ÚOCHB AV ČR

ÚSTAV ORGANICKÉ CHEMIE A BIOCHEMIE
AKADEMIE VĚD ČESKÉ REPUBLIKY
INSTITUTE OF ORGANIC CHEMISTRY AND BIOCHEMISTRY
ACADEMY OF SCIENCES OF THE CZECH REPUBLIC

Institute of Organic Chemistry and Biochemistry

Academy of Sciences of the Czech Republic

VÝZKUMNÉ CENTRUM
UOCHB &
GILEAD SCIENCES
GSRC
GILEAD SCIENCES
& IOCB
RESEARCH CENTRE

Institute of Organic Chemistry and Biochemistry

Academy of Sciences of the Czech Republic

Zdeněk HOSTOMSKÝ
Director

Iva Pichová
Vice-director for Research

Martin Fusek
Vice-director for Strategic and Development

Božena Petschová
Vice-director for Economics

Jiří špička
Vice-director for IOCB Campus Development

CONTENTS

INTRODUCTION

This year the Institute of Organic Chemistry and Biochemistry celebrates 60 years of its existence. I can sympathize with the anniversary as I have recently reached the same age myself, just several months after I became its seventh director on June 1, 2012. Unlike the frailties and transience of an individual human life, however, the Institute at sixty is full of creative energy, new ideas, and it's confidently looking into a bright future. Here is how its present state appears from my perspective.

The Institute continues with the organizational structure introduced in 2007 when it was converted into a Public Research Institution and its internal hierarchy adopted the flat structure model, hence increasing the roles and responsibilities of group leaders where strong scientific personalities are to direct their own programs.

Several important bodies were also created at that time and they continue their active roles in shaping the Institute. The Supervisory Board takes control of the main, mostly economical, decisions of the Institute management. The Board of the Institute prepared a visionary strategic concept of the Institute for the period of 2011 to 2020, and this document is still important for the ongoing effort of defining our future.

The International Advisory Board is the third important body which has a critical role in maintaining the high standards and objectivity in evaluating the quality of science at the Institute. The IAB was fully involved in evaluation of all the research groups in 2012. As a result of this evaluation, three groups have ceased to exist by the end of that year. Two additional groups have ended their activities in this period: one due to the untimely death of Dr. Schröder, the other with Dr. Šrogl transferring to the University of North Carolina.

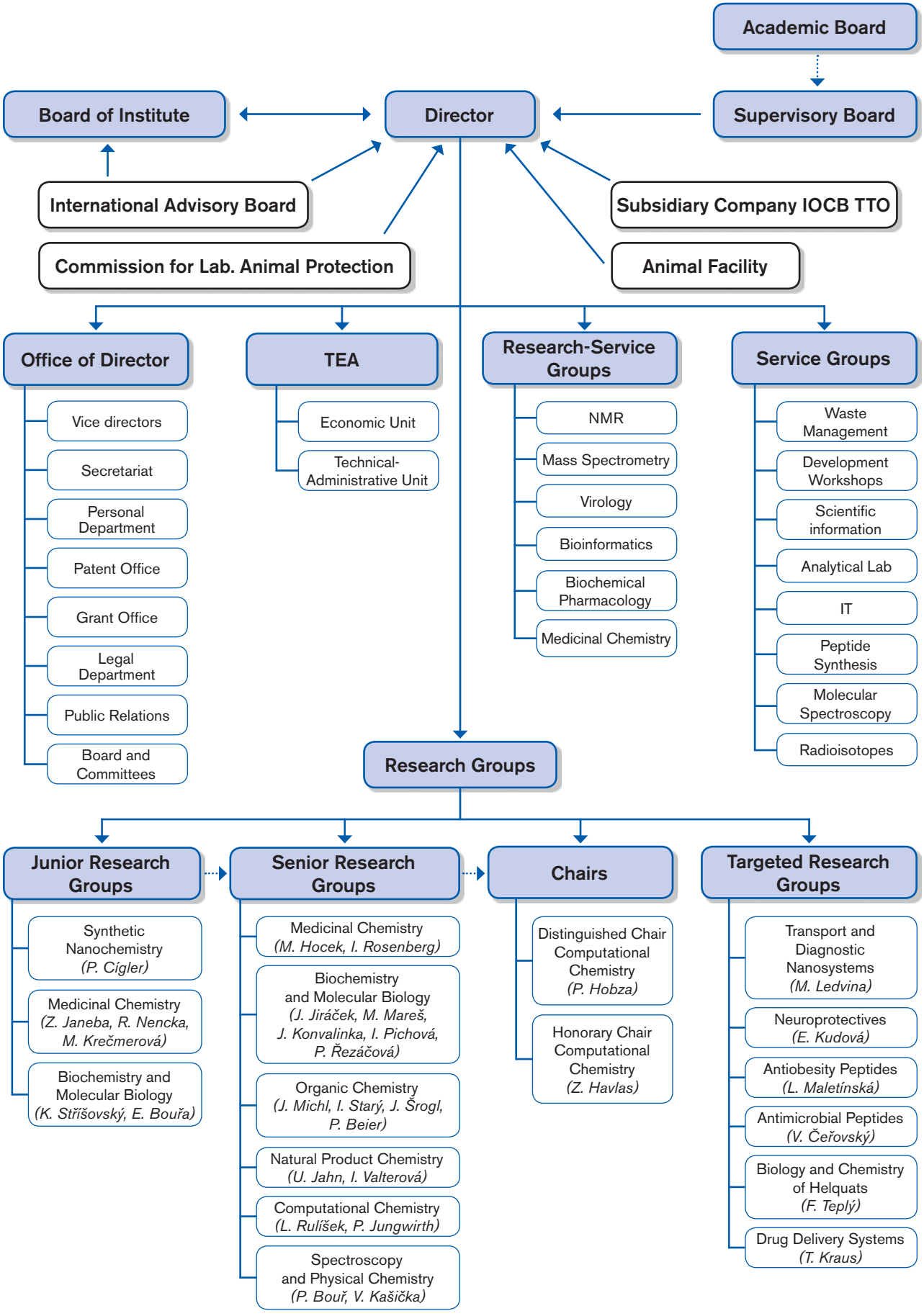
As we pursue a dynamic model of our organizational life, we are launching new junior research groups through a competitive selection process, with the full involvement of the International Advisory Board. This is an excellent opportunity to bring in new talent and exciting new projects to our organization. Three new junior research groups have started in 2012, and several more are about to be established as we talk to selected candidates from the latest series of interviews.

The main ambition of the Institute has always been to be viewed as a premier place for basic research in organic chemistry and biochemistry, as well as in theoretical chemistry. At the same time, the Institute has been traditionally quite successful in discovering new biologically active chemical compounds which were subsequently developed into useful pharmaceutical products. This tradition makes the institute a unique place which recognizes and values the culture of transferring results of high quality research into practical applications. Inspired by and building on past successes, we decided to systematically strengthen this type of research by introducing a new category of research groups which would concentrate on targeted research. These targeted research groups can be described as internal spin-off units, which are financed from non-public sources of the Institute's budget. Currently we have 6 targeted research groups and they are managed through IOCB TTO, the Institute's daughter company established to help with commercialization of intellectual property arising from the IOCB research.

The outer appearance of the Institute site in recent years has been dominated by ongoing remodeling of its campus. The work started in 2009 with the reconstruction of building C and its biochemistry laboratories. The construction of the brand new building B started in June 2012 and its completion by the end of 2013 is in sight. The futuristically designed building B will house modern laboratories for organic synthesis. The ongoing thorough remodeling of the original building A should be finished in 2016. We would like to see this concluding event as symbolically marking a complete transformation, both internal and external, of IOCB into a world-class research institution.

Zdeněk Hostomský
Director of IOCB AS CR

INSTITUTE STRUCTURE



BOARD OF INSTITUTE

Chairman: **Lubomír RULÍŠEK**

Vice-Chairman: **Iva PICHOVÁ**

Internal Members:
Ullrich JAHN
Zlatko JANEBA
Jiří JIRÁČEK
Radek POHL

External Members:
Jitka MORAVCOVÁ
Institute of Chemical Technology, Prague

Tomáš OBŠIL
Charles University in Prague

Hana SYCHROVÁ
Institute of Physiology AS CR

Secretary:
Bohumír KOUTEK
IOCB AS CR

SUPERVISORY BOARD

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Jiří RÁKOSNÍK
Institute of Mathematics AS CR

Vice-Chairman:
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IOCB AS CR

Members:
Jan ZIMA
Academy Council AS CR

Tomáš RUML
Institute of Chemical Technology, Prague

Pavel ŠEBEK
Zentiva, a.s.

Pavel MERTLÍK
The Banking Institute
College of Banking, Prague

Secretary:
Bohumír KOUTEK
IOCB AS CR

INTERNATIONAL ADVISORY BOARD

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Macromolecular Crystallography Laboratory
National Cancer Institute at Frederick, USA

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ETH Zurich
Institute of Pharmaceutical Sciences,
Switzerland

Wilhelm BOLAND
Max-Planck-Institut für Chemische Ökologie, Germany

Cynthia J. BURROWS
University of Utah
Department of Chemistry, USA

Burkhard KÖNIG
Institut für Organische Chemie
Universität Regensburg, Deutschland

Hans-Georg KRÄUSSLICH
Department of Infectious Diseases – Virology
University Hospital Heidelberg, Germany

Marko D. MIHOVILOVIC
Vienna University of Technology
Institute of Applied Synthetic Chemistry, Austria

Barry V. L. POTTER
University of Bath
Department of Pharmacy and Pharmacology, UK

Walter THIEL
Max-Planck-Institut für Kohlenforschung, Germany

Frank TUREČEK
Department of Chemistry
University of Washington, USA

A BRIEF HISTORY OF IOCB...

After World War II, when the activity of universities was renewed, a group of chemical enthusiasts was formed at the Faculty of Chemicotechnological Engineering of the Czech Technical University under the leadership of professor František Šorm.
In 1951, the group moved to the building at Flemingovo square. The building was constructed between 1923 and 1929. Central Chemical Institute was formed. Agricultural research was replaced by the "aroma" of chemical experiments... Formally, the Institute was established on January 1, 1953. Its name was changed to the Institute of Organic Chemistry of the Czechoslovak Academy of Sciences.

The Institute has had many names in history:

- Institute of Technology of Organic and Explosive Substances
- Institute of Technology of Organic Substances
- Institute of Organic Technology (which still exists at the Institute of Chemical Technology)
- Central Chemical Institute
- Institute of Organic Chemistry of the Czechoslovak Academy of Sciences
- Chemical Institute of the Czechoslovak Academy of Sciences (after 1955)

- Institute of Organic Chemistry and Biochemistry of the Czechoslovak Academy of Sciences (1960 – 1992)
- Institute of Organic Chemistry and Biochemistry of the Academy of Sciences of the Czech Republic (1993 – 2006)
- Institute of Organic Chemistry and Biochemistry of the Academy of Sciences of the Czech Republic, v.v.i. (since 2007)

The greatest credit for establishing and developing the Institute belongs to professor **František Šorm** who became the secretary general of the Academy of Sciences and later its chairman.

IN MEMORIAM

Prof. Dr. Antonín Holý, DrSc., Dr.hc. mult (*September 1, 1936, Prague, †July 16, 2012, Prague, Czech Republic)

Antonín Holý studied organic chemistry from 1954 to 1959 at the Faculty of Science of Charles University in Prague. From 1960 he trained at the Institute of Organic Chemistry and Biochemistry (IOCB) of the Czechoslovak Academy of Sciences in Prague and has been a researcher there since 1963. He became the Institute's lead scientist in 1967, and from 1983 headed its working group for nucleic acids. In 1987 he became chief of the Department of Nucleic Acid Chemistry and from 1994 to 2002 he was director of the IOCB. Antonín Holý was promoted to Distinguished Chair of the Institute of Organic Chemistry and Biochemistry in 2007. He published over 650 scientific papers and filed 60 patents.

Areas of main scientific interest include: nucleic acid chemistry - sugar-modified nucleoside analogs, phosphorus-modified nucleotide analogs; enzymes of nucleic acids metabolism: their inhibitors, virus-specific enzymes; biological applications of modified nucleic acids components: antivirals, cytostatics; development of drugs, anti-AIDS drugs.

Several antiretroviral drugs based on Holý's discoveries have been licensed (US biopharmaceutical company Gilead Sciences). In 1996, Vistide was approved for production in the United States and European Union. Viread (tenofovir) was approved in the USA in 2001 for the treatment of AIDS, and Hepsera was approved in 2003 for the treatment of hepatitis B. Truvada, a combination of Viread and emtricibatine, was approved in 2006 for use in the USA. His death occurred two months after America's Food and Drugs Administration approved Truvada for treating HIV, the same day that FDA approved Truvada for HIV prevention.

