Synthesis of a Tyr^3-Octreotate conjugated [$HC_2B_{10}H_{10}$] *Closo*-Carborane: A potential new compound for boron neutron capture therapy

C. Beck, E. Schirrmacher, R. Schirrmacher, N. Trautman, F. Rösch
Institut für Kernchemie, Universität Mainz

Boron neutron capture therapy (BNCT) originates from the idea of delivering a boron compound with enriched ^{10}B to tumour cells and subsequent exposure of those cells to a thermal neutron beam inducing the $^{10}B(n,\alpha)^7Li$ nuclear reaction. The energetic ^4He and ^7Li products are eligible of injuring cancer cells. The application of boron compounds for cancer treatment, e.g., for high grade gliomas and anaplastic astrocytomas has received attention due to the fact that these tumour entities cannot be easily cured via surgery, chemotherapy or conventional radiation therapy. Clinical treatments with BNCT of patients with brain tumours in the early 1960s failed due to a lack of boron compounds with high selectivity for the target tissue. Neutron beams which could deposit the required thermal neutron flux at depths greater than a few centimetres were not available, too. Today an increasing number of boron compounds have been synthesized[3] but among those, only the 4-[^{10}B]boronphenylalanine-fructose complex (BPA-Fr) has been applied in clinical trials.[4] BPA-Fr has the disadvantage of bearing only one boron atom, which is far from being ideal considering that the concentration of ^{10}B should be exceptionally high in the target tissue. The application of boron clusters in BNCT offers a new approach for enhancing the boron density in the target tissue. Some novel boron clusters containing polyamines for example have been reported which displayed no distinct affinity to tumour cells, but may function as building blocks for further syntheses.

The use of peptides as a means of targeting is a promising approach to assess tumors having specific peptide-receptors on the surface.[1-3] Tyr^3-Octreotate is a somatostatin analogue with high affinity for the somatostatin receptor subtype-2 which is often overexpressed on the tumor surface of several tumors of the nervous system, making somatostatin analogues eligible compounds for tumor targeting.[4-6] A prerequisite for efficient BNCT is an internalisation of the boron containing compound into the target tissue.
Somatostatin analogues and conjugates have been proven to internalize into tumor cells[7] which seems to turn Tyr^3-Octreotate-boron clusters into promising compounds for delivering a high number of ^{10}B-atoms to the tumor. Taking these facts into consideration, we synthesised 4-Carboranyl-butyric-acid-Tyr^3-octreotate (figure 1) as a possible compound for the application of BNCT.

The synthesis of the boron cluster 5,6-dicarba-*closo*-dodecaboranyl hexynoic acid was achieved by reacting 6,9-bis (acetonitrile) decaborane[8] and 5-hexynoic acid methyl ester, which was easily synthesized via esterfication of 5-hexynoic acid with methanol under acidic conditions. The resulting boron labeled ester was converted into its acid by trituation with HCl and final purification via column chromatography.

The Tyr^3-Octreotate was synthesized applying standard Fmoc solid phase peptide synthesis via a batchwise procedure i.e. 4 molar equiv. of the amino acid, 4 equiv. of 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetra-methyluronium (HBTU), 10 equiv. of diiso-propylethylamine (DIPEA) in DMF. Cyclisation of the linear octapeptide via formation of the disulphide bridge was achived with 4 equiv. of thallium (III) trifluoroacetate in DMF.[9]
The final coupling of 5-hexynoic acid to the peptide was performed analoguously yielding the final fully protected compound on solid support, which was deprotected and removed from the resin and purified via preparative gradient HPLC.
In conclusion, the synthesis of a novel Tyr^3-Octreotate conjugated [$HC_2B_{10}H_{10}$] *closo*-carborane was achieved in an overall yield of 17 %. This compound might serve as a new substance for BNCT due to its possible internalisation into tumor tissue.

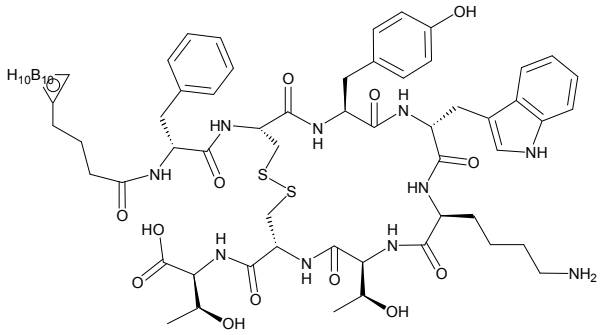

Figure 1: 4-Carboranyl-butyric-acid-Tyr^3-octreotate

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