UNIVERSITÄT LEIPZIG

Multicluster Carborane for Drug Conjugates in BNCT

Novel 1,7-Dicarba-*closo*-dodecaborane (*meta*-carborane)-derived Carboxylic Acids and Amines suitable for Peptide Modification for Application in Boron Neutron Capture Therapy (BNCT)

IDEA

Water soluble ^{10}B-enriched carboranes with low toxicity and high boron loading for use in BNCT which can be conjugated with different selective cell-targeting peptides

DEMONSTRATOR

Efficacy shown in receptor activation and internalization studies with different peptide conjugates in HEK293 cells transfected with human receptors

PROTOTYPE

Animal studies in preparation

BACKGROUND/ MEDICAL PROBLEM

Dicarba-*closo*-dodecaboranes have remarkable biological stability and two carbon atoms as well as specific boron atoms as starting point for various organic modifications. Carboranes for medicinal applications are preferably used as boron carriers to design boron neutron capture therapy (BNCT) agents. Up to now, only two boron-containing compounds have been investigated intensively in clinical trials: 4-dihydroxyborylphenyl-alanine (BPA) and the mercapto-undecahydro-*closo*–dodecaborate (BSH) anion. Due to poor targeting (BSH) and low boron loading per molecule (BPA), comparably large quantities of these boron-delivery agents must be applied for reasonable tumor uptake. However, targeted delivery of ^{10}B into tumor cells and high and selective accumulation in tumor cells are important requirements for a BNCT agent. Another main problems to date are the availability of boron compounds which exhibit the necessary water solubility and low toxicity in high concentrations and the targeted delivery of ^{10}B into the tumor cells.

POTENTIAL APPLICATION

- Flexible applicably boron compounds for non-invasive BNCT treatment

ADVANTAGES

- Water soluble carboranes
- Low toxicity in high concentrations
- Biologically stable
- Can be conjugated with different tumor-selective peptides
- Compounds can be converted to pharmaceutically acceptable salt

Project 19005

TECHNOLOGY OFFER

Picture: Colourbox

TECHNOLOGY/SOLUTION

We have developed a process to synthesize efficiently and to a high purity and yield a wide variety of carborane derivatives. Since the hydrogen atoms of boron clusters have a strong hydridic character, carboranes are extremely phobic and, therefore, poorly hydro soluble in water which can lead to aggregation of the clusters in aqueous media. This problem can be overcome by attaching hydrophilic groups to the compound backbone such as sugar derivatives that strongly increase the solubility of carborane derivatives in water.
Since the enrichment of the compounds has to be cell-specific to avoid unwanted side effects, our carborane moieties feature a carboxylic acid or amine group for conjugation with tumor-selective peptides.

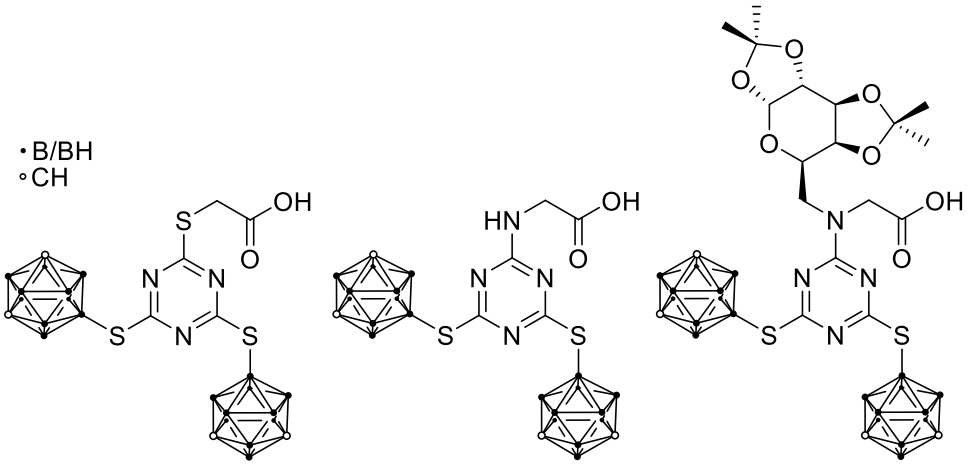

Figure
S-triazine-based carboxylic acids, functionalized with two *meta*-carboranes for high boron loading.

FURTHER READING:

S. Stadlbauer et al., *Europ. J. Org. Chem.* 2009, 6301-6310 (DOI: 10.1002/ejoc.200900813)

S. Stadlbauer et al., *Europ. J. Org. Chem.* 2010, 3129-3139 (DOI: 10.1002/ejoc.201000213)

STATUS OF PROPRIETARY RIGHTS

WO 2019/115617 A1,
positive search report

WO2009/021978 A2

COOPERATION OPTIONS

- R&D Agreement
- License Agreement
- Ownership Agreement

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