Antonín Holý was one of the best Czech scientist and inventor. His work was awarded by State Prize for Chemistry (1984), Hanuš's Medal of the *Czech Chemical Society* (1998), Descartes Prize of the European Union (2001), The Medal of Merit of the Czech Republic (2001), Honorary membership in the Rega Institute for Medical Research, Catholic University of Leuven, Belgium (2003), Award *Praemium Bohemiae* (2004), Medal of the Czech Academy of Sciences: *De scientia et humanitate optime meritis* (2004), Member of the European Academy of Sciences and Arts (2006), State Prize "Czech Head" (2007), Honorary professor of organic chemistry at University of Manchester (UK) (2008), Prof. Holý was declared an *Ambassador of Excellence* by the Secretary General of the European Union (2010).

Doc. Dr. Detlef Schröder (*June 24, 1963, Wilster, Germany †August 22, 2012, Prague, Czech Republic)

Detlef Schröder was born in Wilster, Germany, and studied chemistry at Technical University Berlin (TU Berlin), Germany, graduating in 1989. He completed his Ph.D. at the same university under the supervision of Professor Helmut Schwarz. From 1989 – 2006, he worked as a scientific researcher at the Institute for Organic Chemistry of the TU Berlin. During this time, he also worked towards his Habilitation, which he gained in 2007 from the same university. In 2006, Schröder moved to the Institute of Organic Chemistry and Biochemistry, Prague, Czech Republic, as Senior Scientist. He was promoted to Group Leader for Spectroscopy and Physical Organic Chemistry there in 2007 and to Distinguished Chair of the Institute of Organic Chemistry and Biochemistry in 2011.

Detlef was a well-respected chemist in the area of mass spectrometry. His work involved increasing our fundamental understanding of diatomic molecules, organic reaction mechanisms, and inorganic chemistry and included questions of astrochemical interest as well as biochemical problems. He served as Editor-in-Chief of the *International Journal of Mass Spectrometry*. In 2011 he was elected a member of the Learned Society of the Czech Republic. He published hundreds of papers in prestigious journals.

Dr. Ilya M. Lyapkalo (*July 19,1968, Podolsk, Russia †September 10, 2010, Prague, Czech Republic)

Dr. Lyapkalo received his Masters Degree from Mendeleev University of Chemical Technology in Moscow (1993), and Ph.D. from Zelinsky Institute of Organic Chemistry in Moscow (1996). He continued as Research Scientist in the Zelinsky Institute till 1999. Then he moved to Berlin, where he worked as Humboldt Research Fellow at the Freie Universität till 2003. In 2003 he accepted position of Senior Research Fellow in the Institute of Chemical and Engineering Sciences in Singapore. In 2006 he succeeded in international competition for senior team leader position in the Institute of Organic Chemistry and Biochemistry in Prague and started building his team in Prague.

Ilya was a synthetic organic chemist oriented to transition metal catalysis, target synthesis, synthesis of new materials, process optimization and modeling. In our Institute he worked on two major projects, synthesis and biomedicinal studies of tripyrrole alkaloids and chiral Lewis acids as organocatalysts for enantioselective Aldol reaction. Ilya was a very pleasant coworker, highly educated and motivated, willing to discuss chemistry with everybody. His enthusiasm for chemistry influenced largely his group and colleagues.

RESEARCH CENTRES

Gilead Sciences & IOCB Research Centre

The establishment of the GSRC recognizes the Gilead continued partnership with IOCB and allows for expanded research efforts.
The research groups participating in GSRC.

Medicinal Chemistry

Michal Hocek
Radim Nencka
Zlatko Janeba

Chemistry of Natural Products

Ullrich Jahn

Biochemistry and Molecual Biology

Iva Pichová
Jan Konvalinka

Computational Chemistry

Zdeněk Havlas
Lubomír Rulíšek
Pavel Hobza

VÝZKUMNÉ CENTRUM UOCHB & GILEAD SCIENCES
GSRC
GILEAD SCIENCES & IOCB RESEARCH CENTRE

Center for Development of Original Drugs

The project **Center for Development of Original Drugs** (**CDOD**) in its strategic plan develops traditionally successful fields of Czech science and research: medicinal and pharmaceutical chemistry, pharmacology, pharmacochemistry, and other fields. The mission of **CDOD** project is commercialization and practical application of results of the basic research in the area of development of original drugs.

Technology Agency of the Czech Republic
Centra kompetence

Project **TE01020028** / **Center for Development of Original Drugs** is realized with financial support from the **Technology Agency of the Czech Republic** (TA ČR).

Members of the Consortium

Applicant

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ÚSTAV ORGANICKÉ CHEMIE A BIOCHEMIE AKADEMIE VĚD ČESKÉ REPUBLIKY, v. v. i.
INSTITUTE OF ORGANIC CHEMISTRY AND BIOCHEMISTRY ACADEMY OF SCIENCES OF THE CZECH REPUBLIC, v. v. i.

Institute of Organic Chemistry and Biochemistry AS CR, v.v.i.
(www.uochb.cz)

Partners

APIGENEX

APIGENEX s.r.o.
(www.apigenex.com)

BioTest s.r.o.

BioTest s.r.o
(www.biotest.eu)

Institute of Chemical Technology Prague
(www.vscht.cz)

Institute of Experimental Medicine AS CR, v.v.i.
(www.iem.cas.cz)

Fyziologický ústav Akademie věd České republiky

Institute of Physiology AS CR, v.v.i.
(www.biomed.cas.cz)

IOCB TTO
www.iocb-tto.cz

IOCB TTO s.r.o.
(www.iocb-tto.cz)

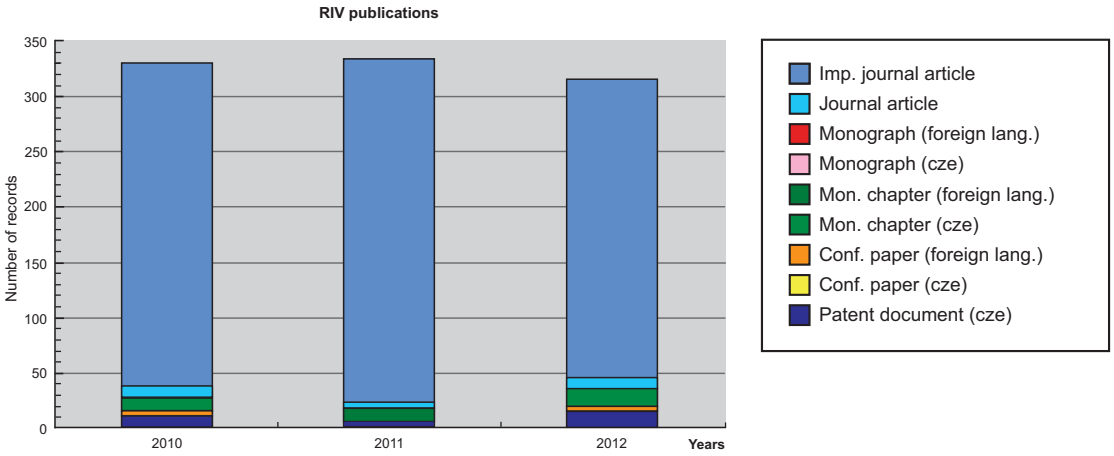
Palacký University Olomouc
(www.upol.cz)

QUINTA ANALYTICA

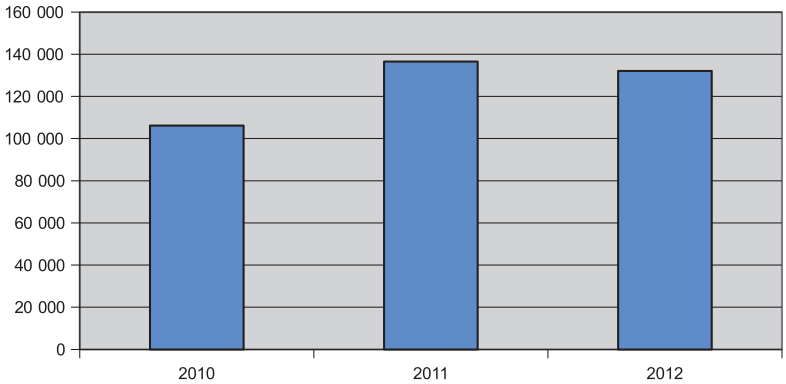
QUINTA-ANALYTICA s.r.o.
(www.quinta.cz)

SCIENTIFIC ACTIVITIES

Statistics of RIV Publications at IOCB in Years 2010 – 2012



Statistics of Downloaded Online Articles at IOCB in Years 2010 – 2012



Statistics of Grants in Years 2010 – 2012

	GACR	TACR	Ministry	AS CR	EU-FP7	Foreign – Outside FP7
2010	19	X	4	X	2	1
2011	13	3	6	X	0	1
2012	15	2	11	6	1	3

ERC Grants

DIPOLAR ROTOR ARRAY – *Regular Arrays of Artificial Surface – Mounted Dipolar Molecular Rotors*
ERC Advanced Grant
GA 227756
Prof. Josef Michl
from 1. 2. 2009, 60 months

HORIZOMS – *New Horizons for Mass Spectrometry*
ERC Advanced Grant
Dr. habil. Detlef Schröder
GA 226373
from 1.7.2009, 60 months, terminated after 45 months in March 2013

Statistics of Patents and Licences in Years 2010 – 2012

	Patents	Licences
2010	11	5
2011	6	
2012	15	

INVITED LECTURES

2010

January 20, 2010
Prof. Aalt BAST
Department of Pharmacology and Toxicology, University of Maastricht, The Netherlands
Antioxidants as Drugs

February 9, 2010
Prof. John E. WALKER
Medical Research Council Mitochondrial Biology Unit, Cambridge, United Kingdom
Energy Conversion in Biology

February 19, 2010
Prof. Antonio M. ECHAVARREN
Institute of Chemical Research of Catalonia, Tarragona, Spain
Gold Catalysis in the Construction of Molecular Complexity

March 12, 2010
Prof. J. Michael McBRIDE
Department of Chemistry, Yale University, New Haven, Connecticut, USA
Did Life Grind to a Start? A Brief History of the Origins of Homochirality

April 16, 2010
Prof. Carl DJERASSI
Department of Chemistry, Stanford University, California, USA
The Chemical History of the Pill

April 30, 2010
Prof. Ben L. FERINGA
Department of Organic Chemistry, Stratingh Institute for Chemistry, University of Groningen, The Netherlands
In Control of Molecular Motion: From Molecular Switches to Molecular Motors

May 10, 2010
Prof. David MILSTEIN
Department of Organic Chemistry, The Kimmel Center for Molecular Design, The Weizmann Institute of Science, Rehovot, Israel
Design of New Catalytic Reactions for „Green" Synthesis and Sustainable Energy

May 28, 2010
Prof. Kenso SOAI
Department of Applied Chemistry, Faculty of Science, Tokyo University of Science, Japan
Asymmetric Autocatalysis and the Origin of Homochirality

June 16, 2010
Prof. Cynthia J. BURROWS
Department of Chemistry, University of Utah, Salt Lake City, Utah, USA
Mechanisms of Guanine Oxidation Leading to DNA Mutations

June 18, 2010
Prof. Gregory C. FU
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA
Palladium- and Nickel-Catalyzed Coupling Reactions of Alkyl Electrophiles

September 20, 2010
Prof. Jacqueline K. BARTON
Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California, USA
DNA-mediated Signaling

October 4, 2010
Prof. C. Oliver KAPPE
Christian Doppler Laboratory for Microwave Chemistry, Institute of Chemistry, University of Graz, Austria
Microwave-Assisted Organic Synthesis: From Laboratory Curiosity to Standard Practice in 25 Years

October 25, 2010
Prof. Janusz M. BUJNICKI
International Institute of Molecular and Cell Biology, Warsaw, and Institute of Molecular Biology and Biotechnology, Faculty of Biology, Adam Mickiewicz University, Poznañ, Poland
New Methods for 3D Structure Prediction of RNAs and RNPs

November 22, 2010
Prof. Burkhard KÖNIG
Institut für Organische Chemie, Universität Regensburg, Regensburg, Germany
Synthetic Receptors for Selective Molecular Recognition and Catalysis

2011

January 5, 2011
Dr. Jiří GRYGAR
Institute of Physics AS CR, Prague, Czech Republic
The Origins of Physics, Chemistry, and Biology or Big Bang is the Culprit

January 25, 2011
Prof. R. Timothy HUNT
Cancer Research UK, Clare Hall Laboratories, South Mimms, London, UK
New Elements in the Control of Mitosis

February 28, 2011
Prof. Georg POHNERT
Institute for Inorganic and Analytical Chemistry, Jena, Germany
Chemical Signalling in Plankton Communities: Towards an Omics Approach

March 4, 2011
Prof. Helmut SCHWARZ
Technische Universität Berlin, Institut für Chemie, Berlin, Germany
Chemistry with Methane: Concepts Rather than Recipes

April 13, 2011
Prof. Erick M. CARREIRA
Laboratory of Organic Chemistry, ETH Zürich, Zürich, Switzerland
Discovery and Surprises with Natural Products

