BORON UNITS AS PHARMACOPHORES – NEW APPLICATIONS AND OPPORTUNITIES OF BORON CLUSTER CHEMISTRY

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Carboranes (dicarba-*closo*-dodecaboranes) are a class of carbon-containing polyhedral boron-cluster compounds showing remarkable hydrophobic character, chemical and thermal stability, and resistance to catabolism in biological environment. These features allow application of boron clusters as new hydrophobic core structure in biologically active molecules that interact hydrophobically with proteins, thus facilitating new drug design. A review with 45 references.

Keywords: Carboranes; Metallacarboranes; Drugs; Pharmacophores; Medicinal chemistry; Hydrophobicity; Nucleosides; Cholesterol mimics.

INTRODUCTION

Boron clusters exhibit structural features and chemical properties which assure their numerous applications in various areas of research and practice[1–5]. Application of boron clusters as modifying entities for biomolecules has been explored since several decades ago but until recently it has been fuelled mainly by the quest for better boron carriers for BNCT [5–7]. In such carrier molecules the designed role for the boron part is reduced to providing a sufficient number of boron atoms. This situation is changing now.

There is a growing interest in less explored advantages of boron clusters and in using them as lipophilic pharmacophores[8,9] in drug design and as lipophilic components in biomolecules, modulating their hydrophobic interactions with other biomolecules. These works open new horizons for boron cluster chemists and pharmacologists.

The structural features responsible for high hydrophobicity of carboranes and carborane/biological molecule conjugates will be discussed. Application of carborane pharmacophores in the design of novel estrogen receptor

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antagonists and agonists[10] and retinoic acid receptor modulators[11] will be shown as well as applications in synthesis of ligands modulating activity of androgen receptors[12] and proteins such us tumor necrosis factor (TNF-α)[13], and carborane-modified transthyretin (TTR) amyloidosis inhibitors[14].

The use of boron clusters and their complexes with metals as modifying units in the synthesis of biologically important nucleoside phosphates with increased lipophilicity, antiviral and anticancer agents, and some other emerging applications will be also discussed.

LIPOPHILICITY OF BORON CLUSTERS AND HYDROGEN BONDING

The dicarba-*closo*-dodecaboranes ($C_2B_{10}H_{12}$, carboranes) are icosahedral carbon-containing boron clusters with extraordinary characteristic properties that afford the opportunity of exploitation in different areas of medicinal chemistry. These features include: (i) spherical geometry, (ii) thermal stability, (iii) resistance to ionizing radiation, (iv) chemical stability, (v) biological stability and resistance to catabolism, (vi) low toxicity, (vii) well established chemistry and susceptibility to derivatization, and (viii) extremely high hydrophobicity. In adition to icosahedral geometry involving hexacoordinated carbon and boron atoms, the electron-deficiency and delocalization of boron bonding accounts for many of carborane properties[15].

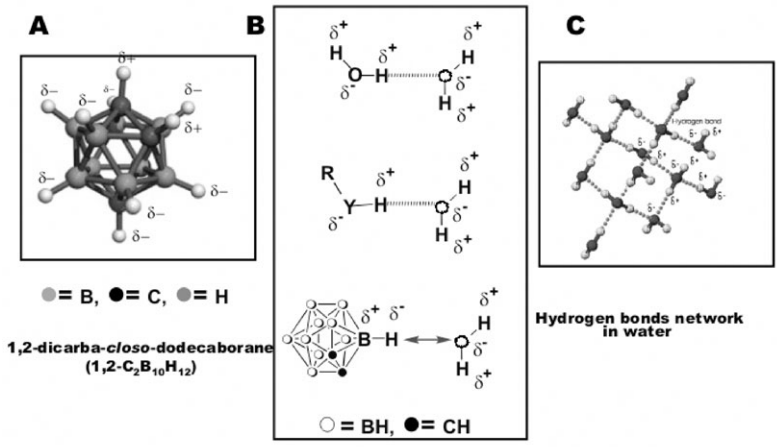

FIG. 1
The hydride character of boron cage hydrogens (A) causes their inability to participate in hydrogen bonding with water (B and C) and contribute to the hydrophobic character of carboranes

Due to the presence of a partial negative charge located on boron hydrogens (the charge density differs for different hydrogens), the hydrogen atoms in B–H groups have a hydride-like character. This prevents them from forming classical hydrogen bonds[16] and, consequently, causes a lipophilic or hydrophobic character of the boron clusters[17–19] (Fig. 1).

