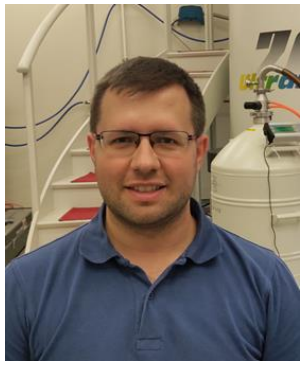
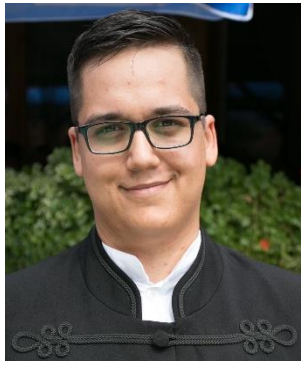
DrugRas: design, synthesis, testing and characterization of compounds against oncogenic K-Ras mutants

András Perczel[1], Gyula Pálfy[1], István Vida[1], György Miklós Keserű[2], Péter Ábrányi-Balogh[2], Zoltán Orgován[2], László Petri[2]
[1]ELTE Laboratory of Structural Chemistry and Biology, [2]RCNS Medicinal Chemistry Research Group






Synthesis / method / protocol: Covalent fragment library screening *via* NMR. Ligand-side confirmation of the covalent action by ^{19}F-NMR and protein-side confirmation of the binding-site by ^{1}H,^{15}N-HSQC spectra.

Scientific Goal: Identification of warheads suitable for covalent modification of K-Ras-G12C oncogene mutant, then combining the appropriate warheads with optimized scaffolds derived from a known K-Ras-G12C inhibitor as well as our own research.

Result: We identified 15 of the 28 investigated warheads suitable for covalent modification of K-Ras-G12C-GDP confirmed by both ligand based ^{19}F-NMR and protein based ^{1}H,^{15}N-HSQC spectra paralelly. Using the latter method further 6 compounds of 7 candidates were found to bind to K-Ras-G12C.