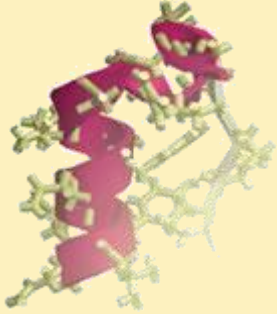

HAS-ELTE Protein Modelling Group

Web: http://www.chem.elte.hu/departments/protmod/

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Members: **Prof. Gábor Náray-Szabó (former head of the Group)**
Prof. Pál Sohár,
Dr. Tamás Beke,
Dr. Viktor Farkas,
Dr. Virág Zsoldosné Mády,
Dr. Veronika Harmat,
Annamária Ángyán

Main research topics :

- Structure, dynamics and interactions of proteins, (crystallography, NMR and other spectroscopic methods)
- Structure and dynamics of protein building blocks (quantum chemical and spectroscopic methods)
- Structure based development of biologically active compounds
- Molecular modelling
- Biotechnology and chemical syntheses
- Chemical crystallography

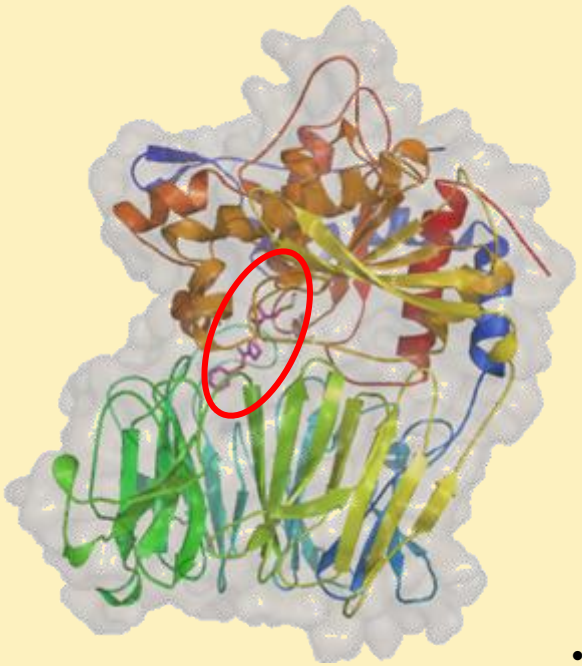
X-ray crystallography: a guide in structure based design of biologically active compounds

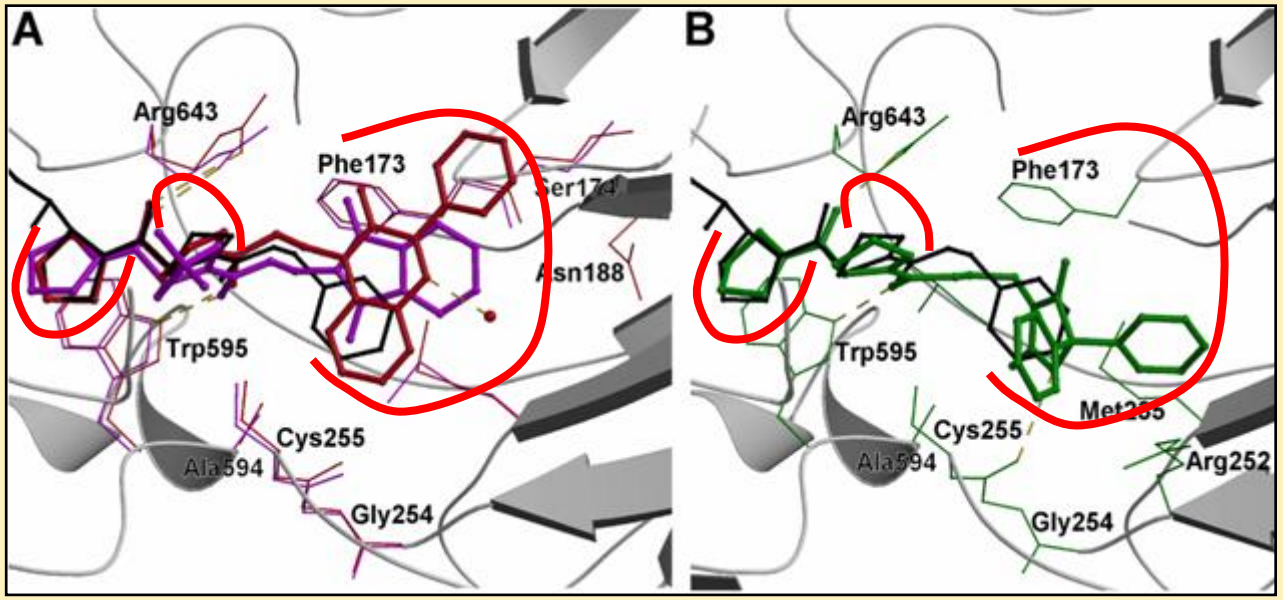
Crystallographic studies on prolyl-oligopeptidase (co-operation: Sanofi-Aventis)

