Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Spl Issue [5] 2022 : 599-605

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

Comparative Studies on Boron Material Dopping for Medical Applications

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ABSTRACT

Boron compounds now have many applications in a number of fields, including Medicinal Chemistry. Although the uses of boron compounds in pharmacological science have been recognized several decades ago, surprisingly few are found in pharmaceutical drugs. The boron-containing compounds epitomize a new class for medicinal chemists to use in their drug designs. Carboranes are a class of organometallic compounds containing carbon (C), boron (B), and hydrogen (H) and are the most widely studied boron compounds in medicinal chemistry. Additionally, other boron-based compounds are of great interest, such as dodecaborate anions, metallacarboranes and metallaboranes. The boron neutron capture therapy (BNCT) has been utilized for cancer treatment from last decade, where chemotherapy and radiation have their own shortcomings. However, the improvement in the already existing (BPA and/or BSH) localized delivery agents or new tumor-targeted compounds are required before realizing the full clinical potential of BNCT. The work outlined in this short review addresses the advancements in boron containing compounds. Here, we have focused on the possible clinical implications of the new and improved boron-based biologically active compounds for BNCT that are reported to have in vivo and/or in vitro efficacy. Advances in the field of boron chemistry have expanded the application of boron from material use to medicine. Boron-based drugs represent a new class of molecules that possess several biomedical applications including use as imaging agents for both optical and nuclear imaging as well as therapeutic agents with anticancer, antiviral, antibacterial, antifungal and other disease-specific activities.

Keywords: *boron chemistry; boron-containing compounds; boron cluster; carborane; boron neutron capture therapy; boron delivery agents for BNCT; medical applications.*

Received 22.10.2022 Revised 20.11.2022 Accepted 16.12.2022

INTRODUCTION

Carbon chemistry has been widely studied over the past two centuries. Despite its neighbor in the periodic table, the study of boron chemistry is relatively a newcomer compared to the chemistry of carbon. However it is rich as building block of its own, and has been mostly used in dealing with carbon chemistry [1].

Boron is generally found in minute amounts in the human body (in an average individual it's not more than 18 mg . However, it has the potential to be considered as facilitator in new biological activities and can be utilized in pharmaceutical drug design. Mainly, the boron-containing bioactive molecules are of two types; one type of molecules contains a single boron atom, while the other is in the form of a boron cluster[2] Boron has the ability to instantly convert from a trigonal planar (sp^2 hybridized) form, that is a neutral form, to a tetrahedral (sp^3-hybridized) form, which is an anionic form in the single boron atom-containing compounds when used under physiological conditions[3].This provides the basis for using boron to design inhibitors for enzyme-catalyzed hydrolytic processes by adopting carbon-based transition states[4]..While the boron atoms as a whole in the cluster compounds are used rather than a separated or single boron atom, the unique interaction with targeted proteins are possible mainly due to their presence in cage structure[5].

unusual nature of the bonding in borane became apparent in 1954 from the research of Lipscomb and co-workers describing the theoretical prediction in icosahedral borane The actual motivation for the advancement of medicinal chemistry of boron was started from the use of boron neutron capture therapy (BNCT) for cancer treatment This is linked with the development in nuclear research technology and the availability of neutrons source suitable for the clinical treatment of cancers via BNCT[6].In 1960s, the discovery of polyhedral boron compounds facilitated the mission of BNCT through new boron carriers containing boron clusters rather than those with a single boron atom per molecule A major area of main

group inorganic/organometallic chemistry has been developed from the study of electron-deficient boron clusters that overlaps with medicinal and organic chemistry to form a new area of bioorganic chemistry involving boron carriers for the treatment of tumor using BNCT model[7]. Among new compounds of low molecular weights for BNCT use are the carborane-containing carbohydrates, amino acids, nucleosides, nucleic acids and bases, lipids, DNA groove binders, and porphyrins .

Boron Clusters for Medical Applications

Boron clusters are the main topic of several review articles and books therefore, in this review only the basic information on boron clusters is provided; however, a little detail is given about their applications in medical field.