June 15, 2011
Prof. Itamar WILLNER
Institute of Chemistry, The Hebrew University of Jerusalem, Jerusalem, Israel
Biomolecular Nanostructures for Sensing, Machinery and Nanocircuitry

INVITED LECTURES

June 30, 2011
Prof. William L. JORGENSEN

Department of Chemistry, Yale University, New Haven, USA
Efficient Drug Lead Optimization Guided by Free-Energy Calculations

October 14, 2011
Prof. Morten MELDAL

Nano Science Center, University of Copenhagen, Copenhagen, Denmark
Encoding in Chemistry and Biology

October 19, 2011
Prof. Ada E. YONATH

Department of Structural Biology, Weizmann Institute of Science, Rehovot, Israel
The Amazing Ribosome

November 24, 2011
Prof. Jeremy SANDERS

Department of Chemistry, University of Cambridge, Cambridge, UK
Adventures in Molecular Recognition: Dynamic Combinatorial Chemistry and Supramolecular Nanotubes

December 2, 2011
Prof. Dawei MA

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, China
Target Synthesis Directed Methodology Development

2012

March 12, 2012
Prof. Christian HAASS

German Center for Neurodegenerative Diseases, Ludwig-Maximilians-Universität, Munich, Germany
The Molecular Clock Work of Alzheimer's Disease

April 18, 2012
Prof. Richard R. SCHROCK

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA
The Unique Abilities of MAP Catalysts for Olefin Metathesis

April 23, 2012
Prof. Kai SIMONS

Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany
Lipids Organizing Cell Membranes

May 10, 2012
Prof. Shankar BALASUBRAMANIAN

Chemistry Department, University of Cambridge, and Cancer Research UK, Cambridge Research Institute, Cambridge, UK
Sequencing Nucleic Acids: From Chemistry to Life Sciences and Medicine

May 25, 2012
Prof. Matthew FREEMAN

MRC Laboratory of Molecular Biology, Cambridge, UK
The Control of Intercellular Signalling by Rhomboid-Like Proteins

June 18, 2012
Prof. F. Dean TOSTE

Department of Chemistry, University of California, Berkeley, California, USA
Concepts and Catalysts for Enantioselective Reactions of C-C Multiple Bonds

June 22, 2012
Prof. Dennis P. CURRAN

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania, USA
Radical, Ionic and Organometallic Reactions of N-Heterocyclic Carbene Boranes

October 5, 2012
Prof. Peter BÄUERLE

Institute of Organic Chemistry II and Advanced Materials, University of Ulm, Ulm, Germany
Functional Thiophene-Based Nanomaterials for Organic Photovoltaic

October 23, 2012
Prof. Andreas HIRSCH

Department of Chemistry and Pharmacy, University of Erlangen-Nürnberg, Germany
Functionalization of Synthetic Carbon Allotropes

November 5, 2012
Prof. Bernd GIESE

Department of Chemistry, University of Fribourg, Fribourg, Switzerland
Electron Transfer through Peptides: Consequences for Enzymatic Reactions

November 16, 2012
Prof. Ronald MICURA

Institute of Organic Chemistry, University of Innsbruck, Innsbruck, Austria
Synthetic modified RNA – Probes to Study Riboswitch and Ribosome Function

December 3, 2012
Prof. M. Christina WHITE

Department of Chemistry, University of Illinois, Urbana, Illinois, USA
C–H Oxidations and Organic Synthesis

December 10, 2012
Prof. Dirk TRAUNER

Ludwig-Maximilians-Universität, München, Germany
Optochemical Genetics

THE IOCB SABBATICAL VISIT PROGRAM

Institute of Organic Chemistry and Biochemistry (IOCB) Academy of Sciences of the Czech Republic, v.v.i. (IOCB), invites applications for positions within the **"IOCB Sabbatical Visit Program"** for prominent scientists from reputable foreign universities and research institutions

Granted Programs – 2010

Prof. Jan GENSER	Celanese Professor of Chemical & Biomolecular Engineering, The University of North Carolina, Raleigh, USA in research group of Jiří Šrogl

Granted Programs – 2013

Prof. Pavel KOČOVSKÝ	University of Glasgow, Glasgow, Scotland, United Kingdom in research group of Jiří Šrogl
Prof. Daniel A. KNOPF	Stony Brook University, Stony Brook, New York, USA in research group of Pavel Jungwirth

IOCB POSTDOCTORAL PROJECTS

Institute of Organic Chemistry and Biochemistry (IOCB), Academy of Sciences of the Czech Republic, v.v.i., is opening postdoctoral positions in chemistry and biochemistry. The IOCB will open up to 10 positions per year. The position is open for one year, with possible extension of one more year, if agreed by both parties. The applicant is expected to have a **Ph.D. degree** from a reputable foreign university, as of the advantage of external experience is greatly sought after.

Granted Projects – 2010

Tibor András ROKOB	**Hungary**; in research group of Lubomír Rulíšek
Aude VIBERT	**France**; in research group of Ullrich Jahn
Imranul HOQ	**Bangladesh**; in research group of Václav Čeřovský
Michal PITOŇÁK	**Slovakia**; in research group of Pavel Hobza (extension for 1 year)
Paul E. REYES-GUTIÉRREZ	**Mexico**; in research group of Filip Teplý
Mario VAZDAR	**Croatia**; in research group of Pavel Jungwirth
Christopher Steven CHAMBERS	**UK**; in research group of Michal Hocek
Audrey COPPÉE	**Belgium**; in research group of Irena Valterová
Shigeki YAMAMOTO	**Japan**; in research group of Petr Bouř (extension for 1 year)
Erik WERNERSSON	**Sweden**; in research group of Pavel Jungwirth (extension for 1 year)
Svetlana POLYAKOVA	**Russia**; in research group of Ilya Lyapkalo (extension for 1 year)

Granted Projects – 2011

Serghei CHERCHEJA	**Moldova**; in research group of Ivo Starý
Zhenjun SI	**China**; in research group of Josef Michl
Tibor András ROKOB	**Hungary**; in research group of Lubomír Rulíšek (extension for 1 year)
Paul E. REYES-GUTIÉRREZ	**Mexico**; in research group of Filip Teplý (extension for 1 year)
Mario VAZDAR	**Croatia**; in research group of Pavel Jungwirth (extension for 1 year)
Christopher Steven CHAMBERS	**UK**; in research group of Michal Hocek (extension for 1 year)

Granted Projects – 2012

Jin WEN	**China**; in research group of Josef Michl
Ali YOUNES	**USA**; in research group of Josef Michl
Daniele PADULA	**Italy**; in research group of Petr Bouř
Dmytro DZIUBA	**Ukraine**; in research group of Michal Hocek
Goar SANCHEZ	**Spain**; in research group of Lubomír Rulíšek
Serghei CHERCHEJA	**Moldova**; in research group of Ivo Starý (extension for 1 year)

Granted Projects – 2013

Jeanne M. KOHAGEN	**Germany**; in research group of Pavel Jungwirth
Manasi MISHRA	**India**; in research group of Michal Mareš
Sebastian ZOLL	**Germany**; in research group of Kvido Stříšovský
Jin WEN	**China**; in research group of Zdeněk Havlas (extension for 1 year)

RESEARCH GROUPS

Benchmark Quantum Chemical Calculations on Model Complexes and Complexes of Biomolecular Building Blocks; Development and Parametrization of New Quantum Chemical Methods

Pavel HOBZA

Computational Chemistry
e-mail: hobza@uochb.cas.cz

Research topics

Noncovalent interactions play an important role in the structure determination of biomolecules and consequently influence their biological functions. For example, the double-helical structure of DNA which is prerequisite for its biological function (storage and transfer of genetic information) results from these interactions among DNA bases, sugars, phosphates and surrounding waters. Theoretical description of noncovalent interactions represents one of the most difficult tasks of the current computational chemistry. Highly accurate methods covering the correlation (dispersion) energy should be applied. Since biological processes occur in a water environment and at room temperature, it is necessary to pass from a static (quantum mechanical) description to a dynamic description realized by molecular dynamic (MD) simulations. Further, reliable description of the solvent environment is required, which is of primary importance for polar or charged systems (like, e.g., inhibitors). Highly accurate description of dynamic processes is obtained by performing the "on-the-fly" ***ab initio*** MD simulations.

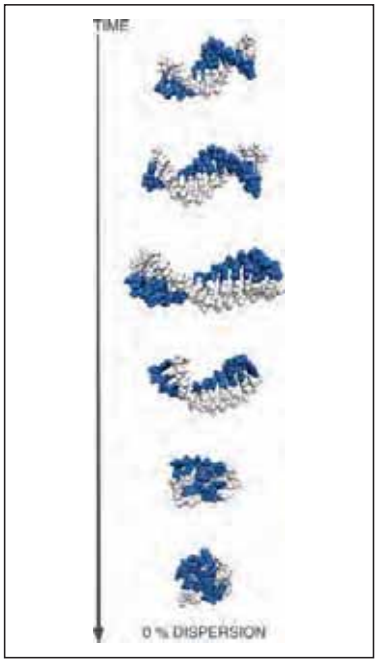
Current research includes theoretical studies of noncovalent interactions in general, hydrogen bonding and improper blue-shifting hydrogen bonding, the role of dispersion energy in biomacromolecules and nanostructures and in protein folding, benchmark calculations of interaction energies and geometries of extended molecular complexes, development and / or modification of computational methods suitable for the prediction of noncovalent interactions in biomolecules, "on-the-fly" ***ab initio*** molecular dynamic simulations of bioprocesses, and, recently, docking and drug design. Intensive cooperation with experimental (chemically and biologically oriented) as well as theoretical groups was established.

Current grant support

Academy of Sciences (RVO:61388963)
Academy of Sciences (Praemium Academiae awarded to Prof. Hobza in 2007).
Czech Science Foundation (P208/12/G016), Prof. Hobza is the principal investigator
Czech Science Foundation (P208/10/0725), Dr. Bludsky
Czech Science Foundation (P208/12/1318), Dr. Nachtigallová
Czech Science Foundation (P106/12/G015), Dr. Bludsky
Czech Science Foundation (P208/11/0436), Dr. Špirko

Selected recent papers

1. Barbatti, M.; Aquino, A. J. A.; Szymczak, J. J.; Nachtigallova, D.; Hobza, P.; Lischka, H., Relaxation mechanisms of UV-photoexcited DNA and RNA nucleobases. *Proceedings of the National Academy of Sciences of the United States of America* **2010,** 107, (50), 21453-21458.
2. Grajciar, L.; Bludsky, O.; Nachtigall, P., Water Adsorption on Coordinatively Unsaturated Sites in CuBTC MOF. *Journal of Physical Chemistry Letters* **2010,** 1, (23), 3354-3359.
3. Nachtigallova, D.; Zeleny, T.; Ruckenbauer, M.; Muller, T.; Barbatti, M.; Hobza, P.; Lischka, H., Does Stacking Restrain the Photodynamics of Individual Nucleobases? *Journal of the American Chemical Society* **2010,** 132, (24), 8261-8263.
4. Riley, K. E.; Pitonak, M.; Jurecka, P.; Hobza, P., Stabilization and Structure Calculations for Noncovalent Interactions in Extended Molecular Systems Based on Wave Function and Density Functional Theories. *Chemical Reviews* **2010,** 110, (9), 5023-5063.
5. Kolar, M.; Kubar, T.; Hobza, P., On the Role of London Dispersion Forces in Biomolecular Structure Determination. *Journal of Physical Chemistry B* **2011,** 115, (24), 8038-8046.
6. Rezac, J.; Riley, K. E.; Hobza, P., S66: A Well-balanced Database of Benchmark Interaction Energies Relevant to Biomolecular Structures. *Journal of Chemical Theory and Computation* **2011,** 7, (8), 2427-2438.
7. Rezac, J.; Riley, K. E.; Hobza, P., Extensions of the S66 Data Set: More Accurate Interaction Energies and Angular-Displaced Nonequilibrium Geometries. *Journal of Chemical Theory and Computation* **2011,** 7, (11), 3466-3470.
8. Riley, K. E.; Hobza, P., Noncovalent interactions in biochemistry. *Wiley Interdisciplinary Reviews-Computational Molecular Science* **2011,** 1, (1), 3-17.
9. Georgakilas, V.; Otyepka, M.; Bourlinos, A. B.; Chandra, V.; Kim, N.; Kemp, K. C.; Hobza, P.; Zboril, R.; Kim, K. S., Functionalization of Graphene: Covalent and Non-Covalent Approaches, Derivatives and Applications. *Chemical Reviews* **2012,** 112, (11), 6156-6214.
10. Hobza, P., Calculations on Noncovalent Interactions and Databases of Benchmark Interaction Energies. *Accounts of Chemical Research* **2012**, 45, (4), 663-672.
11. Rezac, J.; Riley, K. E.; Hobza, P., Benchmark Calculations of Noncovalent Interactions of Halogenated Molecules. *Journal of Chemical Theory and Computation* **2012**, 8, (11), 4285-4292.