Boron clusters as modifying entities for biomolecules offer rich possibilities of tailoring the hydrophobic properties due to different dipole moments and hydrogen binding sites of the molecule though there is only limited knowledge how to reach this in geometrically pre-defined manner. Dicarba-*closo*-dodecaboranes exist in the form of three geometrical isomers (*ortho*-, *meta*- and *para*-) depending on the position of the carbon atoms in the cage scaffold. Removal of the most electrophilic boron atom in lipophilic, neutral dicarba-*closo*-dodecaborane results in the formation of more hydrophilic, anionic dicarba-*nido*-undecaborate ($C_2B_9H_{12}^-$). The hydrophobicity of dicarba-*closo*-dodecaboranes can be reduced by the presence of a dipole moment, which is strongly dependent on the position of carbon atoms in the carborane cage. The hydrophobicity of dicarba-*closo*-dodecaborane isomers increases in the order: *ortho*- < *meta*- < *para*- [2,5,8,20–22] (Fig. 2).

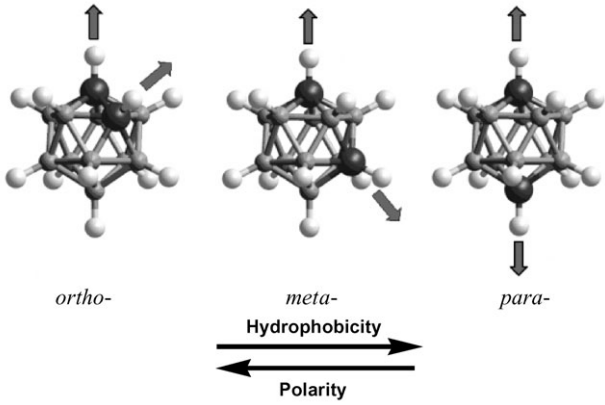

FIG. 2
The effect of dipole moment on hydrophobicity of dicarbadodecaboranes

The electronegativity of hydrogens enables boranes to form unconventional hydrogen bonds, namely dihydrogen bonds. Dihydrogen bonds, also called proton–hydride bonds, generally occur between a positively charged hydrogen atom of a proton donor AH (A = N, O, S, C, halogen) and a bond of a MH proton acceptor (M = electropositive atom, such as boron, alkali metal or transition metal). In boranes, NH···HB, CH···HB and SH···HB

dihydrogen bonds have been found. Another type of interaction was found for CH (carborane)–Y hydrogen-bonded complexes. These complexes were, however, much less stable[16,23] (Fig. 3).

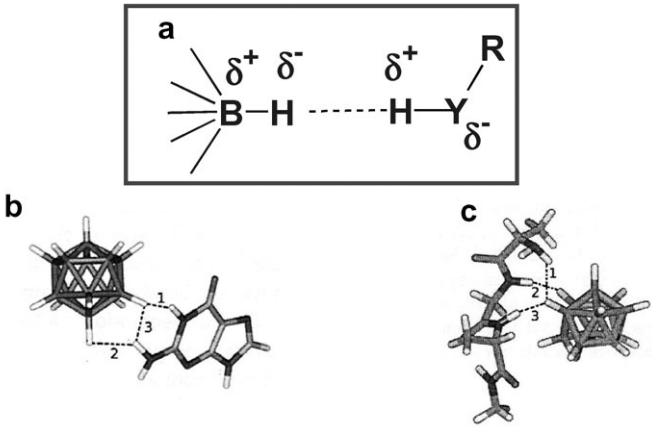

FIG. 3
(a) Proton–hydride bonds formed by boron clusters. (b) Molecular dynamics simulation in vacuum of proton–hydride bond between guanine and $[CB_{11}H_{12}]^-$ (from ref.[16]), and (c) tetrapeptide Ala-Gly-Ala-Ala and [*nido*-1,2-$C_2B_9H_{12}$]$^-$ (from ref.[23])

Hydrophobicity, the dipole moment and the ability to form proton–hydride bonds play an important role in interactions of boron clusters and their complexes with metals (metallacarboranes) with biomolecules. A high affinity of boron clusters possessing negative charge to sites where positive charge is located such as in amino acids and peptides is another factor contributing to these interactions. Selected examples of the use of boron clusters as pharmacophores are presented below. Some other emerging applications are also discussed.

