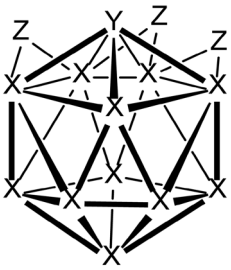
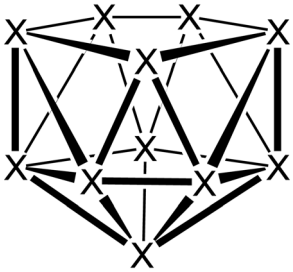
Carborane derivatives as inhibitors of human carbonic anhydrase isoenzymes

Introduction:
Human carbonic anhydrases (CAs) play essential roles in many pathological processes and several CA isoenzymes thus represent diagnostic and therapeutic targets. The development of isoform-specific inhibitor is still an important task in current medicine.

Technology description:
We have developed selective CAIX inhibitors with anticancer properties based on carborane scaffold to the structure-assisted design of novel and original inhibitors targeting therapeutically relevant isoenzymes of human carbonic anhydrase.

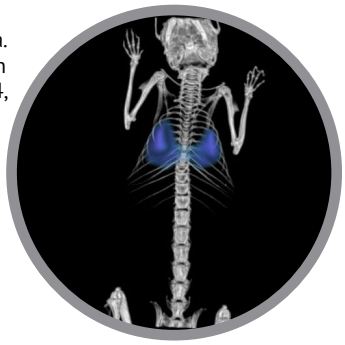




Advantages:
Novelty, in brief, is represented by the intended elaboration of carborane, heteroborane and metalloborane compounds as active-site inhibitors of CA isoenzymes. All currently used inhibitors anhydrase inhibitors contain a sulfonamide or a sulfamate moiety connected to so-called 'ring structure' which is usually a 5- or 6-membered aromatic ring or conjugated ring system containing nitrogen, oxygen, and/or sulfur heteroatoms. The 'ring structure' bears characteristics or functionality which modulates the affinity toward particular CA isoform. The use of three-dimensional boron cluster is a novel approach in the development of isoform-specific CA inhibitors. Selected sulfamides incorporate cluster with inhibitory effects toward CAs (IC50 values in the submicromolar and nanomolar range, some of the inhibitors being more than 50-times more selective toward the tumor-specific CAIX than for CAII abundantly present in normal tissues).

Development status:
Laboratory scale, data on cell lines, crystal structure, limited ADME/Tox data, *in vivo* pharmacology and pharmacodynamics.

Publications:
Mader P., A. Pecina, P. Cígler, M. Lepšík, V. Šícha, P. Hobza, B. Grüner, J. Fanfrlík, J. Brynda, P. Řezáčová. Carborane-based carbonic anhydrase inhibitors: insight into CAII/CAIX specificity from a high-resolution crystal structure, modeling, and quantum chemical calculations. BioMed research international. 2014, 389869. ISSN: 2314-6141. IF: 2.583. PMID: 25309911



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