Metallacarboranes as Specific and Potent Inhibitors of Medicinally Revelant Pharmaceutical Targets

Petr Cigler[1,3], Milan Kozisek[1], Jana Pokorna[1], Jaromir Plesek[2], Bohumil Gruner[2], Pavlina Rezacova[4], Michal Mares[1], Jochen Bodem[5], Hans-Georg Kraeusslich[5], Vladimir Kral[3] and Jan Konvalinka[1]

[1]Institute of Organic Chemistry and Biochemistry, Academy of Science of the Czech Republic, Prague, [2]Institute of Inorganic Chemistry, Academy of Science of the Czech Republic, Rez near Prague, [3]Department of Analytical Chemistry, Institute of Chemical Technology, Prague, [4]Institute of Molecular Genetics, Academy of Science of the Czech Republic, Prague, [5]Department of Virology, University of Heidelberg, Germany

Boron cluster compounds and their metallocomplexes are characterized by exceptional hydrophobicity, delocalized negative charge, rigid geometry and remarkable thermal and chemical stability. Due to such properties, they are predetermined as proper pharmacophores, which could possess strong interactions with receptors, combining hydrophobic and electrostatic effects.

Here we present the discovery of completely artificial non-peptide and non-peptidomimetic class of inhibitors of several medicinally relevant enzymes based on metallacarboranes. They exhibit IC50 in nanomolar/micromolar range towards various human and viral enzymes that are proven pharmaceutical targets both in the assays with recombinant enzymes and in tissue cultures. The inhibition kinetics of the compounds was carefully analysed using fluorogenic and chromogenic cognate substrates and, consequently, competive, non-competitive as well as acompetitive inhibitors were found. The toxicity of novel compounds, mode of binding to the corresponding targets and the potential of metallacarboranes as a novel pharmacophore will be discussed.