It degrades proline-containing neuropeptides involved in the processes of memory and learning, it is thought to be involved in depression and control of blood-pressure.

R-Pro-(decarboxy-Pro) type inhibitors, study on structure-activity relationships:

- The optimal length of the linker chain of the R-group depends on the shape of the group in the terminal position.





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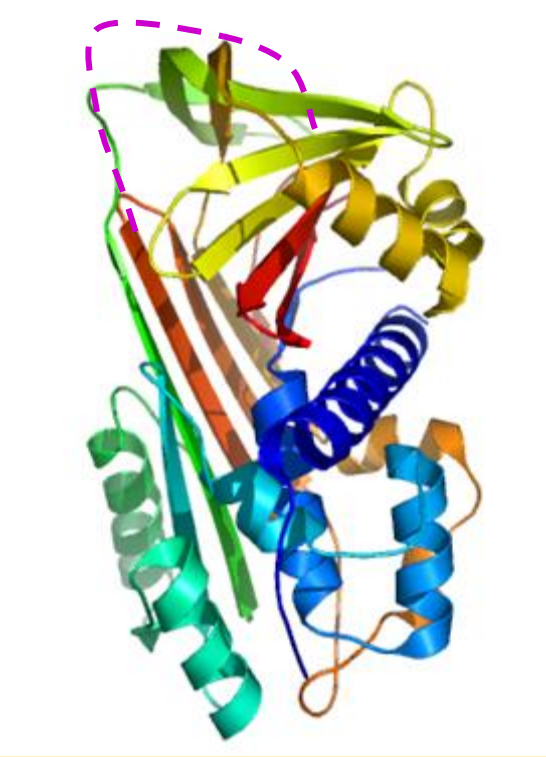
Structure-function relationships by protein crystallography and molecular modelling

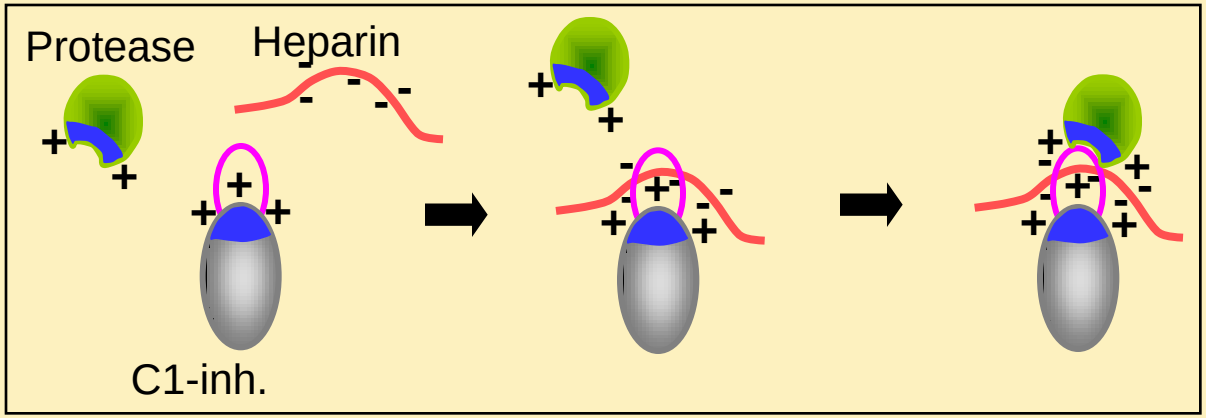
Crystallographic studies on C1-inhibitor (co-operation: HAS Institute of Enzymology)

A major downregulator of inflammatory processes in blood. Genetic deficiency of C1-inhibitor results in hereditary angioedema potentially lethal disease.

