MS04-1-1 Structure-assisted drug discovery: cyclin-dependent kinase 2
#MS04-1-1

S. Djukic [1], J. Škerlová [1], M. Peřina [2], J. Radek [2], V. Kryštof [2], P. Řezáčová [3]
[1]Institute of Organic Chemistry and Biochemistry - Prague (Czech Republic), [2]Palacký University - Olomouc (Czech Republic), [3]Insitute of Organic Chemistry and Biochemistry - Prague (Czech Republic)

Abstract
Cyclin-dependent kinase 2 (CDK2) is a Ser/Thr protein kinase that is active during G1 and S phase of the cell cycle and works as check point control. During the G1 phase of the cell cycle, it is activated by binding to cyclin E and in S phase by binding to cyclin A [1]. It is dispensable in healthy cells, as other CDKs can take over its role, but it is essential for proliferation of cancer cells. This makes CDK2 an interesting target in discovery of anticancer compounds [2].We are using X-ray crystallography in the structure-assisted drug discovery approach to study CDK2/cyclin A complex in design of new inhibitors of this protein and to understand the protein-inhibitor interactions.Enzyme was prepared by heterologous expression in E. coli and purified in high yields and purity necessary for crystallographic studies. Crystallization conditions for CDK2/cycA were identified through wide screening and optimization. Diffraction data have been collected on BL14.1 at the BESSY II electron storage ring operated by the Helmholtz-Zentrum Berlin and crystal structures were determined at high resolution (1.7-2.5 Å). Structural study of the crystal structures allowed us to analyse protein-inhibitor interactions and to identify essential residues in the active site (Figure1).The knowledge we obtained from these structures will play an important part in future design of inhibitors specific to CDK2 and other enzyme isoforms.

References
1.Echalier A, Endicott JA, Noble ME: Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics 2015, 1804 (3): 511–9.

2. Wood DJ et al. Cell Chemical Biology. 2018; 26 (1): 121–130.e5.

3. Dayal N et al. J Med Chem 2021; https://doi.org/10.1021/acs.jmedchem.1c00330

Figure1: Crystal structure of CDK2/cyclin A in com