Structure Features of Boron Clusters

The best-known types of polyhedral boron compounds which are most often used in medicinal chemistry are icosahedral dicarbadodecarboranes ($C_2B_{10}H_{12}$), in which two CH units replaced the two BH vertices. Icosahedral carboranes have been known for more than half a century and are topologically symmetrical or globular molecules .. The molecular size of carboranes is almost larger than the volume of a rotated benzene ring and or adamantine, and the bonds of B–B and C–B in carboranes are of 12-vertex and are approximately 1.8 angstroms (Å) in length.

Carboranes have a highly delocalized electron hydrophobic surface, and are reflected to be inorganic benzenes or three-dimensional aromatic compounds . The carborane occupied almost 50% greater space than that of the rotating phenyl group. The carboranes are found in three isomeric forms due to the position of two carbon atoms within the cage as shown in Figure 1 The carborane system has the ability to enter in the substitution reaction at both boron and carbon atoms without degradation of the carborane cage. This is considered to be one of the most important features of this system for participation in various types of substitution reactions.

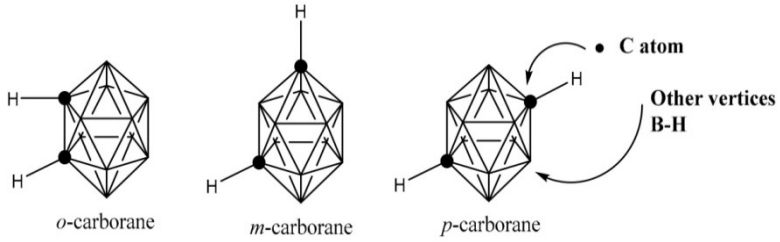

Figure 1 Structure of carborane due to the attachment of carbon at different sites.

Properties of Boron Clusters for Medical Applications

The most widely studied compounds of boron in medicinal chemistry are carboranes, which are a class of cage-structured borons. In addition to carboranes, other boron clusters of dodecaborate anion and coordination compounds, accommodating different sizes and cage-structural topographies (metallacarboranes and metallaboranes), are also of great interest. Apart from these properties of desirable biological applications, the main advantage of boron cluster and their complexes is their abiotic nature and, consequently, they are biologically and chemically orthogonal to intuitive cellular constituents and resilient to catabolism.

Boron Cluster Implication for Drug Design

The ability of boron clusters to influence the integrity and structure of a lipid membrane, and the strong binding of ionic boron clusters towards common cyclodextrins hydrophobic interior is an indication for the penetration of ionic boron clusters towards the hydrophobic environment of cell membranes. These properties are highly desirable for any type of drug design because boron clusters will not only convey water solubility to the compounds, but also allow them to penetrate the membrane. This behavior is required for a drug to reach to its target. Various studies were carried out to show the solubility of such compounds in a hydrophobic environment.Recently some of the researchers demonstrated that a fluorescent dye can penetrate and accumulate in the cellular membrane of mammalian cells.

Computational methods, to handle boron clusters used in medicinal chemistry, have been explored by some studies as reported in many of the research papers. In organic structures, force fields have been developed for each functional group and are routinely applied in docking programs. However, no such field exists for boron and, particularly, for boron clusters. Therefore, the carbon force fields were used to treat the boron cluster (almost as an adamantane) to obtain the data in the literature . The computational outcomes obtained from imitating boron clusters with carbon force fields must be considered fairly unreliable. The properties of the boron cluster are vastly different in comparison to adamantanes or carboxylic acid, which are shown by the lack of activity of adamantane-substituted *m*-, and *p*- carbonyl derivative when compared to *o*-derivative of indomethacin , or the huge difference in nicotinamide

phosphoryltransferase inhibitors comprising either a neutral carborane or an adamantane .Therefore, appropriate force fields need to be developed for ionic and neutral boron clusters before incorporating them in docking programs.