- The crystal structure helped identifying the heparin binding site of C1 inhibitor.
- Understanding the accelerating effect of heparin on the C1 inhibitor/protease reaction by a novel mechanism.



Sandwich mechanism: the negatively charged heparin (red) a compensates the positive charges (blue) of the interacting proteins.

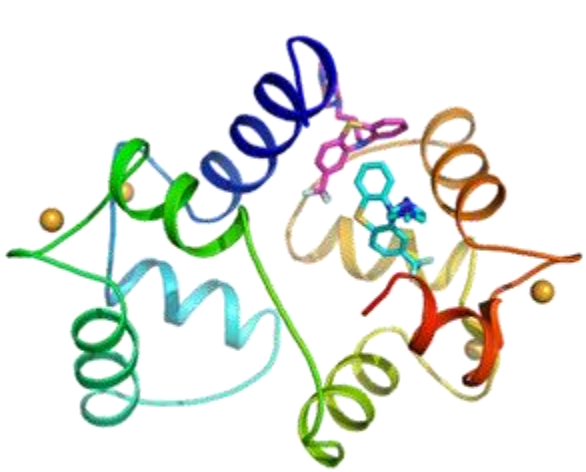


- Beinrohr L et al J Biol Chem 282: 21100 - 21109 (2007)

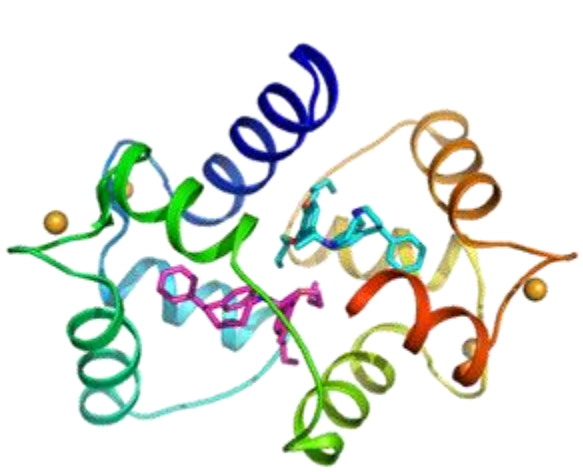
Ligand binding of proteins at atomic level

Crystallographic studies on calmodulin-antagonist complexes (co-operation: HAS Institute of Enzymology)

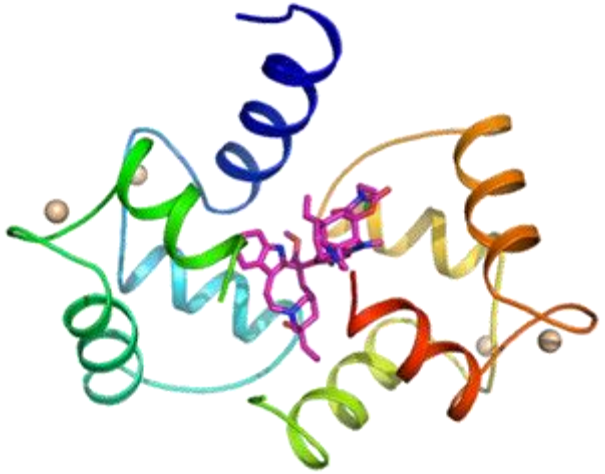
- The complexes formed with small molecules of different molecular frames show differences in the residues involved in binding. Most of the contacts are hydrophobic. In contrast to the other two compounds, KAR-2 is not a competitive antagonist, which is explained based on the structure.



