Structure-assisted design of inhibitors of CA IX enzyme based on polyhedral boron compounds

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This poster describes structure-assisted design of inhibitors of human carbonic anhydrase IX (CA IX) based on three-dimensional carborane and cobalt bis(dicarbollide) clusters. CA IX enzyme is known to play crucial role in cancer cell proliferation and formation of metastases. The new class of potent and selective CA IX inhibitors combines structural motif of bulky inorganic cluster with an alkylsulfamido or alkylsulfonamido anchor group for Zn^{2+} atom in the enzyme active site. Detailed structure-activity relationship (SAR) study of a large series containing 50 compounds is corroborated by almost 50 high resolution structures of compounds bound to CA IX active site and the active site of CA II. Structural features of the cluster-containing inhibitors that important for efficient and selective inhibition of CA IX activity were uncovered and used in structure-assisted design. Preclinical evaluation of selected compounds revealed low toxicity, favourable pharmacokinetics and ability to reduce tumour growth. Cluster-containing inhibitors of CA IX can thus be considered as promising candidates for drug development and/ or for combination therapy in boron neutron capture therapy.

Keywords: carborane, cobal bis(dicarbollide), carbonic anhydrase, enzyme inhibition, SAR study