BORON CLUSTERS AS PHARMACOPHORES

The cage-like, spherical dicarbadodecaborane structure mimics well the dodecahedral volume created by rotation of the planar benzene ring over 360° but it is much more hydrophobic moiety. Its higher volume and surface area in comparison with the benzene ring may explain the observed, often high efficacy of carborane-containing biomolecule interactions with hydrophobic domains of proteins such as receptors. These advantages were first exploited for modification of amino acids and peptides.

ortho-Carboranyl-L-alanine and several other carborane-modified amino acids were synthesized in the late seventies[24,25]. The lipophilicity of *ortho*-carboranyl-L-alanine found by partition coefficient measurement was much higher than that of parent L-phenylalanine and higher than another lipophilic phenylalanine analogue, adamantyl-L-alanine[19] (Fig. 4). Subsequently, several analogues of biologically active peptides such as enkephalin[26], angiotensin[27], bradykinin, substance P[28], and insect neuropeptide pyrokinin[29] (Fig. 4) in which the Phe and/or Tyr residues were replaced with carborane bearing an amino-acid analogue, have been synthesized. An often highly increased biological activity was achieved, e.g. a carborane modified pyrokinin analogue exhibited 30-fold increase in pheromonotropic activity *in vitro* and 10-fold increase in *in vivo* studies. It was also significantly more stable to aminopeptidase[29]. Several homopeptides containing carborane-bearing amino-acid analogue for antibody modification and subsequent BNCT studies have also been prepared[25].

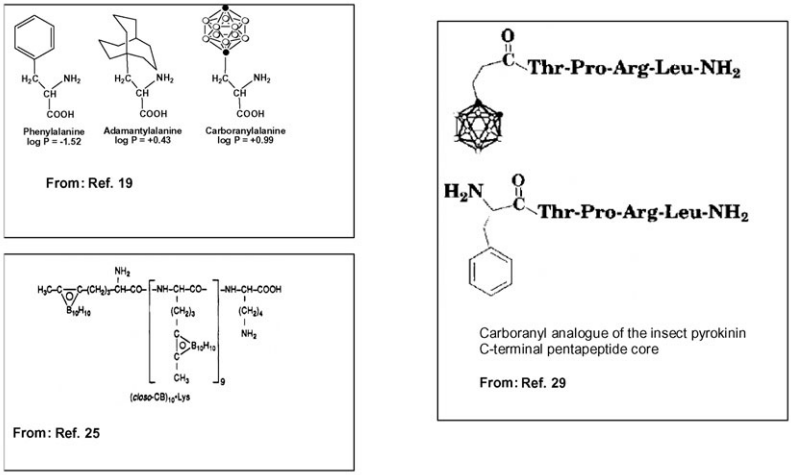

FIG. 4
Carborane-containing amino acids and peptides

The revival of the studies on boron clusters as pharmacophores is due to the groundbreaking concept developed by Endo et al. for the synthesis of carborane analogues of *all-trans*-retinoic acid[30] and estradiol in which carborane is used as a hydrophobic skeletal structure increasing hydrophobic interactions in the receptor ligand complexation[10,31]. The steroid hormone estrogen influences the growth, differentiation, and functioning of many target tissues. Estrogen plays an important role in the female and

male reproductive system, and also in bone maintenance, in the central nervous system and in the cardiovascular system. The first step in these activities is mediated by binding of hormonal ligands to the α and β estrogen receptor (ER) monomers resulting in formation of the ER dimer; hydrophobic interactions play an important role in this process. Several novel carborane-containing estrogenic agonists have been synthesized, of which 1-(hydroxymethyl)-12-(4-hydroxyphenyl)-1,12-dicarba-*closo*-dodecaborane (**2**) proved to be ten times more active than its natural counterpart, 17β-estradiol[10] (Fig. 5).