calmodulin/TFP
1:2 complex



calmodulin/arylalkylamine
1:2 complex

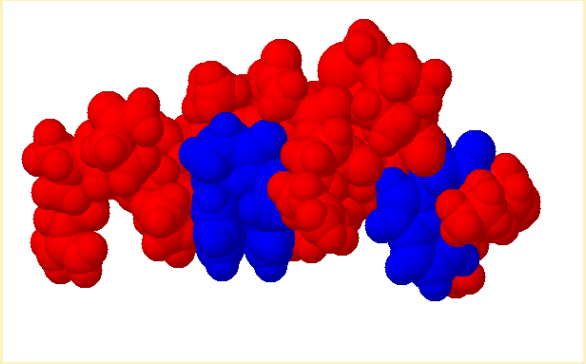


calmodulin/KAR-2
1:1 complex

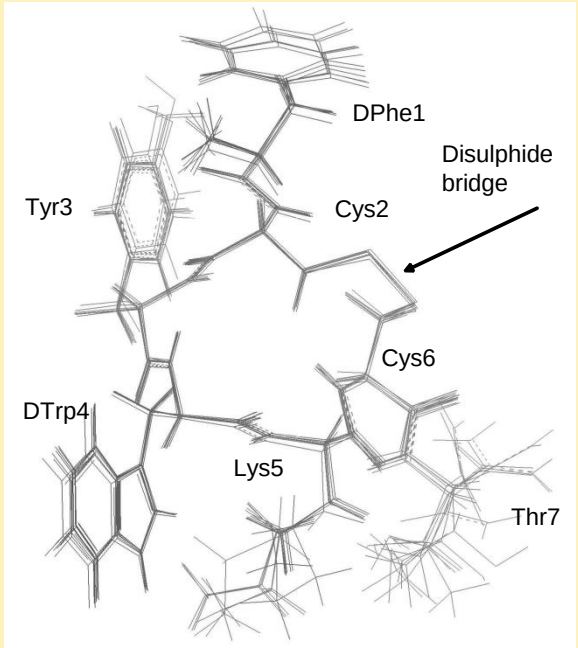
- Horvath I et al J Biol Chem 280: 8266-8274 (2005)
- Harmat V et al J. Mol Biol 297: 747-755 (2000)
- Vértessy BG et al Proteins Struct Funct Gen 28: 131-134 (1997)

NMR-studies on dynamics, structure and stability of peptidic drug candidates

- **Penetratin** have a possible role in the transport of drug molecules to the nucleus.
  Structures of the natural and mutant forms (NMR) revealed structure-function relationships.



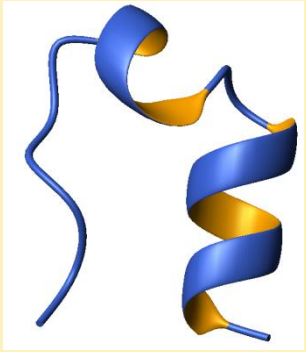
- **TT-232** is a somatostatin-analogue in clinical phase.
  Solving the its structure in water solution served better understanding the mechanism of its action.



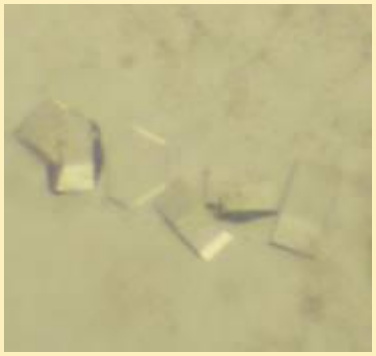
- Simon Á et al Biochem Biophys Res Comm 316: 1059-1064 (2004)
- Letoha T et al J Mol Recognit 16: 272-279 (2003)
- Czajlik A et al J Pept Sci 8: 151-171 (2002)

Cloning, expression, and crystallization of proteins

- Preparation and purification of protein samples by molecular biology methods for NMR methods and X-ray crystallography
- Isotope labelling
- Expression of oligopeptides and miniproteins in fusion systems (fusion partner: ubiquitin or GFP)
- Crystallization using vapour diffusion methods
- High throughput crystallization using crystallization robot



Tc5b, a 20 residue miniprotein was expressed in GFP fusion system for NMR spectroscopic studies

