

Selective Carbonic anhydrase IX inhibitors

<https://www.iocbtech.cz/project/selective-carbonic-anhydrase-ix-inhibitors/>

CHALLENGE

A novel approach of cervical, colon, renal or other tumors treatment can be found among urgent and unmet medical needs in oncology. Insufficient delivery of oxygen (hypoxia) and accumulation of acidic products of the glycolytic metabolism (acidosis) is often observed in the growing tumor tissue, which is connected with increase of tumors aggressiveness, metastatic spread and poor response to therapy. Carbonic anhydrases (CAs) are in focus of scientist studding hypoxia and acidosis, because CAs catalyze reversible hydration of CO₂ and regulate pH in all cells. Carbonic anhydrase IX (CAIX) isoform is a transmembrane protein that is overexpressed in approximately 75% of cervical, colon, and 95% renal cancers, but not in the corresponding normal tissues. Selective inhibition of CAIX can cause hypoxia and begin apoptosis of tumor cells, while normal tissue remains unaffected. Moreover, CAIX is considered to be one of the best cellular biomarker of hypoxia. To our knowledge, all currently described carbonic anhydrase inhibitors face to limited CA isoforms selectivity and/or increased toxicity which reduce pharmaceutical potential of CAIX inhibitors. The use of three-dimensional (3D) carborane cluster is a novel approach in development of isoform-specific CAIX inhibitors with significant treatment potential.

TECHNOLOGY

Carboranes are very stable hydrophobic icosahedral 3D clusters with very low toxicity to normal tissues. Excellent water solubility and activity of the molecule is driven by terminal sulfamide anchor easily attached to cluster by a short linker. These carborane derivatives are bioavailable and non-toxic in mice, furthermore, the inhibitory effect (IC₅₀ in low μM and sub-μM range) is highly selective toward the tumor specific CAIX. The inhibitors of human CAIX of this invention are promising candidates for use as active compounds of pharmaceuticals for diagnostics and/or therapy of cancer diseases.

COMMERCIAL OPPORTUNITY

The technology is offered for co-development and licensing.

DEVELOPMENT STATUS

Early preclinical stage, in vitro and in vivo testing, lead optimization, toxicology.

PATENT SITUATION

Patent application in international (PCT) phase with priority date in Oct 2011.

IP OWNERS

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- Institute of Molecular Genetics AS CR, v.v.i.
- Institute of Inorganic Chemistry AS CR, v.v.i.
- Palacký University Olomouc

FURTHER READING

Brynda J., et al. Carborane-based carbonic anhydrase inhibitors. *Angew Chem Int Ed Engl.* 2013 52(51):13760-3.