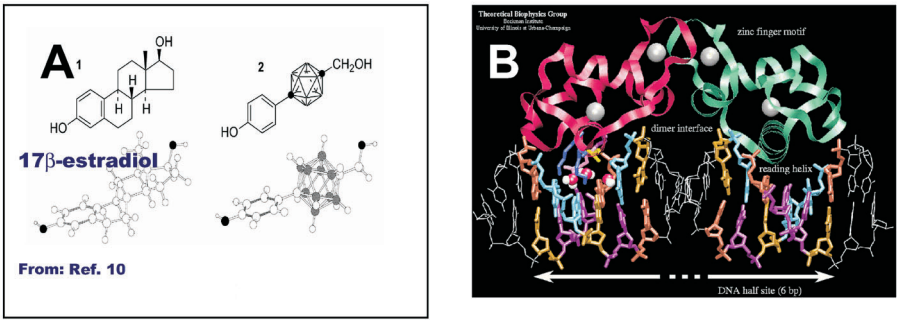

FIG. 5
(A) Highly active estrogen receptor (ER) agonist based on carborane structure **2**. (B) ER dimer bound to the specific promoter DNA sequence, 5′-GGTCAnnnTGACC-3′ (n = any nucleotide)

Several other biological targets where the unique properties of carboranes proved beneficial have been identified. These include a retinoic acid receptor[11,30] and androgen receptor[12] (Fig. 6). Further success in using carboranes resulted in the discovery of powerful carboranyl analogues of the anti-estrogen tamoxifen[32], the controversial drug thalidomide[13] and, more recently, promising nonsteroidal anti-inflammatory drugs (NSAIDs) that impart kinetic stabilization to transthyretin (TTR), a protein that has been implicated in a variety of amyloid-related diseases[14].

Retinoids and their analogues are of particular interest as chemopreventive and therapeutic agents in the field of dermatology and oncology. Biological activities of retinoids are mediated by binding to and activation of retinoic acid receptors (RARs), following modulation of the gene transcription by the complex. High binding activity requires a carboxylic acid moiety and an appropriate hydrophobic group which interacts with the hydrophobic cavity of the RAR-ligand-binding domain. Among the synthesized compounds[11], 4-[4-(2-propyl-1,2-dicarba-*closo*-

dodecaboran-1-yl)phenylamino]benzoic acid (Fig. 6, R_1 = *n*-C_3H_7, R_2 = H, R_3 = H), exhibited biological activity almost equal to that of the natural ligand.

Androgen receptor (AR) is a member of the nuclear receptor superfamily of ligand-regulated transcription factors and plays a key role in the development and maintenance of the male reproductive system. Its functions are initiated by the binding of the steroid hormones, testosterone and/or 5α-dihydrotestosterone, to the AR, and intricate machinery, involving translocation of AR into the nucleus, binding to specific DNA sites, formation of a transcriptional complex, and activation of the expression of specific genes. AR ligands have been applied clinically in the treatment of diseases such as aplastic anemia and prostate cancer.

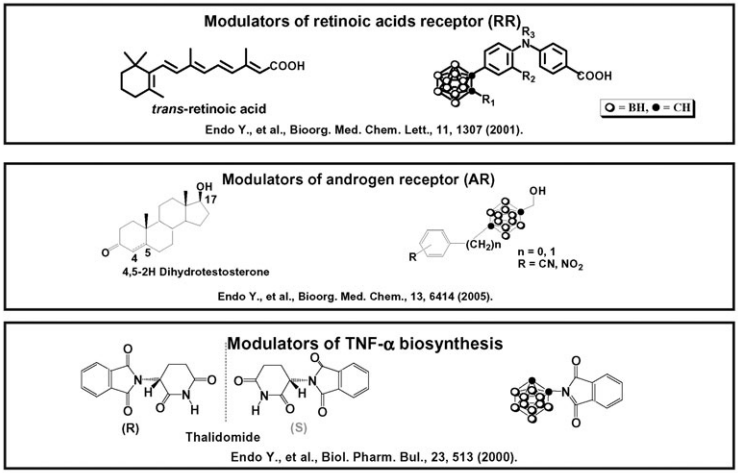

FIG. 6
Selected examples of modification of receptor ligands with boron

Nonsteroidal androgen antagonists with a *para*-dicarba-*closo*-dodecaborane cage in place of steroidal C, and D rings of testosterone or 5α-dihydrotestosterone have been developed[33]. Second-generation, more potent AR antagonists containing cyanophenyl and nitrophenyl groups instead of the cyclohexene ring were also proposed. The potency of compounds with the CN and NO_2 groups in *meta*-position (Fig. 6) was superior to that of hydroxyflutamide, a nonsteroidal AR antagonist used clinically for treatment of prostate cancer[12,34]. It was suggested that the hydrophobic interaction of the carborane structure with the hydrophobic region of the AR ligand-binding pocket may account for its high binding affinity to AR,

and, owing to the bulky carborane cage, the conformation of the AR–ligand complex may not be appropriate for interaction with cellular co-regulators, resulting in antagonistic activity.