Computer simulations allow us to study the delicate balance of non-covalent interactions in biomolecules. Figure depicts the disruption of a DNA double-helix in the course of molecular dynamics, which was modified to lack London dispersion forces.

In Silico Drug Design; Development of Quantum Mechanical Based Scoring Functions; Development of Explicit and Implicit Solvation Models

DIPLOMA THESES

Držata Tomáš	Design, parameterization and verification of a coarse-grained model of DNA	Faculty of Sciences, Charles University in Prague
Hostaš Jiří	Variational and pertubational calculations of interaction energies of noncovalent clusters	Faculty of Sciences, Charles University in Prague

POSTDOCTORAL PROJECTS

Řezáč Jan	Czech Republic	Pavel Hobza
Fanfrlík Jindřich	Czech Republic	Pavel Hobza
Lepšík Martin	Czech Republic	Pavel Hobza
Šímová Lucia	Slovak Republic	Pavel Hobza
Granatier Jaroslav	Slovak Republic	Pavel Hobza
Brahmkshatriya Pathik	India	Pavel Hobza
Ramachandran Gnanasekanar	India	Pavel Hobza
Palanisamy Deepa	India	Pavel Hobza

SIGNIFICANT AWARDS

Pavel Hobza	Doctor Honoris Causa	Lifelong achievements in Science	Institute of Chemical Technology, Prague
Pavel Hobza	Silver medal of the Senate of the Czech Republic	Lifelong achievements in Science and attitude to life	Senate of the Czech Republic
Michal Kolář	Award of the Learned Society of the Czech Republic	Teaching award	The Learned Society of the Czech Republic
Michal Kolář	Jean-Marie Lehn Award for Chemistry		Franch Embassy and Rhodia s.r.o.

TEACHING ACTIVITIES

Current Chemistry	Pavel Hobza	Faculty of Sciences, Palacký University Olomouc
Physical Chemistry III	Jan Řezáč	Faculty of Sciences, Palacký University Olomouc
Non-covalent Interactions	Pavel Hobza and Jan Řezáč	Faculty of Sciences, Charles University in Prague
Excited States in nano- and biosystems	Dana Nachtigallová	Faculty of Sciences, Charles University in Prague
Mesoscopic modelling	Filip Lankaš	Faculty of Sciences, Charles University in Prague
Programming in Matlab	Ota Bludský	Faculty of Sciences, Charles University in Prague
Molecular Symmetry	Ota Bludský	Faculty of Sciences, Charles University in Prague
Theoretical rotational-vibrational spectroscopy	Ota Bludský	Faculty of Sciences, Charles University in Prague

Pavel Hobza / Head of the Group

Ota Bludský / Scientist
Filip Lankaš / Scientist
Dana Nachtigallová / Scientist
Jindřich Fanfrlík / Postdoc
Jaroslav Granatier / Postdoc
Martin Lepšík / Postdoc
Deepa Palanisamy / Postdoc
Gnanasekaran Ramachandran / Postdoc
Jan Řezáč / Postdoc
Lucia Šímová / Postdoc
Tomáš Držata / Ph.D. Student
Lukáš Grajciar / Ph.D. Student
Susanta Haldar / Ph.D. Student
Jiří Hostaš / Ph.D. Student
Michal Kolář / Ph.D. Student
Michaela Nekardová / Ph.D. Student
Adam Pecina / Ph.D. Student
Róbert Sedlák / Ph.D. Student
Cemal Köprülüglu / Ph.D. Student
Martina Zámečníková / Student
Martin Benroth / Student
Jakub Klemsa / Student
Jakub Trnka / Student
Helena Černá / Research Assistant
Jiří Polách / Technician

Theoretical Chemistry

Zdeněk HAVLAS

Computational Chemistry
e-mail: havlas@uochb.cas.cz

Research topics

The team is engaged in quantum chemical examination of selected ground- and excited-state properties of molecules (organic dyes, transition metal complexes; carbenes, silylenes and other, often heavy atom containing, reactive intermediates), as well as in the development of quasirelativistic methods for their calculation. First, we contribute to the Singlet Fission project, in collaboration with other laboratories all over the world. The singlet fission process produces a pair of triplet states in dimers of chromophores from initial singlet excitation of one of the chromophore. It can be used in the construction of the efficient solar cells. We focus on computational prediction of the proper chromophores and on understanding of the structure of chromophore dimer with enhanced triplet yield.

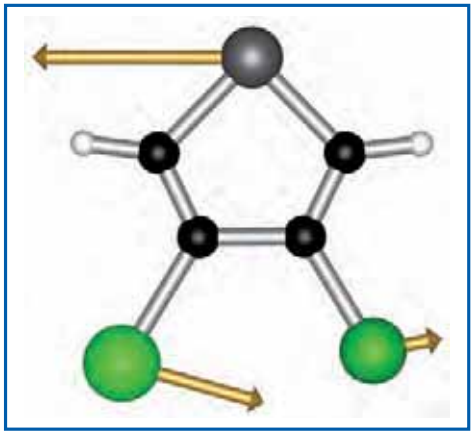
Second, we explore relativistic effects responsible for zero-field splitting of spin degenerate states, radiative and radiationless spin-forbidden transitions, or tiny differences between electronic state energies of enantiomers. The main focus is on designing molecules having appealing, often anomalous, properties (e.g. those showing inverse heavy-atom effect on the rate of spin-forbidden transitions or those with a measurable electronic excitation frequency shift due to parity violation).

Current grant support

Center of Excellence, P208/12/G016 (Czech Science Foundation, PI: P. Hobza)
Competence Center, TE01010028 (Czech Technology Agency, PI: Z. Havlas)
GSRC (Gilead Sciences Research Centre, PI: Z. Havlas)

Selected recent papers

1. **Toward Designed Singlet Fission: Solution Photophysics of Two Indirectly Coupled Covalent Dimers of 1,3-Diphenylisobenzofuran.** Johnson, J. C.; Akdag, A.; Zamadar, M.; Chen, X.; Schwerin, A.F.; Paci, I.; Smith, M.B.; Havlas, Z.; Miller, J.R.; Ratner, M.A.; Nozik, A.J.; Michl, J.; *J. Phys. Chem. B*, **2013**, *117* , 4680–4695.
2. **Search for a Small Chromophore with Efficient Singlet Fission: Biradicaloid Heterocycles.** Akdag, A.; Havlas, Z.; Michl, J.; *J. Am. Chem. Soc.*, **2012**, *134*, 14624-14631.
3. **Toward Designed Singlet Fission: Electronic States and Photophysics of 1,3-Diphenylisobenzofuran.** Schwerin, A.F.; Johnson, J.C.; Smith, M.B.; Sreearunothai, P.; Popovic, D.; Cerny, J.; Havlas, Z.; Paci, I.; Akdag, A.; MacLeod, M.K.; Chen, XD.; David, D.E.; Ratner, M.A.; Miller, J.R.; Nozik, A.J.; Michl, J.; *J. Phys. Chem. A*, **2010**, *114*, 1457-1473.
4. **Calculation of Transition Matrix Elements by Nonsingular Orbital Transformations.** Kyvala, M.; *Int. J. Quantum Chem.* **2009**, *109*, 1200-1227.
5. **Effect of spin-orbit coupling on reduction potentials of octahedral ruthenium(II/III) and osmium(II/III) complexes.** Srnec, M.; Chalupsky, J.; Fojta, M.; Zendlova, L.; Havran, L.; Hocek, M.; Kyvala, M.; Rulisek, L.; *J. Am. Chem. Soc.* **2008**, *130*, 10947-10954.



Inverse heavy-atom effect on spin-orbit coupling between S_0 and T_1 in 3-bromo-4-iodo-1-silacyclopentadienylidene

PHD THESES

Jakub Chalupský	Accurate Multireference Calculations of Electronic States and some of their Properties in Organic and Bioinorganic Molecules	Faculty of Sciences, Charles University in Prague

POSTDOCTORAL PROJECTS

Mathew K. MacLeod	USA	Zdeněk Havlas
Abdul Wahab	India	Zdeněk Havlas
Akin Akdag	Turkey	Zdeněk Havlas
Milena Jovanovic	Serbia	Zdeněk Havlas
Jahn Burghard	Germany	Zdeněk Havlas

SIGNIFICANT AWARDS

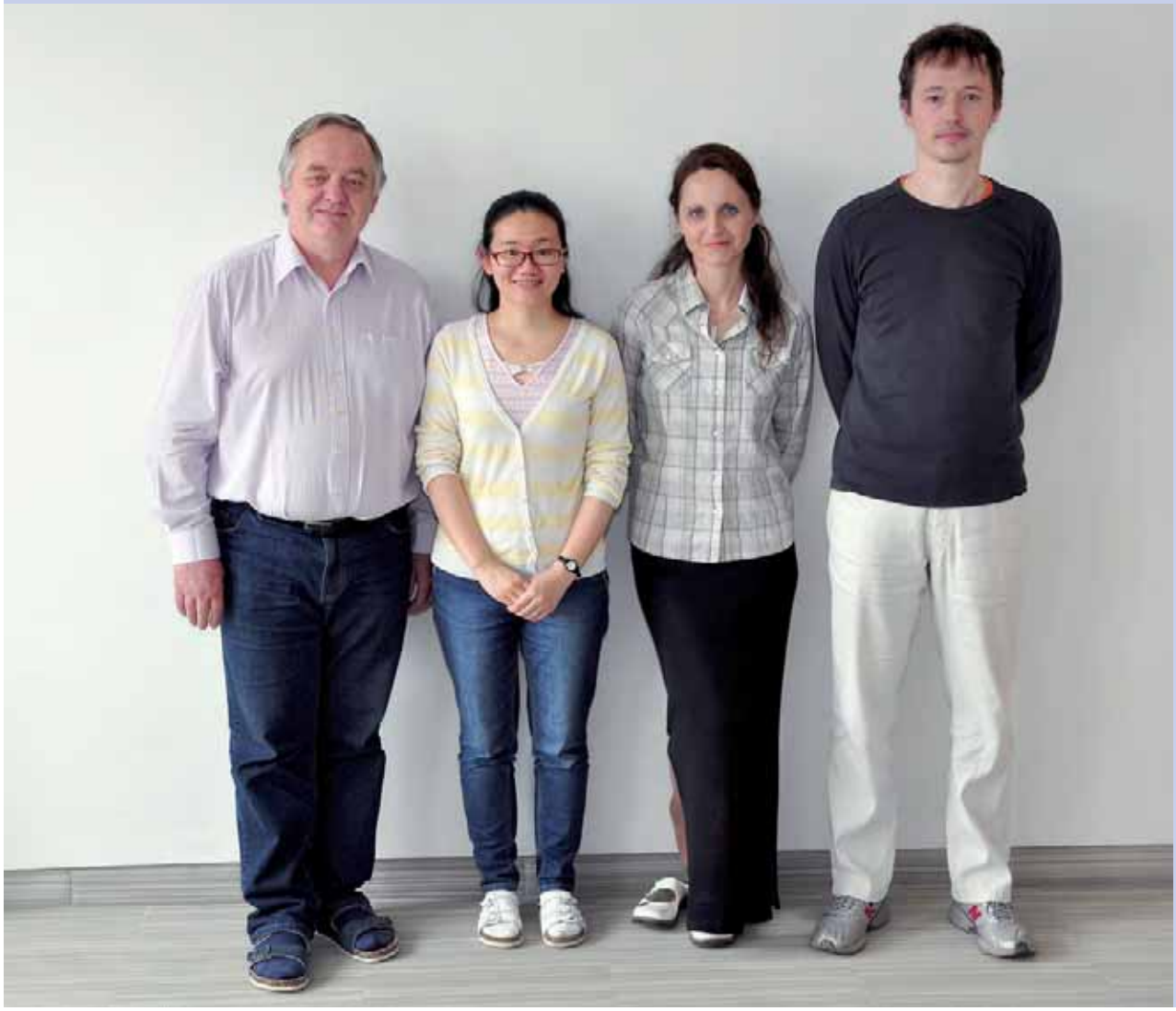
Zdeněk Havlas	Award of the Learned Society of the Czech Republic	For contribution to theoretical chemistry	The Learned Society of the Czech Rebublic
Zdeněk Havlas	Jan Hellich Prize	For promotion in science	City of Poděbrady
Zdeněk Havlas	Medal of the University of Leuven	For contribution to collaboration	KU Leuven, Belgium
Zdeněk Havlas	Medal of the Czech Chemical Society	Lifetime Achievement Award	Czech Chemical Society
Zdeněk Havlas	Honorary Chair	For merits in advancement of Institute	Institute of Organic Chemistry and Biochemistry

TEACHING ACTIVITIES

Structureal analysis of natural products	Zdeněk Havlas	Institute of Chemical Technology, Prague

Zdeněk HAVLAS / Head of the Group

Mojmír Kývala / Scientist
Burkhard Jahn / Postdoc
Mohamed Wahab Abdul / Postdoc
Jakub Chalupský / Ph.D. Student



Bioorganic and Medicinal Chemistry of Nucleic Acids
Joint Laboratory of IOCB and Charles University

Michal HOCEK

Bioorganic & Medicinal Chemistry
e-mail: hocek@uochb.cas.cz
web: www.uochb.cas.cz/hocekgroup

Research topics

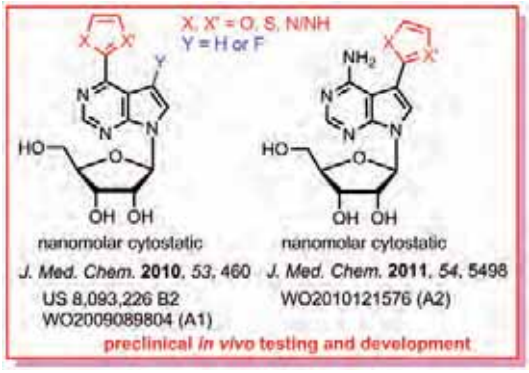
Novel types of modified derivatives and analogues of nucleobases, nucleosides, nucleotides and nucleic acids are designed and prepared for applications in all areas of biomedicinal sciences. Basic developments of methodology are performed largely cross-coupling and C-H arylation reactions. Systematic biological activity screening led to the discovery of several new types of potent nucleoside cytostatics. Polymerase construction of functionalized nucleic acids bearing diverse useful substituents has been developed and their applications are pursued in bioanalysis (e.g. redox or fluorescent labeling for diagnostics of mutations of DNA) and chemical biology (reactive labeling for cross-linking or protection for switching of interactions with proteins).