Boron Neutron Capture Therapy (BNCT)

Mechanism of BNCT

Recently, boron neutron capture therapy (BNCT) has attracted attention because it is a strategy for binary targeting and noninvasive treatment of cancer. BNCT is a possible treatment methodology for cutaneous melanomas, extramammary Paget's diseases of genital regions, vulvar melanoma, neck and head cancers, and high-grade gliomas. In clinical applications, the ^{10}B enriched boron carriers are used due to its higher neutron capture cross-section 3837 barns as compared to 0.005 barns of ^{11}B. Alpha particles are more valuable than X-ray for radiotherapy, due to their following properties (a) no need of oxygen for alpha particles to increase their biological effectiveness,(b) much higher relative biological effect (RBE) of alpha particles , and (c) Both dividing and nondividing tumor cells can be killed by alpha particles .These properties enable alpha particles tagged with B-10 to selectively kill various types of cancer cells without damaging the normal cells, that helps to prevent the side effects for patients.

Current BNCT Agents

In order for BNCT to be successful, it must get enough boron to the tumor cell . Two types of boron-containing drugs have been utilized for clinical treatment for more than 1000 patients using BNCT. These are mercaptoundecahydrodecaborane (BSH) and boronophenylalanine (BPA), whose structures are illustrated in Figure 3 []. However, the ideal dosage of either BPA or BSH or the combination of the two in the delivery system to the patients with high grade gliomas has yet to be establishedThe 4-borono-2-^{18}F-fluorophenylalanine (^{18}F-BPA) is one of the examples of a dual modality BNCT agent, which is a radiolabeled derivative of BPA as shown in Figure 3 The ^{18}F-BPA uptake for head and neck cancers can be correlated with the uptake of ^{18}F-fluorodeoxyglucose . The ^{18}F-BPA administration has also been reported for numerous types of tumors such as malignant melanomas, malignant gliomas and various head and neck cancers with tumor/normal tissue ratios ranging from 1.5 to 7.8 .

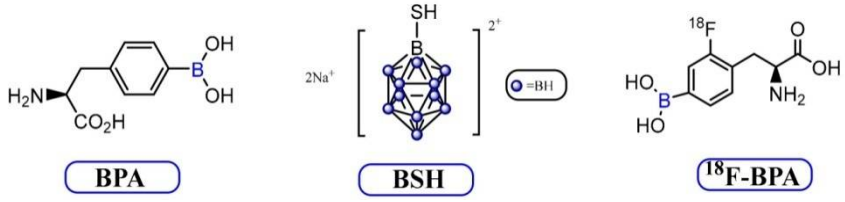

Figure 3 Structures of BPA, BSH and ^{18}F-BPA.

Development of Novel BNCT Agents

Recently, many small molecule-based boron carriers have been explored in the preclinical trials, some of which are discussed here. However, due to their insufficient accumulation of boron in tumor cells, clinical studies have been limited .

Researchers tried to overcome this problem by developing boron-containing nanoparticles for delivering at least 20 ppm of boron to the tumor cells . Some of the developed boron-containing nanoparticles have significantly improved the delivery efficacy of boron to the tumor cells and exhibited excellent tumor destruction in animal models . Nevertheless, boron-containing nanoparticles shows in vivo toxicity i.e., resistance to degradation, which is the main concern for its clinical translation . A third generation of boron-containing compounds were recently investigated. A stable boron cluster is attached to a tumor-targeting moiety via a hydrolytically stable linkage, such as low or high molecular weight agents. Boron-containing amino acids, biochemical precursors, polyhedral boranes, DNA-binding agents, mannose, glucose, ribose, galactose, fucose, lactose molecules, amines, benzamides, nitroimidazole, nicotinamides, phosphates, phosphonates, isocyanates, azulenes, phenylureas, thioureas, and deualinium derivates are included in low molecular weight agents while high molecular weight agents include liposomes, receptor-targeting agents, and monoclonal antibodies. These new generation boron-containing agents show better selective targeting properties when compared to the old generation boron compounds .However, their biological properties depend on the density of the targeted sites and very little data have been reported to date on the third-generation of boron-containing agents. Some of these newly reported boron-containing agents are discussed below.