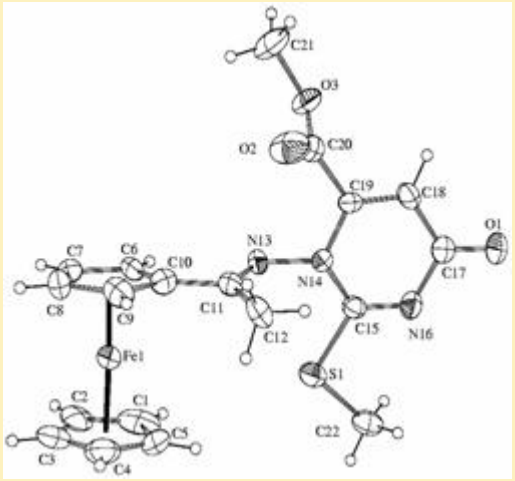


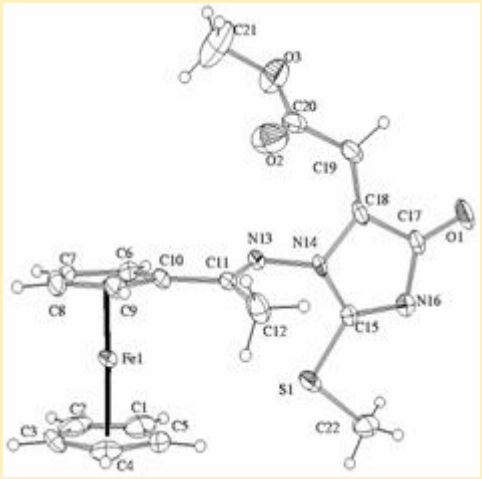
Crystals of a calmodulin complex, acylpeptide hydrolase, and MASP-2 grown in hanging drops

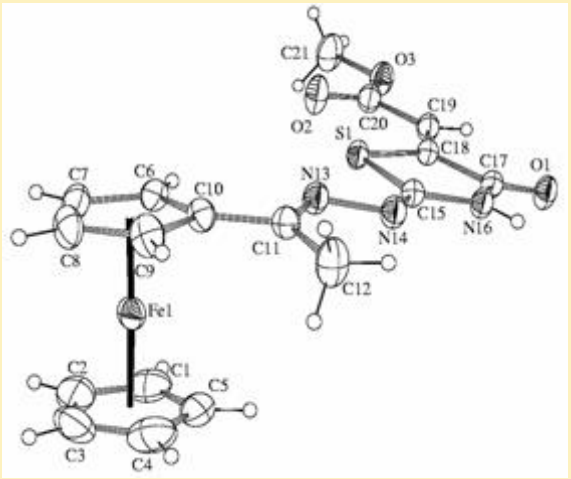
Synthesis of biologically active ferrocene derivatives

Ferrocenyl-substituated tiazolones,

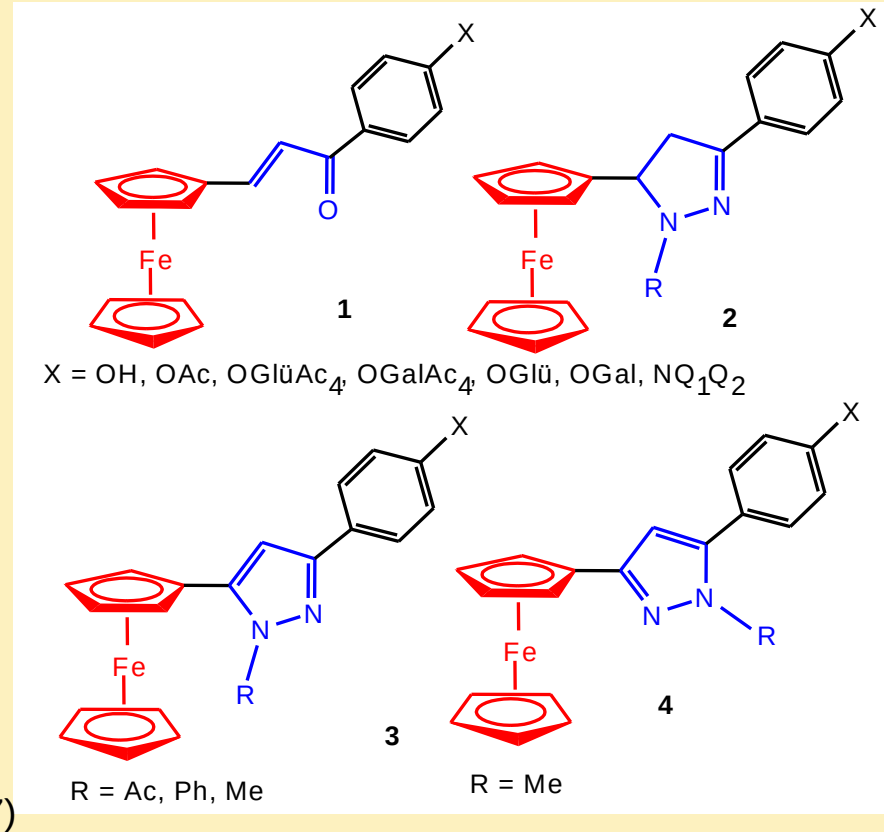
1,3-tiazinones, pirimidones and imidazolones.