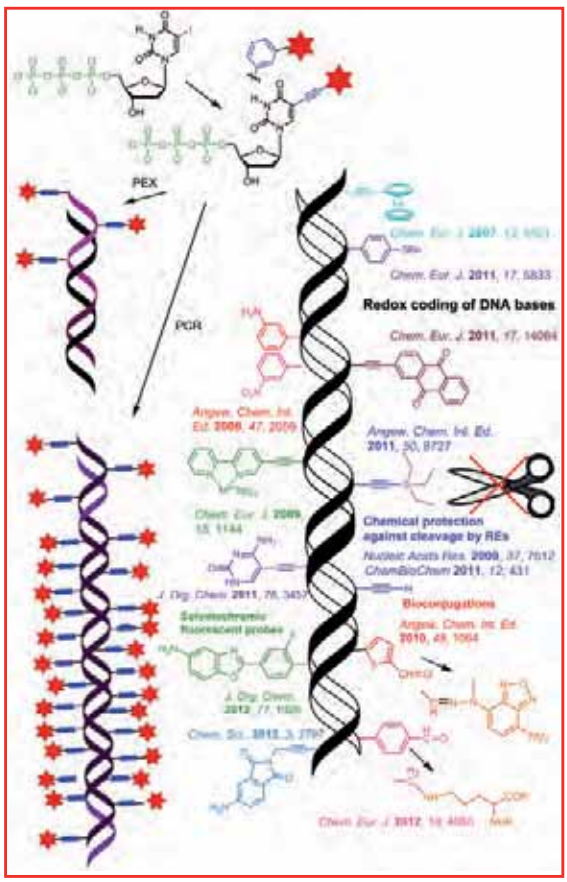
Current grant support

Academy of Sciences (Z40550506), Czech Science Foundation (203/09/0317, 207/11/0344, P206/12/G151), Grant Agency of the ASCR (IAA40040901) and by Gilead Sciences, Inc. (Foster City, U.S.A.).

Selected recent papers

1. Raindlová, V.; Pohl, R.; Šanda, M.; Hocek, M.* "Direct polymerase synthesis of reactive aldehyde-functionalized DNA and its conjugation and staining with hydrazines" *Angew. Chem. Int. Ed.* **2010**, *49*, 1064-1066.
2. Nauš, P.; Pohl, R.; Votruba, I.; Džubák, P.; Hajdúch, M.; Ameral, R.; Birkuš, G.; Wang, T.; Ray, A. S.; Mackman, R.; Cihlar, T.; Hocek, M.* "6-(Het)aryl-7-Deazapurine Ribonucleosides as Novel Potent Cytostatic Agents" *J. Med. Chem.* **2010**, *53*, 460-470.
3. Bourderioux, A.; Nauš, P.; Perlíková, P.; Pohl, R.; Pichová, I.; Votruba, I.; Džubák, P.; Konečný, P.; Hajdúch, M.; Stray, K. M.; Wang, T.; Ray, A. S.; Feng, J. Y.; Birkus, G.; Cihlar, T.; Hocek, M.* "Synthesis and significant cytostatic activity of 7-hetaryl-7-deazaadenosines" *J. Med. Chem.* **2011**, *54*, 5498-5507.
4. Štefko, M.; Slavětínská, L.; Klepetářová, B.; Hocek, M.* "General and Modular Synthesis of Isomeric 5-Substituted Pyridine-2-yl and 6-Substituted Pyridine-3-yl C-Ribonucleosides Bearing Diverse Alkyl, Aryl, Hetaryl, Amino, Carbamoyl and Hydroxy Groups" *J. Org. Chem.* **2011**, *76*, 6619-6635.
5. Kielkowski, P.; Macíčková-Cahová, H.; Pohl, R.; Hocek, M.* "Transient and switchable (triethylsilyl)ethynyl protection of DNA against cleavage by restriction endonucleases" *Angew. Chem. Int. Ed.* **2011**, *50*, 8727-8730.
6. Ménová, P.; Hocek, M.* "Preparation of Short Cytosine-Modified Oligonucleotides by Nicking Enzyme Amplification Reaction" *Chem. Commun.* **2012**, *48*, 6921-6923.
7. Riedl, J.; Pohl, R.; Ernsting, N. P.; Orsag, P.; Fojta, M.; Hocek M.* "Labelling of nucleosides and oligonucleotides by solvatochromic 4-aminophthalimide fluorophore for studying DNA-protein interactions" *Chem. Sci.* **2012**, *3*, 2797-2806.





PHD THESES

Zbyněk Hasník	Study of the Scope and Limitations of Cross-coupling Reactions for Introduction of Functionalized C-Substituents to Purines and related Heterocycles	Institute of Chemical Technology Prague
Hana Macíčková – Cahová	Enzymatic Synthesis of Modified DNA for Bioanalytical Applications and Study of its Interaction with Restriction Endonucleases	Institute of Chemical Technology Prague
Martin Štefko	Synthesis of Novel Types of Benzene and Pyridine C-Nucleosides	Institute of Chemical Technology Prague
Jan Bárta	Synthesis of C-Nucleosides Derived from Five-Membered Heterocycles	Institute of Chemical Technology Prague
Lubica Kalachová	Preparation of Nucleosides, Nucleotides and Nucleic Acids Bearing Bipyridine-Type Ligands	Faculty of Sciences, Charles University in Prague
Jan Riedl	Redox and Fluorescent DNA Labelling by Enzymatic Incorporation of Modified Nucleoside Triphosphates	Institute of Chemical Technology Prague
Pavla Perlíková	Synthesis of Novel Cytostatic Deazapurine Nucleosides and Pronucleotides	Faculty of Sciences, Charles University in Prague
Veronika Raindlová	Construction of Novel Types of Nucleosides and Nucleic Acids Bearing Functional Groups	Institute of Chemical Technology Prague

POSTDOCTORAL PROJECTS

Dmytro Dziuba	Ukraine	Michal Hocek
Christopher Chambers	UK	Michal Hocek

TEACHING ACTIVITIES

Bioorganic chemistry	Michal Hocek	Faculty of Sciences, Palacky University Olomouc
Bioorganic chemistry	Michal Hocek	Institute of Chemical Technology Prague
Organic Chemistry	Michal Hocek	Faculty of Sciences, Charles University in Prague

Michal Hocek / Head of the Group

Chris Chambers / Postdoc
Dmytro Dziuba / Postdoc
Vincent Malnuit / Postdoc
Petr Nauš / Postdoc
Jana Balintová / Ph.D. Student
A. Michael Downey / Ph.D. Student
Miroslava Čerňová / Ph.D. Student
Jitka Daďová / Ph.D. Student
Pavel Kielkowski / Ph.D. Student
Martin Klečka / Ph.D. Student
Tomáš Kubelka / Ph.D. Student
Michaela Mačková / Ph.D. Student
Petra Ménová / Ph.D. Student
Nazarii Sabat / Ph.D. Student
Anna Simonova / Ph.D. Student
Michal Tichý / Ph.D. Student
Anna Tokarenko / Ph.D. Student
Zuzana Vaníková / Ph.D. Student
Juraj Konč / Student
Matouš Krömer / Student
Kamila Havlíčková / Technician

Structurally Diverse Phosphonate Nucleotides & Oligonucleotides

Ivan ROSENBERG

Bioorganic & Medicinal Chemistry
e-mail: rosenberg@uochb.cas.cz

Research topics

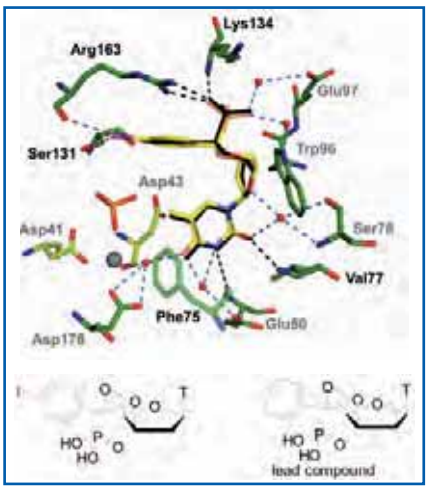
Scientific program of the Group of Nucleotides and Oligonucleotides has been directed toward basic research in the area of *(A) Nucleoside Phosphonic Acids (NPAs)* as potential antimetabolites and *(B) Phosphonate Oligonucleotide Analogs* as antisense compounds capable of interfering with gene expression and other types of oligonucleotides with a regulatory role (2',5'-oligoadenylates, CpG oligonucleotides).

(A) Nucleoside Phosphonic Acids. Our investigation in the area of the chemistry of *NPAs* has provided an impressive number of novel structurally diverse compounds containing both classical (furanose)[2] and modified (pyrrolidine, prolinol, piperidine, and some other heterocyclic) rings. Among them, several potent inhibitors of selected enzymes of nucleoside and nucleotide metabolism were found (human *thymidine and purine nucleoside phosphorylases*[4], *hypoxanthine-xanthine-guanine phosphoribosyl transferase (P. falciparum),* human *pyrimidine specific mitochondrial and cytosolic 5'(3')-nucleotidases,* etc.). These results prompt us to devote, in the near future, much more attention to the biochemical and biological evaluation of our *NPAs* within broadly-based collaborations. In addition, the knowledge obtained with the synthesis of *NPAs* is unique as such and will be fully utilized in new projects directed to a new generation of nucleotide analogs.

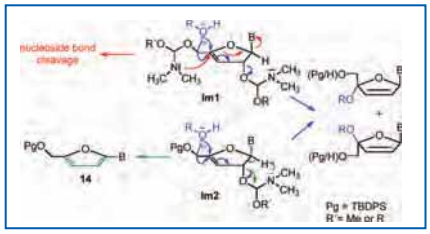
(B) Phosphonate Oligonucleotide Analogs. The pool of our nucleoside phosphonic acids *NPAs* provided several types of these compounds which were evaluated as monomers for the synthesis of modified oligonucleotides.[1,3] We elaborated the synthesis of protected monomers in deoxyribo and ribo series suitable for the 3' → 5' and 5' → 3' directions of the solid phase synthesis using advanced phosphotriester method, and developed the first non-silyl protecting group used in the solid phase synthesis of modified oligoribonucleotides in the reverse direction. Superior nuclease stability of the phosphonate internucleotide linkages, their abilitiy to enhance hybridization together with ability to elicit RNase H activity more efficiently then the natural oligodeoxynucleotides, may clasify these compounds for their use in biochemistry and biology. Series of several types of modified oligonucleotides with isopolar isosteric and non-isosteric phosphonate-based internucleotide linkages have been prepared and evaluated as antisense compounds and siRNAs.