Thalidomide was first developed as a sedative agent and was used as a racemic mixture of both enantiomers. Because of its severe teratogenicity assigned later to the S enantiomer it was withdrawn from the market. An approach to market thalidomide in the enantiomerically pure R form met serious obstacles due to detected racemization. In spite of this, there has been a resurgence of interest in thalidomide in recent years due to its potential usefulness in treatment of various diseases including leprosy, rheumatoic arthritis and AIDS. Various biological activities of thalidomide have been attributed to its regulating activity in biosynthesis of tumor necrosis factor α (TNFα)[35]. Several carborane thalidomide analogues active as regulators of TNFα production in HL-60 cells have been synthesized (Fig. 6)[13]. These findings supported earlier observations that a hydrophobic substituent at the nitrogen atom of the phthalimide ring is critical for potent activity.

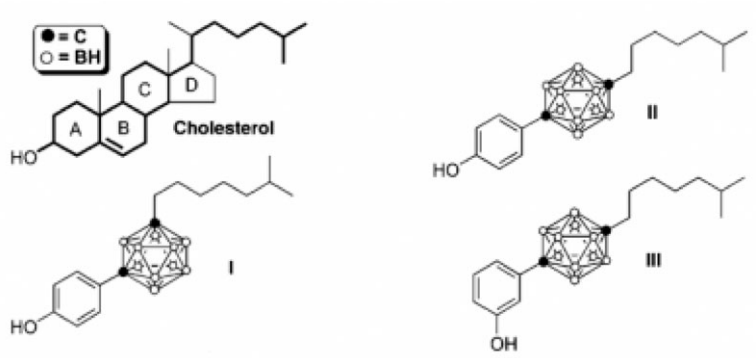

FIG. 7
Boronated cholesterol mimics for liposomal delivery of boron in BNCT (from ref.[36])

Cholesterol is an important constituent of mammalian cell membranes, and the frequently used component of liposomal formulations in drug delivery technology. Numerous cholesterol derivatives containing boron cluster attached to cholesterol skeleton as external entity have been synthesized as potential boron carriers for BNCT. Recently novel cholesterol derivatives containing boron cluster as a pharmacophore were proposed[36]. A major structural feature of these boronated cholesterol mimics is replacement of the B and C rings of cholesterol with a boron cluster, analogously to estradiol modification proposed earlier[10] (Figs 5 and 7).

Transthyretin (TTR) is a tyrosine-transport protein found in the blood that has been implicated in a variety of amyloid-related diseases. Previous investigations have identified a variety of nonsteroidal anti-inflammatory drugs, such as flufenamic acid or diflunisal, and structurally related derivatives that impart kinetic stabilization to TTR, thus inhibiting its dissociative fragmentation and subsequent aggregation to form putative toxic amyloid fibrils. Several carborane analogues of these drugs have been synthesized and evaluated for inhibition of amyloid fibril formation. Some of them showed also a greatly decreased cyclooxygenase (COX) activity, a highly desired property. The most promising of these compounds is 7-(3-fluorophenyl)-1,7-dicarba-*closo*-dodecaborane-1-carboxylic acid[14] (Fig. 8).

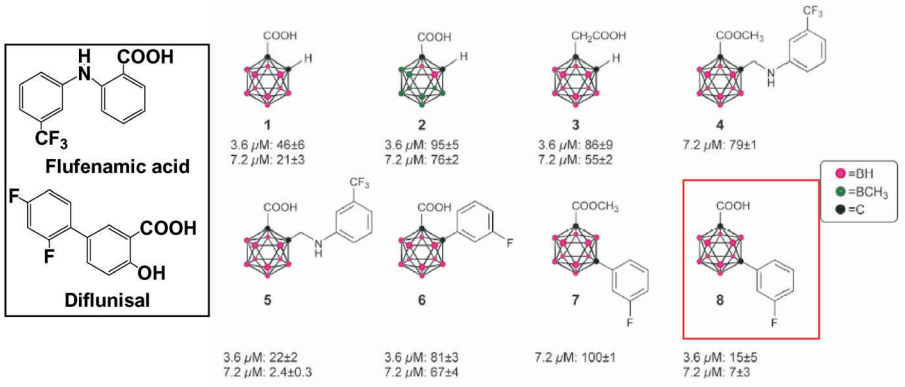

FIG. 8

Transthyretin (TTR) amyloidosis inhibitors, analogues of nonsteroidal anti-inflammatory drugs flufenamic acid and diflunisal, containing carborane pharmacophores. Inhibitor concentration and per cent fibril formation in TTR assay are given below each compound (from ref.[14])