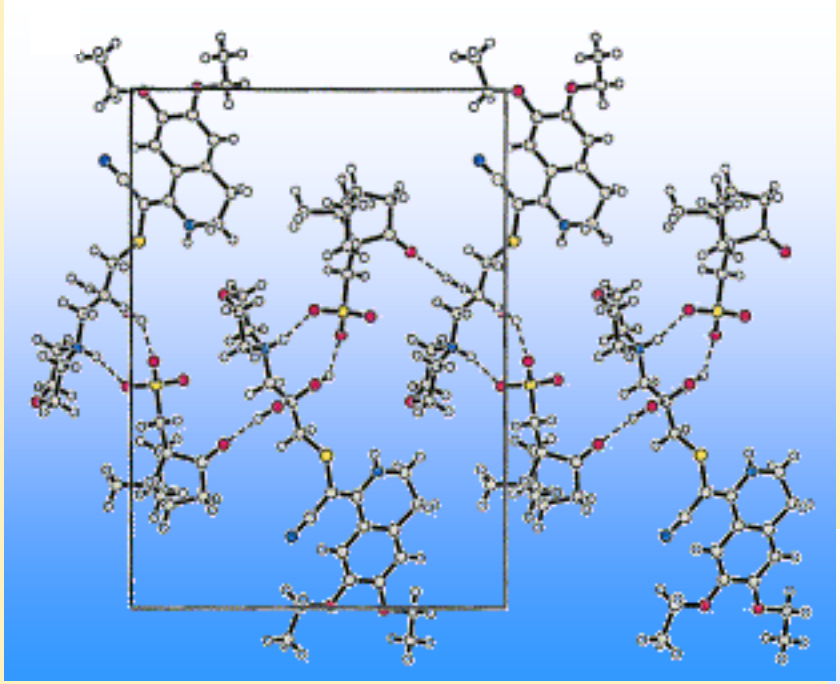


Biologically active ferrocenyl-calcones and ferrocenyl-pirazoles. Some compounds exhibited remarkable antiproliferative effect against human leukemia cells (HL-60) in vitro.



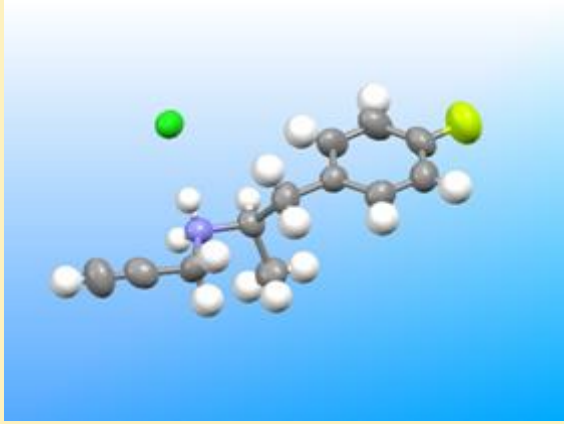
- Miklan Z et al Biopolymers (Pept. Sci.) 88: 108-114 (2007)
- Zsoldos-Mády V et al Chem Med Chem 1:1119-1125 (2006)

Chemical crystallography:
determining absolute configuration, studies on molecular recognition, structure-reactivity relationships

