MS04 Structure in Cancer Biology

MS4-04
Structure-assisted design of carborane inhibitors of human carbonic anhydrase IX
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Abstract
Carbonic anhydrases (CAs) are zinc metalloenzymes playing an important role in many physiological processes. Several CAs are also involved in various pathological processes in humans and represent thus targets for drug development. Specifically, human carbonic Anhydrase IX (CA IX), isoform overexpressed in solid hypoxic tumours, is a target for cancer therapy and diagnostics. We have previously identified carboranes as a promising class of specific inhibitors of CA IX [1]. Here we report recent advances in the structure-assisted design of carborane and metallacarborane inhibitors targeting CA IX.

We chose carboranes, three-dimensional scaffolds, which act as as space-filling fragments. We modified boron cages to synthetize carboranes and metallacarboranes substituted by sulfamide, sulfonamide or sulfamate groups, i.e. functions known to bind tightly to the zinc atom in the active site of CAs. Consequently, the small library of ca. 70 substituted carboranes and metallacarboranes was. Several compounds exhibit selective inhibitory activity toward CAIX with Ki values in low nanomolar or even picomolar range. Selected inhibitors were tested for their effect on tumor growth in BALB/c mice orthotopically implanted with 4T1 cells and SCID mice subcutaneous transplanted with HT-29 cells.

References
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Structure of CA with Carboran Inhibitor