Current grant support

Czech Science Foundation (203/09/0820, 202/09/0193, and 13-26526S)



Binding of *(S)*-1-[2-deoxy-3,5-*O*-(4-iodo-phosphonobenzylidene)-β-D--threo-pentofuranosyl] thymine to the mitochondrial pyrimidine specific 5'(3')-deoxynucleotidase (mdN). Polar interactions of inhibitor with the mdN active site are represented as dashed lines. Direct hydrogen bonds and water mediated hydrogen bonds are colored black, and light blue, respectively. Halogen bonds are shown in purple. Interacting residues and catalytic residues are shown in green and lime, respectively. Position of lead compound as bound in crystal structure is shown in thick black lines.
[Ondřej Šimák, Petr Pachl, Milan Fábry, Miloš Buděšínský, Tomáš Jandušík, Pavlína Řezáčová, Magdalena Petrová, Jiří Brynda, Ivan Rosenberg. *J. Med. Chem.* submited]



Proposed mechanism of DMF-DMA mediated allylic rearangement on the nucleoside skeleton.[2]

Selected recent papers

1. Liboska, R., Snášel, J., Barvík, I., Buděšínský, M., Pohl, R., Točík, Z., Páv, O., Rejman, D., Novák, P., Rosenberg, I. (2011). 4´ Alkoxy Oligodeoxynucleotides: A Novel Class of RNA Mimics. *Organic and Biomolecular Chemistry*, **9**, 8261-8267.
2. Petrová, M., Buděšínský, M., Zborníková, E., Fiedler, P., Rosenberg, I. (2011). A Ferrier-type allylic rearrangement of 3´-deoxy-3´,4´-didehydronucleosides mediated by DMF dimethyl acetal: Direct access to 4´-Alkoxy-2´,3´-didehydro-2´,3´-dideoxynucleosides. *Organic Letters,* **13**, 4200-4203.
3. Páv, O., Košiová, I., Barvík, I., Pohl, R., Buděšínský, M., Rosenberg, I. (2011). Synthesis of oligoribonucleotides with phosphonate-modified linkages. *Organic and Biomolecular Chemistry,* **9**, 6120-6126.
4. Rejman, D., Panova, N., Klener, P., Maswabi, B., Pohl, R., Rosenberg, I. (2012). N-Phosphono-carbonylpyrrolidine Derivatives of Guanine: A New Class of Bi-Substrate Inhibitors of Human Purine Nucleoside Phosphorylase. *Journal of Medicinal Chemistry,* **55**, 1612–1621.

PhD THESES

Eva Zborníková	Spontaneous oligomerization of phosphonate AMP analogs	Faculty of Sciences, Charles University in Prague
Ondřej Kostov	Oligonucleotides with phosphonothioate and thiophosphonoamidate internucleotide linkage	Institute of Chemical Technology Prague

Ivan Rosenberg / Head of the Group

Dominik Rejman, Ph.D. / Scientist
Radek Liboska / Scientist
Natalya Panova / Scientist
Magdalena Petrová / Scientist
Ondřej Kostov / Ph.D. Student
Ivana Dvořáková / Technitian
Ondřej Šimák / Scientist
Ondřej Páv / Scientist
Eva Zborníková / Ph.D. Student
Šárka Rosenbergová / Scientist
Pavel Novák / Technitian
Tomáš Jandušík / Undergraduate Student
Valentine Krug / Undergraduate Student

Chemistry and Biology of Insulin and Insulin-like Growth Factors

Jiří JIRÁČEK

Biochemistry and Molecular Biology
e-mail: jiracek@uochb.cas.cz

Research topics

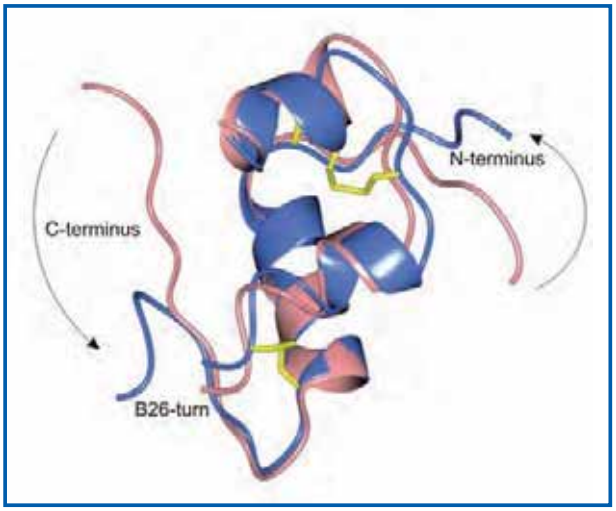
Our research group is engaged in structure-activity studies of insulin and insulin-like growth factors 1 and 2 (IGFs). These important hormones share similar 3-D structures and cell membrane receptors. Our general goal in insulin/IGF research is understanding of the structural basis for the different cellular responses, metabolic and mitogenic, generated by insulin and IGFs, respectively. We develop analogues of insulin and IGFs to study their interaction with cognate receptors (IR-A, IR-B and IGF-1R).
We have been also involved in the development of inhibitors for betaine-homocysteine *S*-methyltransferases 1 and 2 to study their functions in mammalian metabolism of methionine and homocysteine.
Our group comprises of biochemists and organic chemists and combines chemical synthesis with biochemical studies. We have a close collaboration with structural biologists at the University of York in U.K. (crystal structures) and at IOCB (NMR).

Current grant support

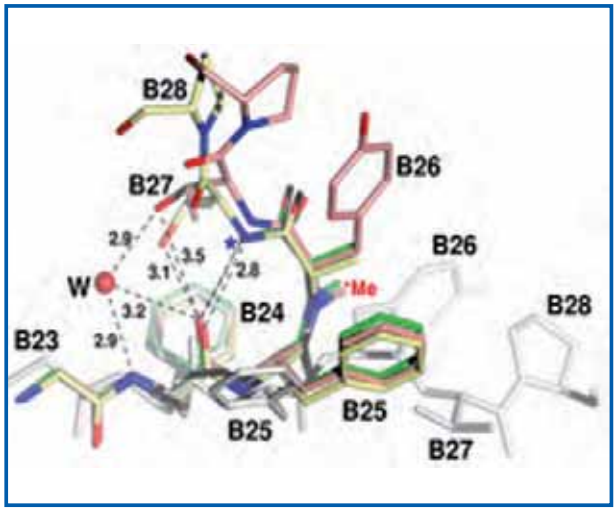
Grant Agency of the ASCR (P207/11/P430) and Medical Research Council Research Grant (MR/K000179/1, MRC, U.K.).

Selected recent papers

1. Vaněk, V., Buděšínský, M., Kabeleová, P., Šanda, M., Kožíšek, M., Hančlová, I., Mládková, J., Brynda, J., Rosenberg, I., Koutmos, M., Garrow, T. A., Jiráček, J. "Structure-activity study of new inhibitors of human betaine-homocysteine S-methyltransferase" *J. Med. Chem.* **2009**, 52, 3652-3665.
2. Jiráček, J., Žáková, L., Antolíková, E., Watson, C. J., Turkenburg, J. P., Dodson, G. G., Brzozowski, A. M. "Implications for the active form of human insulin based on the structural convergence of highly active hormone analogues" *Proc. Natl. Acad. Sci. USA* **2010**, 107, 1966-1970.
3. Antolíková, E., Žáková, L., Turkenburg, J. P., Watson, C. J., Hančlová, I., Šanda, M., Cooper, A., Kraus, T., Brzozowski, A. M., Jiráček, J. "Non-equivalent role of inter- and intramolecular hydrogen bonds in the insulin dimer interface" *J. Biol. Chem.* **2011**, 286, 36968-36977.
4. Mládková, J., Vaněk, V., Buděšínský, M.G., Elbert, T., Demianová, Z., Garrow, T.A., Jiráček, J. "Double-headed sulfur-linked amino acids as first inhibitors for betaine-homocysteine S-methyltransferase 2" *J. Med. Chem.* **2012**, 55, 6822-6831.
5. Menting, J. G., Whittaker, J., Margetts, M. B., Whittaker, L. J., Kong, G. K. W., Smith, B. J., Watson, C. J., Žáková, L, Kletvíková, E., Jiráček, J., Chan, S. J., Steiner, D. F., Dodson, G. G., Brzozowski, A. M., Weiss, M. A., Ward, C. W., Lawrence, M. C., "How insulin engages its primary binding site on the insulin receptor" *Nature* **2013**, 493, 241-245.
6. Žáková, L., Kletvíková, L., Veverka, V., Lepšík, M., Watson, C. J., Turkenburg, J. P., Jiráček, J., Brzozowski, A. M. "Structural integrity of the B24 site in human insulin is important for hormone functionality" *J. Biol. Chem.* **2013**, 288, 10230-10240.



Insulin activation



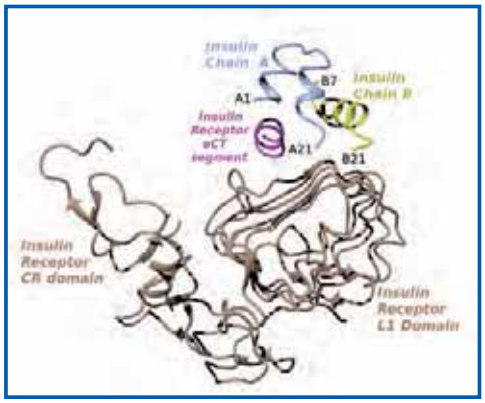
Detail of B26 – turn in insulin

DIPLOMA THESES

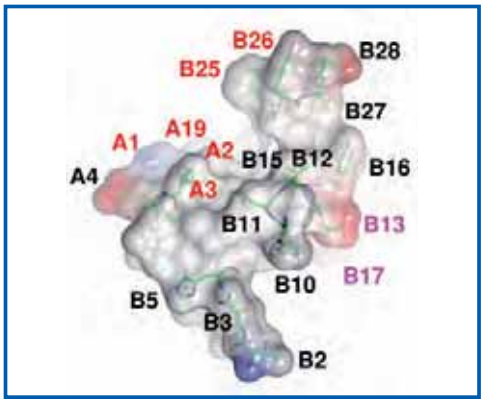
Vojtěch Kaplan	New analogues of human insulin with covalently stabilized cyclic structures in the C-terminus of the B-chain	Faculty of Sciences, Charles University in Prague
Lucie Kosinová	The study of conformation of the N-terminus of the B chain of insulin and its role in binding to the insulin receptor	Faculty of Sciences, Charles University in Prague
Květoslava Křížková	Synthesis and characterization of selective analogues of insulin and IGF-2 for different isoforms of insulin receptor	Faculty of Sciences, Charles University in Prague
Martina Chrudinová	Studies of interactions of insulin, IGF-1 and IGF-2 analogues with their respective receptors	Faculty of Sciences, Charles University in Prague

PhD THESES

Miloslav Šanda	The use of mass spectrometry in the study of immunity and cancer	Institute of Chemical Technology Prague
Emília Kletvíková-Antolíková	Synthesis and characterization of new insulin analogues with aim to clarify the interaction of insulin with its receptor	Faculty of Sciences, Charles University in Prague
Jana Mládková	The study of physiological functions of betaine-homocysteine S-methyltransferases 1 and 2	Faculty of Sciences, Charles University in Prague



Insulin – insulin receptor complex



Molecular shape of activated insulin

Jiří Jiráček / Head of the Group

Michaela Collinsová / Scientist
Jan Pícha / Scientist
Irena Selicharová / Scientist
Lenka Žáková / Scientist
Václav Vaněk / Research Assistant
Emília Kletvíková / Ph.D. Student
Jana Mládková / Ph.D. Student
Martina Chrudinová / Student
Lucie Kosinová / Student
Květoslava Křížková / Student
Jitka Viková / Technician

Cathepsin Proteases in Pathology

Michael MAREŠ

Biochemistry and Molecular Biology
e-mail: mares@uochb.cas.cz

Research topics

Our research focuses on cathepsin proteases involved in parasitic diseases and cancer.

In **blood-feeding parasites**, cathepsins function as digestive enzymes responsible for the breakdown of host blood proteins and represent pharmacological targets. We investigate two parasites: (a) *Schistosoma* blood flukes cause **schistosomiasis**, which afflicts more than 250 million people; our project is on structure-based drug design of inhibitors of *Schistosoma* cathepsins. (b) *Ixodes* ticks are the vectors of encephalitis and borreliosis; we characterize and evaluate tick cathepsins and their inhibitors as potential **anti-tick vaccines**.

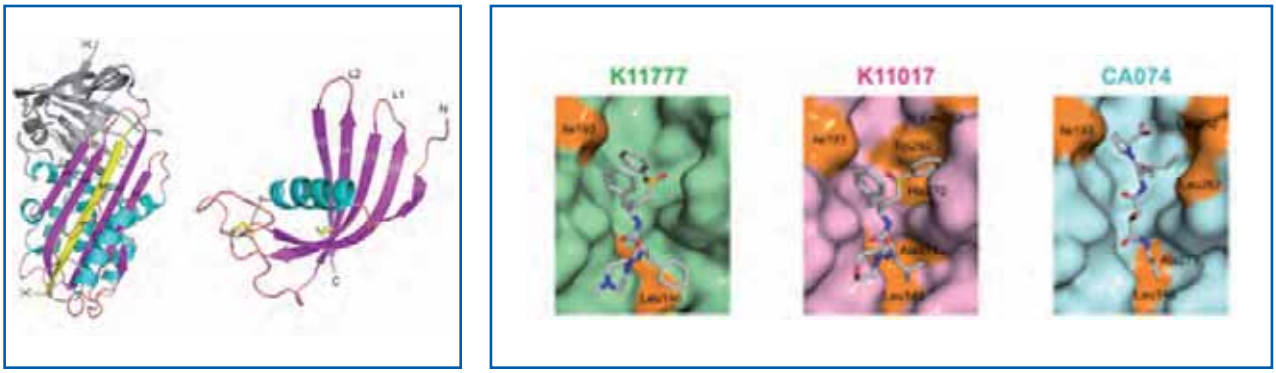
Human cathepsin D is a critical player and prognostic marker in **breast cancer**, and we study biochemical mechanisms of its activity regulation relevant to biomedicine.

