhibits COX enzymes with the same, but less pronounced isoform selectivity trend as aspirin [50].

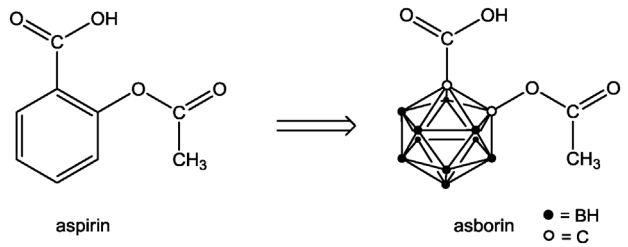


Fig. 2 Asborin, the carbaborane analogue of aspirin.

However, asborin proved to be a highly potent aldo/keto reductase 1A1 (AKR1A1) inhibitor instead [51]. Salborin, the deacetylated version of asborin, was also a competitive AKR1A1 inhibitor, while the phenyl analogues, salicylic acid and aspirin, showed only very poor AKR1A1 inhibition [51]. Asborin's mode of action is unique, as it irreversibly acetylates lysine residues first and thereby eliminates salborin, which in addition is a competitive AKR1A1 inhibitor. The increased acetylation potential of asborin can be attributed to the strongly electron-withdrawing character of the *ortho* isomer transmitted by the cluster carbon atoms. Additionally, the shape of the cluster can be used to modify a drug for hydrophobic targets with a preference for bulky inhibitors, like the AKR TIM barrel. Compared to their phenyl analogues, both carbaborane derivatives, asborin and salborin, were more toxic with almost equal IC_{50} values, whereas detoxification was observed upon deboronation. This reaction occurred under aqueous conditions at ambient temperature [52].

AKR1A1 proved to be an excellent model enzyme to investigate the general mode of inhibition. However, for medicinal applications, other AKR members are more interesting, e.g., AKR1C, implicated in epilepsy, depressive disorders, and development of cancer, or AKR1B members, involved in diabetic neuropathy [53]. Since the general protein structure and especially the cofactor binding domain are highly conserved within all AKRs, they usually share the same inhibitors [54,55]. Thus, these results will facilitate the identification of further AKR targets and the adjustment and optimization of the lead structure, asborin.

Indomethacin is also a very potent NSAID used to treat fever, swelling, and pain [56]. This drug emerged as a powerful scaffold which allowed various modifications to influence the selectivity for COX-1 and COX-2, which is the therapeutically relevant isoform. Previous studies showed that addition of substituents, either at the carboxyl group or at the chlorophenyl ring, increased the COX-2 selectivity [57–60]. Hence, these two positions were modified with selected carbaborane isomers (Fig. 3).

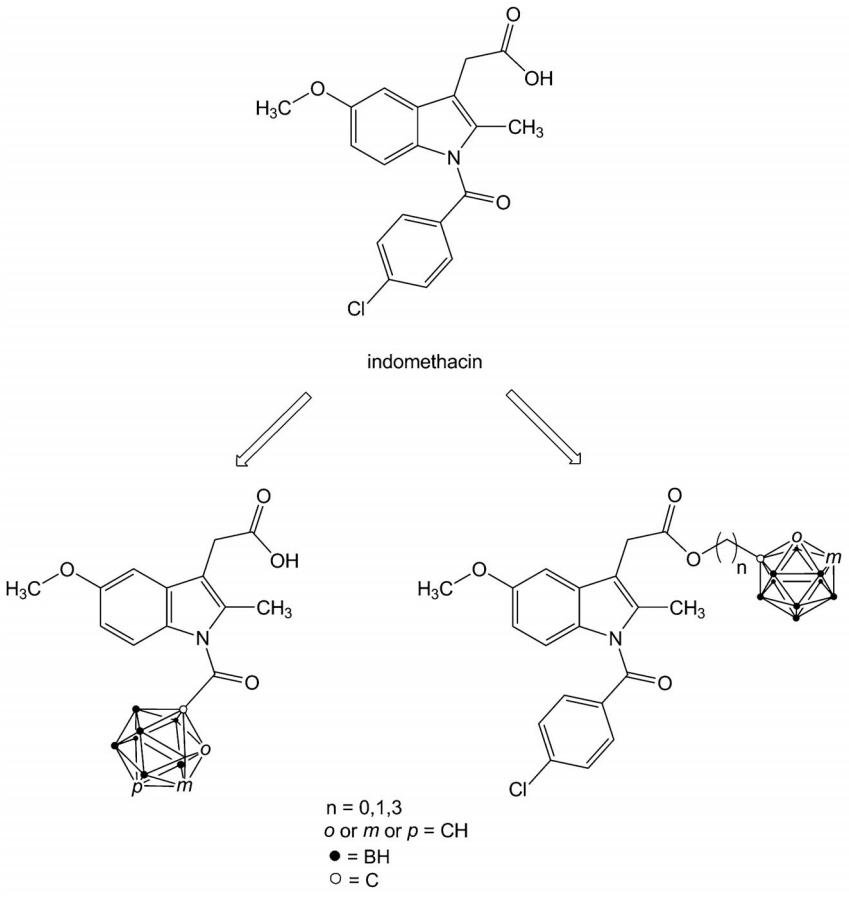


Fig. 3 Carbaborane-modified indomethacin analogues.

Thus, *ortho*- and *meta*-carbaboranyl entities were connected either directly or via spacers to the carboxylic acid group of indomethacin. Only the ester in which *ortho*-carbaborane was directly attached to the carboxyl group was active in the micromolar range; the corresponding adamantyl and *meta*-carbaboranyl derivatives were inactive [61]. Similarly, replacement of the chlorophenyl ring with unsubstituted carbaborane isomers revealed the most promising analogues again with the *ortho* isomer [62].

CONCLUSIONS

Two different strategies for the development of selective BNCT agents were presented. Firstly, a suitable synthesis of galactosylated water-soluble *meta*-carbaboranyl bis-phosphonates was developed. The corresponding disodium salts exhibit low cytotoxicity. Preliminary results on the in vivo toxicity and biodistribution of two compounds in mice indicated a lack of selectivity for the CRL tumor chosen for the experiment. A second, different strategy focuses on the incorporation of a carbaborane-modified lysine derivative into breast tumor-selective modified neuropeptide Y, [F^7, P^{34}]-NPY. Preliminary studies show no significant changes in receptor binding affinity and signal transduction.

Furthermore, two examples were given for use of carbaboranes as pharmacophores: asborin, the carbaborane analogue of aspirin, and indomethacin derivatives. Asborin is a rather weak COX-1 and COX-2 inhibitor, but a highly potent AKR1A1 inhibitor. In contrast, modification either at the carboxyl

group or at the chlorophenyl ring in indomethacin with *ortho*- and *meta*-carbaboranyl derivatives gave active COX inhibitors, but only for the *ortho*-carbaborane directly attached to the carboxyl group, while the corresponding adamantyl and *meta*-carbaboranyl derivatives were inactive.

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