Boron Nanoparticles with BNCT

Due to significant boron content in the pure boron nanoparticles, they are considered as potentially promising boron carrier agents. Although they can be prepared by various synthetic methods, the commonly employed techniques are pyrolysis, chemical vapor deposition (CVD), thermal plasma, reduction in solution, ball milling and arc discharge .Icten et al. reported the use of the ball milling method for the preparation of magnetic dopamine-functionalized boron nanoparticles,

which show a size range of 100–700 nm. As a result, the ball milling method produces, in one step, both boron nanoparticles and their functionalization. This group further investigated the synthesis of magnetic nanocomposites containing polyethylene glycol, Fe_3O_4 and mono or bis(ascorbatoborate) .The resulting nanocomposites had an average size of 10–15 nm and show good paramagnetic behavior at 300 K .These materials are considered to be the potential constituents for magnetic biomedicine, since the composites combined with ascorbic acid are recognized as useful antitumor and radical scavenging agents.

Recently, Sing et al. reported the synthesis of pure boron nanoparticles comprised of a liposome of azolectin-based phospholipid using the water-in-oil emulsion method. This new material contains polyethylene glycol (PEG) and poly(maleic anhydride-alt-1-octadecene) (PMAO) on the surface, and boron nanoparticles and Cy5 near infrared (NIR) fluorescent dye in the core (3PCB) as shown in Figure 4, which is considered as an alternative BNCT agent. For improvement in accumulation and targeted delivery of boron to cancer cells, a tumor-specific targeting ligand, folic acid (FA), was conjugated to PEG to produce a folate-functionalized liposome (FA-3PCB). The liposomes exhibited a zeta potential of —38.0 ± 1.5 mV and an average diameter of 100–120 nm. The targeting capability of FA-conjugated liposomes was confirmed by monitoring the cellular uptake by fluorescence microscopy. It was observed that the accumulation of FA-conjugated liposomes in C6-brain tumor cells was much higher than that of non-FA conjugated liposomes under the same conditions. The quantification of sufficient accumulation of boron in cancer cells for therapeutic benefit from BNCT was confirmed by Inductively Coupled Plasma Mass Spectrometry (ICP-MS). These liposomes show blood-brain barrier (BBB) crossing ability, excellent stability, and low cytotoxicity under physiological conditions. Thus, these liposomes are considered to be promising new boron carriers for BNCT.

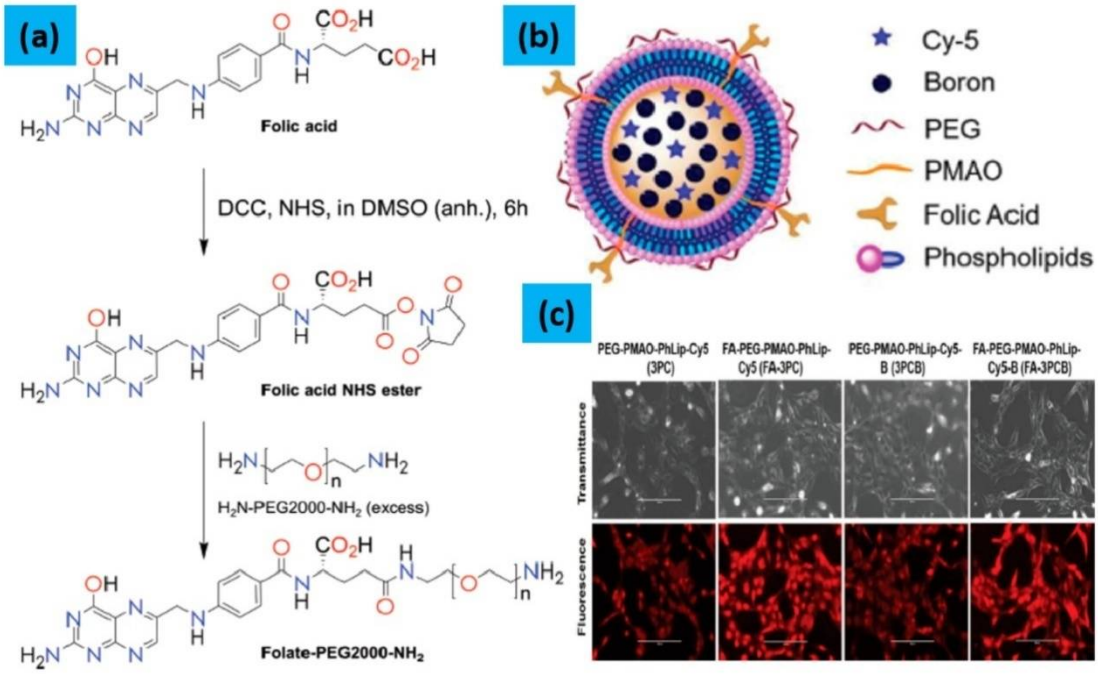

Figure 4 Schematic image of boron encapsulated liposome (Adopted from Boron-Based Amino Acids for BNCT