Current grant support

Academy of Sciences (M200550912), Czech Science Foundation (P207/10/2183, P302/11/1481, 203/09/1585, 525/09/P600), Grant Agency of the ASCR (IAA400550705, IAA600960910), Ministry of Education, Youth and Sports of the CR (LH12023), and European Co-operation in Scientific and Technical Research (OC09007).

Selected recent papers

1. Jílková, A.; Řezáčová, P.; Lepšík, M.; Horn, M.; Váchová, J.; Fanfrlík, J.; Brynda, J.; McKerrow, J.H.; Caffrey, C.R.; Mareš, M. "Structural basis for the inhibition of the cathepsin B drug target from the human blood fluke *Schistosoma mansoni*" *J. Biol. Chem.* **2011,** *286*, 35770–35781.
2. Horn, M.; Jílková, A.; Vondrášek, J.; Marešová, L.; Caffrey, C.R.; Mareš, M. "Mapping the pro-peptide of the *Schistosoma mansoni* cathepsin B1 drug target: modulation of inhibition by heparin and design of mimetic inhibitors" *ACS Chem. Biol.* **2011**, *6*, 609-617.
3. Žebrakovská, I.; Máša, M.; Srp, J.; Horn, M.; Vávrová, K.; Mareš, M. "Complex modulation of peptidolytic activity of cathepsin D by sphingolipids" *Biochim. Biophys. Acta* **2011**, *1811*, 1097-1104.
4. Salát, J.; Paesen, G.C.; Řezáčová, P.; Kotsyfakis, M.; Kovářová, Z.; Šanda, M.; Majtán, J.; Grunclová, L.; Horká, H.; Andersen, J.F.; Brynda, J.; Horn, M.; Nunn, M.A.; Kopáček, P.; Kopecký, J.; Mareš, M. "Crystal structure and functional characterization of an immunomodulatory salivary cystatin from the soft tick *Ornithodoros moubata*" *Biochem. J.* **2010**, *429*, 103-112.
5. Nussbaumerová, M.; Srp, J.; Máša, M.; Hradilek, M.; Šanda, M.; Reiniš, M.; Horn, M.; Mareš, M. "Single- and double-headed chemical probes for detection of active cathepsin D in a cancer cell proteome" *Chembiochem* **2010**, *11*, 1538-1541.



X-ray structures of cathepsin inhibitors IRS-2 and OmC2 from tick saliva (left panels) and *Schistosoma* cathepsin B1 with lead inhibitors (right panels).

DIPLOMA THESES

Jaroslav Srp	Digestive aspartic protease of Colorado potato beetle	Faculty of Sciences, Charles University in Prague
Jana Váchová	Recombinant aspartic proteases of blood-feeding parasites	Faculty of Sciences, Charles University in Prague
Pavla Fajtová	Prolyl endopeptidase of the blood fluke *Schistosoma mansoni*	Faculty of Sciences, Charles University in Prague
Markéta Čermáková	Digestive proteases of termites	Faculty of Sciences, Charles University in Prague
Pavel Talacko	Cathepsin L from the hard tick *Ixodes ricinus*: analysis of proteolytic activity and its regulation	Faculty of Sciences, Charles University in Prague

Bachelor Theses

Pavel Talacko	Cathepsin L from the hard tick *Ixodes ricinus*	Faculty of Sciences, Charles University in Prague
Olívia Petrvalská	Prolyl endopeptidase from the tick *Ixodes ricinus*	Faculty of Sciences, Charles University in Prague

PhD THESES

Martin Máša	Regulation of cathepsin D activity and activation	Faculty of Sciences, Charles University in Prague

Michael Mareš / Head of the Group

Martin Horn / Scientist
Lucie Marešová / Research Assistant
Jana Pytelková / Postdoc
Adéla Jílková / Ph.D. Student
Iva Žebrakovská / Ph.D. Student
Zuzana Kovářová / Ph.D. Student
Jaroslav Srp / Ph.D. Student
Pavla Fajtová / Ph.D. Student
Jakub Benýšek / Ph.D. Student
Jana Váchová / Student
Markéta Čermáková / Student
Pavel Talacko / Student
Irena Oupicová / Student
Michal Buša / Student
Olívia Petrvalská / Student
Irena Pražáková / Technician

Proteases of Human Pathogens

Jan KONVALINKA

Biochemistry and Molecular Biology
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Research topics

In our laboratory we identify and study different proteases as possible targets for therapeutic intervention. Currently, we work on three different enzymes. The first one, an already well established therapeutic target, is *HIV protease.* We study the structure, function, and inhibition of this enzyme, as well as development of antiviral resistance in AIDS patients treated by protease inhibitors. We are also interested in inhibition of viral assembly by rationally designed low-molecular weight compounds.

Another target is *glutamate carboxypeptidase II*, a membrane bound peptidase expressed in a number of tissues, including the brain and prostate. In the human brain it plays an important role in several pathological processes (stroke, diabetic neuropathy, Alzheimer's disease, *etc.*). Inhibitors of this enzyme might serve as neuroprotectants, potential anticancer drugs or address for specific antitumor drug delivery. We study the structure and function of the enzyme, design its specific inhibitors and analyze the expression and function of the enzyme and its homologs in cancer development. Finally, we focus on a receptor of proteasomal degradation containing a retroviral protease-like domain, *DNA damage-inducible protein*. We study the structure, activity and role of this modular protein and its orthologs in molecular recognition and intracellular protein degradation.

Current grant support

GSRC – Gilead Sciences and IOCB Research Centre Prague, Gilead Sciences (Group Leader – Biology), 2011-2015

Grant Agency of the Academy of Sciences of the Czech Republic (2009 – 2013), Functional derivatives of cluster compounds of boron as inhibitors of viral enzyme

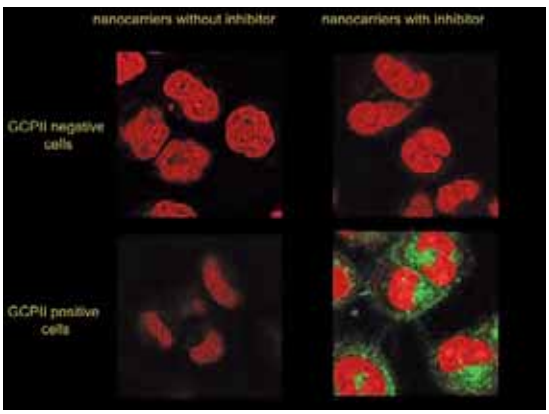
Grant Agency of the Czech Republic (2011 – 1013), Inhibitors of protease from HIV and resistance development

Grant Agency of the Czech Republic (2012 – 2014) Glutamate Carboxypeptidase II and its role in cancer development

Grant Agency of the Czech Republic (2013 – 2015) Assembly of HIV virions as a therapeutic target

Selected recent papers

1. Grantz Šašková K. *et al*, (2009). Molecular Characterization of Clinical Isolates of HIV Resistant to the Protease Inhibitor Darunavir. *J. Virol.* 83, 8810-8818
2. Jirásková-Vaníčková, J. *et al.* (2011). Inhibition of Human Serine Racemase, an Emerging Target for Medicinal Chemistry. *Curr. Drug Targets.* 12, 1037-1055
3. Plechanovová, A. *et al.* (2011). Novel Substrate-based Inhibitors of Glutamate Carboxypeptidase II with Enhanced Lipophilicity. *J. Med. Chem.* 54, 7535-46
4. Hlouchová, K. *et al.* (2012) GCPII Variants, Paralogs and Orthologs. *Curr. Med.Chem.* 19,1316-1322
5. Kožíšek, M. *et al.* (2012) Mutations in HIV-1 Gag and Pol Compensate for the Loss of Viral Fitness Caused by a Highly Mutated Protease. *Antimicrob. Agents Chemother.* 56, 4320-4330
6. Schimer, J. *et al.* (2012) Structure-aided Design of Novel Inhibitors of HIV Protease Based on a Benzodiazepine Scaffold. *J. Med. Chem.* 55, 10130-10135



Example of a specific delivery of a nanocarrier to GCPII-expressing tumor cells using specific ligand. The inhibitor of GCPII specifically directs the nanocarrier towards the cells expressing the tumor marker.

DIPLOMA THESES

Bäumlová Adriana	Expression and characterization of homologs of human glutamate carboxypeptidase II – 2012	Faculty of Sciences, Charles University in Prague
Sivá Monika	Expression and characterization of recombinant capsid protein from HIV and its mutants; towards inhibition of virus assembly – 2011	Faculty of Sciences, Charles University in Prague
Began Jakub	Mechanism of action of non-peptide inhibitors of HIV protease – 2011	Faculty of Sciences, Charles University in Prague
Svoboda Michal	Analysis of the mechanism of action of metallacarborane inhibitors of HIV protease – 2011	Faculty of Sciences, Charles University in Prague
Knedlík Tomáš	Cloning, expression and biochemic characterisation of mouse glutamate carboxypeptidase II – 2010	Faculty of Sciences, Charles University in Prague
Schimer Jiří	New inhibitors of HIV protease: design, synthesis and activity testing aktivity – 2011	Faculty of Sciences, Charles University in Prague
Nováková Ilona	Cloning, expression and characterization of the mutants of human serine racemase – 2010	Faculty of Sciences, Charles University in Prague

PhD THESES

Kožíšek Milan	Overcoming drug resistance: The discovery, design and characterization of new nonpeptidic inhibitors of HIV-1 protease – 2010	Faculty of Sciences, Charles University in Prague
Grantz Šašková Klára	HIV-1 Protease: Insights into drug resistance development – 2010	Faculty of Sciences, Charles University in Prague
Hoffman Hillary E.	Characterization of recombinant human serine racemase – 2010	Faculty of Sciences, Charles University in Prague
Jirásková Jana	Mammalian Serine Racemase as a Pharmaceutical Target – 2010	Faculty of Sciences, Charles University in Prague

Jan Konvalinka / Head of the Group

Pavel Šácha / Scientist
Milan Kožíšek / Scientist
Klára Grantz Šašková / Scientist
Taťána Majerová / Scientist
Klára Hlouchová / Postdoc
Jana Pokorná / Research Assistant
Michal Navrátil / Ph.D. Student
Václav Navrátil / Ph.D. Student
Jan Tykvart / Ph.D. Student
Tomáš Knedlík / Ph.D. Student
František Sedlák / Ph.D. Student
Jiří Schimer / Ph.D. Student
Michal Svoboda / Ph.D. Student
Barbora Vorlová / Ph.D. Student
Monika Sivá / Ph.D. Student
Jan Tužil / Diploma Student
Kristýna Blažková / Diploma Student
Helena Jindrová / Bachelor Student
Jan Parolek / Bachelor Student
Jan Belza / Bachelor Student
Jindřich Durčák / Bachelor Student
Jitka Krčmářová / Assistant
Jana Starková / Technician
Karolína Šrámková / Technician
Iva Flaisigová / Technician

Microbial Proteins

Iva PICHOVÁ

Biochemistry and Molecular Biology
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Research topics

Our research group is primarily interested in the functional and structural study of key proteins of three human pathogens and their interaction with cellular proteins and cellular machineries.

In projects focused on retroviruses, we investigated mechanism of assembly and maturation. Combination of biochemical characterization of proteins, *in vitro* assembly analysis, tissue culture experiments with mutated viruses, and structure determination of retroviral protease monomer and immature Gag shell from Mason-Pfizer monkey virus in collaborating laboratories, allowed to define the protein interfaces mediating retrovirus assembly and maturation. Our findings may help to design new types of anti-retroviral therapies.

Our long-term objective in pathogenic *Candida* project is a complex description of the extracellular proteolysis of *Candida spp.* We analyzed expression, synthesis, and trafficking of secreted aspartic proteases (Saps) in *C. parapsilosis* under various conditions. Solution of the crystal structure of *C. parapsilosis* Sapp1p in complex with pepstatin and Ritonavir provided also information for development of more selective inhibitors.