New application of metallacarboranes (boron cluster complexes with metal) results from the finding that metallacarboranes act as potent and specific inhibitors of HIV-1 protease[37]. HIV protease is responsible for cleaving viral polyprotein into mature, functional enzymes and structural proteins. This process is required for the progeny virion to become replication-competent and infectious. Inhibition of the polyprotein maturation may stop the virus replication and subsequently cause therapeutic effect. Even though there are currently several HIV protease inhibitors in clinical practice, they suffer, as most antiviral drugs, from the drug-resistance problem. Therefore, there is a continuing need for the design of new antiviral molecules. Metallacarboranes seem a most interesting new option in the quest for anti-HIV compounds (Fig. 9).

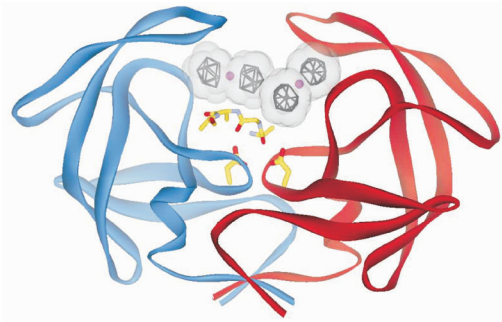

FIG. 9
Structure of the HIV protease–3-cobalt bis(1,2-dicarbollide) complex (from ref.[37])

The original rationale for the design and synthesis of boron-containing nucleosides was the use of such compounds as boron carriers for BNCT. Such compounds may be selectively accumulated in rapidly multiplying tumor cells after their conversion to the corresponding nucleotides trapped within the cell or, ideally, incorporated into nuclear DNA of tumors. More recently, encouraged by the superior antiviral profiles of (–)-β-L-2′,3′-dideoxy-3′-thiacytidine (3TC) and (–)-β-L-2′,3′-dideoxy-5-fluoro-3′-thiacytidine (FTC) and other nucleoside analogues, several modified sugar residues were introduced into the carborane-containing nucleosides and the obtained derivatives were tested for antiviral activity[5] (Fig. 10).

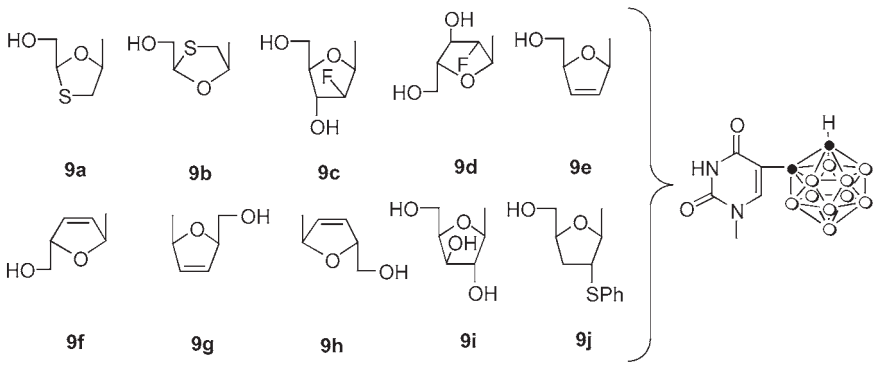

FIG. 10
Modulation of lipophilic properties of antiviral and anticancer nucleosides. Sugar-modified 5-(*o*-carboranyl)uracil nucleosides: β-D/L-5-(*o*-carboranyl)-2′,3′-dideoxy-3′-thiacytidine (CTU, **9a**/**9b**), 5-(*o*-carboranyl)-1-(2-deoxy-2-fluoroarabinofuranosyl)uracil (CFAU, β-D **9c**, α-D **9d**), 5-(*o*-carboranyl)-2′,3′-didehydro-2′,3′-dideoxyuridine (D4CU, β-D **9e**, α-D **9f**, β-L **9g**, α-L **9h**), 5-(*o*-carboranyl)-1-(β-D-xylofuranosyl)uracil (**9i**), β-D-5-(*o*-carboranyl)-2′,3′-dideoxy-2′-(phenylthio)uridine (**9j**) (ref.[5], and references therein)

In addition to exploitation of boron clusters as pharmacophores, new applications still emerge[38]. They include, among others, the use of metallacarboranes as boron donors in boron carriers for BNCT [3,39,40], application of carboranes and metallacarboranes as potential electrochemical labels[41,42] for biomolecules, labels detectable by IR and Raman spectroscopy[43,44], or lipophilic components useful in the synthesis of biophosphates with increased lipophilicity[45] (Fig. 11).