Most of the amino acids utilized in BNCT for precise treatment of malignant brain tumors have been reported and the review published recently reported the development of a metabolically stable boron-derived tyrosine (expressed as fluoroboronotyrosine, FBY) as a theranostic agent for both boron delivery and cancer diagnosis, leading to PET imaging-guided BNCT in the treatment of cancer as shown in Figure 9a. The computational study of FBY, Tyrosine, and BPA showed similarities between them to a greater extent. The FBY, Tyrosine, and BPA chemical structures and molecular electrostatic potential (MEP) images were shown in Figure 9b, where red indicates the distribution of negative charge and blue indicates the distribution of positive charge. The Figure 9c exhibited LAT-1 (gray) in solid ribbon

representation, the predicted structure of the LAT-1 and FBY (yellow)/Tyrosine (green)/BPA (pink) complex, LAT-1. The hydrogen bonds between LAT-1 and ligands are known to be highly conservative involving residues Trp202, Ser26, Gly27, Ile205, and Ile23 which are shown as dotted sky-blue lines. The [^{18}F]FBY was synthesized in high radiochemical purity (98%)
with high radiochemical yield (50%).
It was also demonstrated that the prepared FBY showed high similarity with natural tyrosine. The uptake of FBY in murine melanoma B16-F10 cells was L-type amino acid transporter (LAT-1) dependent and reached up to 128 μg/10^6 cells. While the FBY displayed high stability in PBS solution, the [^{18}F]FBY PET showed up to 6% ID/g in B16-F10 tumor and notably low normal tissue uptake (tumor/muscle = 3.16 ± 0.48; tumor/blood = 3.13 ± 0.50; tumor/brain = 14.25 ± 1.54). Moreover, the administration of [^{18}F]FBY tracer along with a therapeutic dose of FBY showed high accumulation in B16-F10 tumor and low normal tissue uptake.
The FBY enriched tumor having more than 20 ppm of boron and a desired correlation was established between tissue boron concentration and uptakes from PET imaging. The PET images, were recorded nearly 75 min after injection of 20 mg of FBY and [^{18}F]FBY, intravenously. While the CT and PET-CT images of the brain coronal showing the [^{18}F]FBY uptake, the representative transverse CT and PET-CT images of lung tumor and liver showed prominent [^{18}F]FBY uptake in the B16-F10 lung tumor and the increased liver retention of [^{18}F]FBY, respectively. The correlation between PET-image and boron biodistribution was established indicating the possibility of estimating boron concentration via a noninvasive approach. Using thermal neutron irradiation, B16-F10 tumor-bearing mice injected with FBY showed significantly prolonged median survival without exhibiting obvious systemic toxicity. In conclusion, FBY holds great potential as an efficient theranostic agent for imaging-guided BNCT by offering a possible solution of measuring local boron concentration through PET imaging and can be used for clinical trials.

Boron-Based Polymers for BNCT

A review, published recently by Chauhan et al. covered the syntheses of most of the boron-based polymers and their application in BNCT treatment. This review discusses a few boron-based polymers that could be useful for biomedical applicationsreported polymer composites based on boron-doped diamond powder (BDDP), which have been utilized for the treatment of dental problems. The BDDP-based polymer was considered to be the practical species, since it possesses qualities, such as hard to crack or peel, and appreciable durability even with repeated bending during electrolysis proposed the use of iRGD-modified polymeric nanoparticles for active targeted delivery of boron and doxorubicin (DOX) in BNCT. They covalently grafted the ^{10}B-enriched BSH by PEG-PCCL for the prearation of ^{10}B-polymer and then modified its surface by iRGD, followed by incorporation of DOX into polymers, physically. The resulting polymers show enhanced accumulation of ^{10}B in tumors when compared to BSH and prolonged blood circulation, along with the favorable boron concentration ratios for tumor:normal tissue (tumor:muscle = 19.49, tumor:blood = 14.11) in A549 tumor-bearing mice after 24 h of injection. The highest tumor accumulation of DOX was confirmed from both quantitative measurement and fluorescence imaging at 24 h after injecting iRGD-modified polymers However, more future studies are required to utilize these types of polymers for clinical trials. The properties, such as electrical carrier injection, transport, photoluminescence, solid-state luminescent, and reflective index make such boron-based polymers useful for molecular machines, multiphoton microscopy, and waveguides, optical data storage, cell biology, and tumor hypoxia .