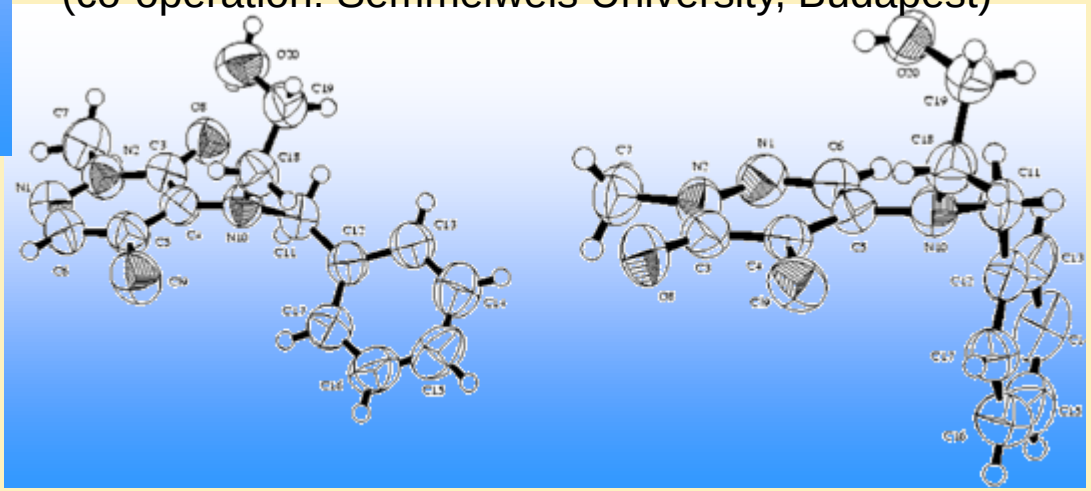


Structural basis of solid solution formation during chiral resolution
(co-operation: Sanofi-Aventis)

Metabolites of anti-parkinson drugs
(co-operation: Sanofi-Aventis)



Aminopyridazinone regioisomers
(co-operation: Semmelweis University, Budapest)



- Anwair MAS et al J. Agricult. Food. Chem. 51: 5262-5270 (2003)
- Barabas O et al Tetrahedron-Asymm.11, 4061 (2000)
- Simon K et al Acta Cryst C54: 811-813 (1998)

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Gal P, Harmat V, Kocsis A, Bian T, Barna L, Ambrus G, Vegh B, Balczer J, Sim RB, Naray-Szabo G, Zavodszky P:
A true autoactivating enzyme - Structural insight into mannose-binding lectin-associated serine protease-2 activations
J Biol Chem **280**, 33435-33444(2005) impact factor: 5.854 number of citations: 19

Wiles AP, Shaw G, Bright J, Perczel A, Campbell ID, Barlow PN:
NMR studies of a viral protein that mimics the regulators of complement activation
J Mol Biol **272**, 253-265(1997) impact factor: 5.673 number of citations: 90

Náray-Szabó G, Ferenczy GG:
Molecular Electrostatics
Chem Rew **95,** 829-847(1995) impact factor: 14.513 number of citations: 164

Perczel A, Hollósi M, Tusnády G, Fasman GD:
Convex constraint analysis: a natural deconvolution of circular dichroism curves of proteins.
Protein Eng **4,** 669-679(1991) impact factor: 3.224 number of citations: 246

Warshel A, Náray-Szabó G, Sussman F, Hwang JK :
How do serine preoteases really work
Biochemistry **28**, 3629-3637(1989) impact factor: 4.240 number of citations: 321

Protein building blocks:

Perczel A, Hudaky P, Palfi VK:
Dead-end street of protein folding: Thermodynamic rationale of amyloid fibril formation
J A Chem Soc **129**, 14959-14965(2007) impact factor: 7.885 number of citations: 7

Perczel A, Angyan JG, Kajtar M, Viviani W, Rivail JL, Marcoccia JF, Csizmadia IG:
Peptide models.1. Topology of selected peptide conformational potential-energy surfaces (glycine and alanine derivatives)
J Am Chem Soc **113,** 6256-6265(1991) impact factor: 4.585 number of citations: 190

Synthesis and characterization of compounds with biological activity:

Wamhoff H, Hohmann C, Sohar P:
An efficient synthesis of thioisomunchnones derived from uracils and uridine: Novel type of mesoionic nucleosides
Org Lett **2**, 581-584(2000) impact factor: 3.367 number of citations: 4

Stájer G, Csende F, Bernáth G, Sohár P:
Preparation and steric structure of tricyclic and tetracyclic saturated or partially saturated 1,3-heterocycles containing a saturated isoindolone moiet
Heterocycles **37**, 883-890(1994) impact factor: 0.982 number of citations: 34