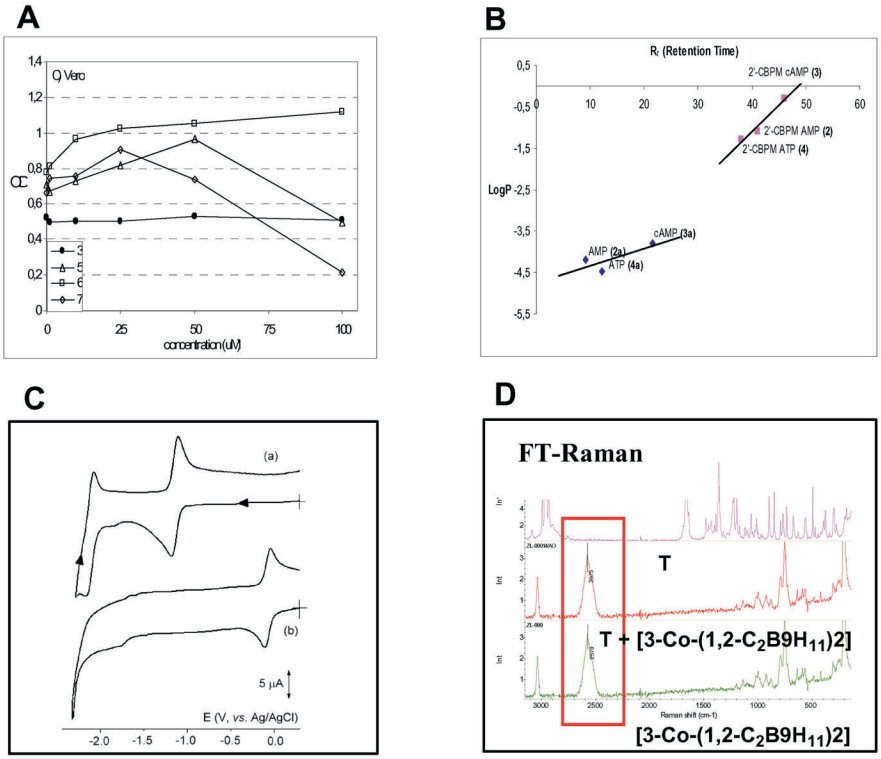

FIG. 11

Applications of boron clusters. (A) Nucleoside/metallacarborane conjugates are highly lipophilic and low-toxic, an important feature for boron carriers in BNCT: dose-dependent cytotoxicity curves in Vero cells for thymidine **3** and its 3-cobalt bis(1,2-dicarbollide) conjugates (**5**-N[3]) and (**6**-O[4]), and 8-(5-hydroxy-3-oxa-pentoxy)-3-cobalt bis(1,2-dicarbollide) (**7**)[39]. (B) Lipophilic modulators for synthesis of biophosphates with increased lipophilicity: log *P* vs HPLC R_t for unmodified and carborane modified (2′-CBM) AMP, cAMP and ATP [45]. (C) Carboranes and metallacarboranes as potential electrochemical labels for biomolecules: simultaneous detection by cyclic voltammetry at a glassy carbon electrode 2′-deoxyadenosine/metallacarborane conjugates containing Co or Fe [41,42]. (D) Boron clusters as labels for biomolecules detectable by Raman or IR spectroscopy[43,44]

In summary, it can be assumed that the substitution of aromatic rings by boron clusters as pharmacophores may enhance biological activity, particularly where hydrophobic and steric interactions are important in the mechanism of substrate bonding. Enzymatic systems, and in particulary those acting via degradation of benzene rings, would hardly be able to split the boron cage with different kind of bonds. Higher activity against resistant mutation forms of various infections can be anticipated.

The steric bulk, rigidity, an ease of derivatization of boron and carbon centers in boron clusters, and lack of π-interactions associated with hydrophobic carboranes may be exploited for enhancing the selectivity of previously identified bioactive molecules, and facilitate the design of entirely new drugs.

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