Treatment of Different Cancer Tumor with BNCT

Recurrent Head and Neck Regional Tumor Treatment with BNCT

The treatment of recurrent tumors of the head and neck (HN) region by using BNCT have been applied to the second largest group of patients who had no other treatment options or reached normal tissue tolerance level. Although the number of patients treated in Taiwan, Finland and Japan by this method are relatively small, the result of this treatment shows some very remarkable clinical consequences .
Wang et al reported that a total number of 17 patients with recurrent HN tumors were treated with two doses of BNCT over 28 day intervals using BPA-F as the boron delivery agent. Although the toxicity was acceptable and the response rate was high (12 out of 17 patients), the tumor recurrence was common near or within the treatment site. Similar results were observed by Finnish and Japanese clinicians, who also treated the recurrent HN tumor patients. The resulting recurrence after treatment with BNCT might be due to the poor microdistribution of BPA-F in some region of the tumor, such as non-homogenous uptake of BPA-F by the tumor cells .

While the "best" boron delivery agent are yet to be developed, the optimal dose and delivery of BPA (alone or in grouping with BSH) is the best hope to improve the response and success rates. Consequently, reported that the uptake and microdistribution of BPA-F in HN or glioma cancer patients could be increased by pulsed ultrasound suggesting that it should be evaluated clinically as a possible option for BNCT treatment .

Recently, Jai-Cheng reported the comparison of dose distributions in gross tumor volume between BNCT alone and BNCT combined with intensity modulation radiation therapy (IMRT) for head and neck cancer. He suggested that compared to single-fraction BNCT, the multi-fraction IMRT combined with single-fraction BNCT improves the treatment conformity and homogeneity and possibly local tumor control, especially for tumor whose volume is greater than 100 cm . A recent study, published in Radiotherapy and Oncology, demonstrated the efficiency of BNCT in the treatment of locally recurrent head and neck squamous cell carcinoma (HNSCC) patients and also the factors that are favorable for the treatment response and survival .This study, comprising 79 patients with locally recurrent HNSCC, who were treated with BNCT in Finland, between February 2003 and January 2012. Some exciting findings of this study, highlighted by Ying Sun , are as follows:

CONCLUSIONS

No inherent limitations have been reported for introducing boron into pharmaceuticals. Only a few boron-containing drugs are available on the market. It is predicted that more boron-based drugs will be explored based on the development in nanotechnology, boron chemistry and newer installations of neutron resources in Asia. In this short review, some of the possible boron-based drugs were discussed, including those currently used in clinical trials.

The BNCT could serve as a promising therapy for malignant tumors, however the only clinically used boron delivery agents BPA and BSH have moderate selectivity. This encourages the search for new boron-based delivery agents. This review summarizes some of the recently reported boron delivery agents utilized with BNCT for in vivo and/or in vitro efficacy in theraupatic area. However, there are several critical issues, as itemized below, that must be addressed before applying BNCT as a useful modality for cancers treatment.

ACKNOWLEDGEMENT:

The authors acknowledge Chancellor Shri A.Srinivasan , Dhanalakshmi Srinivasan Group of Institutions, for the financial support of this work .

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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CITATION OF THIS ARTICLE

S. Suguna, R. Shanmugapriya, V. S. Sangeetha, V. Bakkiyajothi, Sathiyaraj, P.Dhatshanamoorthi, T.Sivaraman and Sneh Lata Verma: Comparative Studies on Boron Material Dopping For Medical Applications. Bull. Env.Pharmacol. Life Sci., Spl Issue [5]: 2022: 599-605.