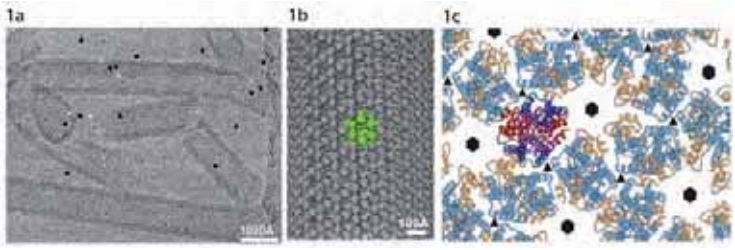
We collaborated with our partners from the FP7 project on analysis of metabolism of *Mycobacterium tuberculosis.* We characterized selected enzymes from central carbon metabolism that were predicted to play regulating role in the switch of Mtb metabolism under hypoxia.

Current grant support

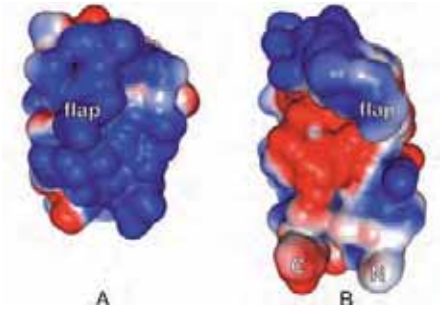
FP7- Collaborative project, SysteMtb HEALTH-F4--2010-241587; Technology Agency of Czech Republic (TA01011461), Czech Science foundation (204/09/1388) and Gilead Sciences, Inc. (Foster City, USA)

Selected recent papers

1. Böhmová, K., Hadravová, R., Štokrová, J., Tůma, R., Ruml, T., Pichová, I., & Rumlová, M. **(2010).** The effect of dimerizing domains and basic residues on in vitro and in vivo assembly of Mason-Pfizer monkey virus and Human immunodeficiency virus. *J. Virol.*, 84, 1977-1988.
2. Zábranský, A., Hoboth, P., Hadravová, R., Štokrová, J., Sakalian, M., & Pichová, I. (**2010).** The Noncanonical Gag Domains p8 and n Are Critical for Assembly and Release of Mouse Mammary Tumor Virus. *J. Virol.*, **84**, 11555-11559.
3. Gilski, M., Kazmierczyk, M., Krzywda, S., Zábranská, H., Cooper, S., Popovic, Z., Khatíb, F., Dímaio, F., Thompson, J., Baker, D., Pichová, I., & Jaskolski, M. **(2011)**. High-resolution structure of a retroviral protease folded as a monomer. *Acta Crystallographica Section D-Biological Crystallography,* D67, 907-914.
4. Vinterová, Z., Šanda, M., Dostál, J., Hrušková, O., Pichová, I. (**2011**). Evidence for the presence of proteolytically active secreted aspartic proteinase 1 of Candida parapsilosis in the cell wall. *Protein Science,* 20, 2004-2012.
5. Bharat, TAM, Davey, NE., Ulbrich, P., Riches, JD, de Marco, A., Rumlova, M.**,** Sachse, C., Ruml,T. & John A. G. Briggs, JAG. (**2012**). Structure of the immature retroviral capsid at 8 angstrom resolution by cry-electron microscopy. *NATURE* , 487, 385-389



Electron microscopic image of retroviral particle (1a), a real-space reconstruction (1b), arrangement of individual domains in an immature particle (1c).



The structure of monomeric M-PMV protease (A) compared to its HIV-1 counterpart extracted from the dimeric context (B).

DIPLOMA THESES

Martin Obr	Effect of capsid protein mutations on assembly of the Mason-Pfizer monkey virus particles	Institute of Chemical Technology, Prague
Martin Obr	NMR structure of an assembly defective mutant of the N-trminala domain of the capsid protein from Mason-Pfizer monkey virus.	Faculty of Sciences, Charles University in Prague
Lucie Marečková	The secreted aspartic proteases of Candida parapsilosis	Faculty of Sciences, Charles University in Prague
Lenka Mynářová	The study of mutual interaction between pathogenic yeasts of the genes Candida and bacterium Pseudomonas aeruginosaduring cocultivation	Faculty of Sciences, Charles University in Prague

PhD THESES

Aleš Buček	Characterization of fatty acid desaturases involved in insect pheromone biosynthesis	Faculty of Sciences, Charles University in Prague
Václava Bauerová	Proteases of Candida albicans	Institute of Chemical Technology, Prague
Michal Doležal	Structural analysis of biologically relevant interactions of retroviral and cellular proteins	Institute of Chemical Technology, Prague
Alena Keprová	The study of cellular proteins affecting retroviral replication cycle.	Institute of Chemical Technology, Prague
Iva Machová	The study of key enzymes of Mycobacterium tuberculosis	Institute of Chemical Technology, Prague
Darina Prchalová	The study of enzymes involved in the pheromone biosynthesis of Bombus species	Institute of Chemical Technology, Prague
Karolína Strohalmová	Interactions of retroviral and cellular proteins and nucleic acids	Institute of Chemical Technology, Prague
Zuzana Vinterová	Secretion of aspartic proteinases of the pathogenic yeast Candida parapsilosis	Faculty of Sciences, Charles University in Prague

TEACHING ACTIVITIES

Gene and Protein engineering	Iva Pichová	University of South Bohemia

Iva Pichová / Head of the Group

Michaela Rumlová / Scientist
Olga Hrušková / Scientist
Aleš Zábranský / Junior Scientist
Jan Snášel / Junior Scientist
Helena Zábranská / Junior Scientist
Dostál Jiří / Postdoc
Václava Bauerová / Ph.D. Student
Zuzana Vinterová / Ph.D. Student
Karolína Strohalmová / Ph.D. Student
Aleš Buček / Ph.D. Student
Michal Doležal / Ph.D. Student
Darina Prchalová / Ph.D. Student
Iva Machová / Ph.D. Student
Alena Keprová / Ph.D. Student
Mária Čechová / Research Assistant
Romana Hadravová / Research Assistant
Ivana Křížová / Research Assistant
Jitka Štokrová / Scientist
Romana Cubínková / Technician
Elena Dolejší / Technician
Dagmar Grundová / Technician

Organic Synthesis

Josef MICHL

Organic Synthesis
e-mail: michl@uochb.cas.cz

Research topics

Our research group is engaged in molecular electronics in a broad sense of the term.

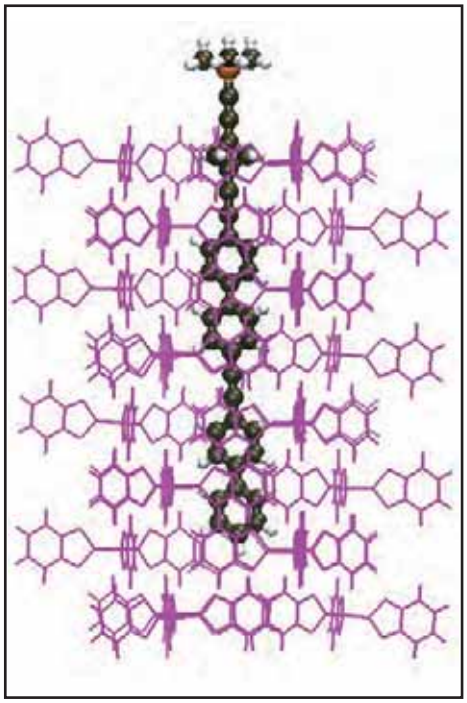
- We are attempting to fabricate artificial ferroelectric surfaces by preparing dipolar molecular rotors and mounting them in regular arrays
- We are developing new ways of attaching organic molecules to metal surfaces
- We are looking for new singlet fission sensitizers for solar cells
- We are studying the strongest oxidants known in the bulk phase

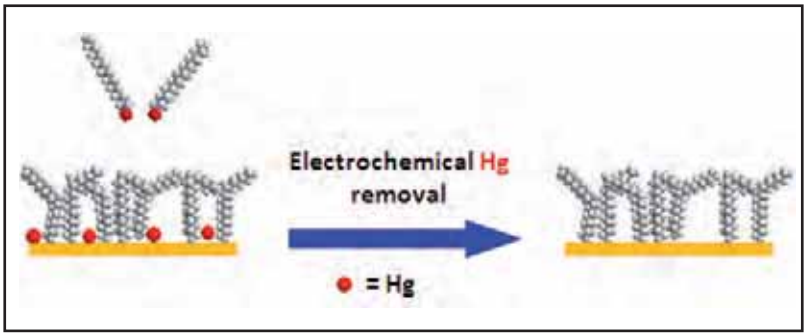
Current grant support

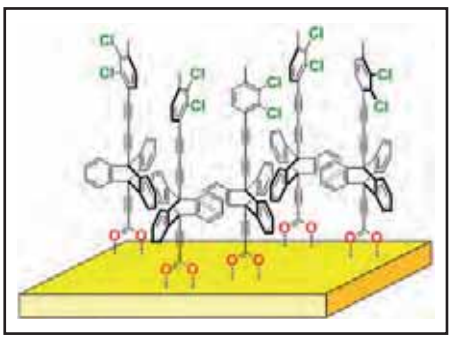
ERC IDEAS 2009-2013 FP7: ERC-2008-AdG 227756 Dipolar Rotor Array; FUNMOL 213382; Grant Agency of the Czech Rep. 203/09/J058; Grant Agency of Academy of Sciences: M200550906 and IAA400550708

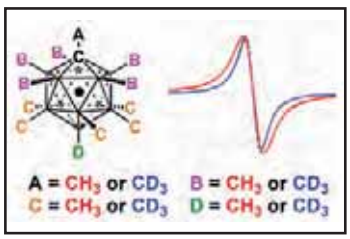
Selected recent papers

1. Dudič, M., Císařová, I. - Michl, J.: Synthesis of Hexadehydrotribenzo[a,e,i][12]annulenes by Acetylene Insertion into an Open-Chain Precursor, *Journal of Organic Chemistry* 77, 1, 68-74, **2012**.
2. Kaleta, J., Tarábek, J., Akdag, A. Pohl, R., Michl, J.: The 16 $CB_{11}(CH_3)_n(CD_3)_{12-n}$· Radicals with 5-Fold Substitution Symmetry: Spin Density Distribution in $CB_{11}Me_{12}$·, *Inorganic Chemistry* 51: 20, 10819-10824, **2012**.
3. Akdag, A., Havlas, Z., Michl, J.: Search for a Small Chromo-phore with Efficient Singlet Fission: Biradicaloid Heterocycles, *Journal of the American Chemical Society* 134, 35, 14624-14631, **2012**.
4. Kobr, L., Zhao, K., Shen, Y., Polívková, K., Shoemaker, R. K., Clark, N. A., Price, J. C., Rogers, C. T., Michl, J.: Inclusion Compound Based Approach to Arrays of Artificial Dipolar Molecular Rotors. Bulk Inclusions, *Journal of Organic Chemistry* 78, 1768, **2013**.
5. Mucha, M., Kaletová, E., Kohutová, A., Scholz, F., Stensrud, E. S., Stibor, I., Pospíšil, L., von Wrochem, F., Michl, J.: Alkylation of Gold Surface by Treatment with $C_{18}H_{37}HgOTs$ and Anodic Hg Stripping, *Journal of the American Chemical Society*, published online, Feb. 19, **2013**, http://dx.doi.org/10.1021/ja3117125.









PhD THESES

Filip Šembera	Synthesis and study of fys. chem. properties of low nucleofile anion CB11H12-	Institute of Chemical Technology, Prague

POSTDOCTORAL PROJECTS

Jin Wen	China	Josef Michl
Ali Younes	Lebanon	Josef Michl

SIGNIFICANT AWARDS

Josef Michl	American Chemical Society Fellow	American Chemical Society
Josef Michl	President of the International Academy of Quantum Molecular Sciences	International Academy of Quantum Molecular Sciences

TEACHING ACTIVITIES

Organic Chemistry	Josef Michl	University of Colorado at Boulder, CO, USA
Organic Chemistry lessons	Filip Šembera	Institute of Chemical Technology, Prague

Josef Michl / Head of the Group

Zbyněk Janoušek / Scientist
Lubomír Pospíšil / Scientist
Jan Hajduch / Scientist
Jiří Kaleta / Postdoc
Eva Kaletová / Postdoc
Anna Kohutová / Postdoc
Jan Plutnar / Postdoc
Milan Mašát / Postdoc
Martina Čížková / Postdoc
Jin Wen / Postdoc
Ali Younes / Postdoc
Filip Šembera / Ph.D. Student
Kateřina Čmelová / Secretary

Former Members:

Ivan Stibor / Scientist
Jaroslav Vacek / Scientist
Michal Valášek / Postdoc
Felipe Luis Chazaro Ruiz / Postdoc
Miroslav Dudič / Postdoc
Elizabeth Stensrud / Postdoc
Kenneth Stensrud / Postdoc
Malgorzata Mucha / Postdoc
Nitesh Amrutkar / Postdoc
Kateřina Polívková / Ph.D. Student
Juri Ugolotti / Postdoc
Sagar Kesarkar / Postdoc
Marco Cipolloni / Postdoc
Akin Akdag / Postdoc
Himansu Sekhar Sahoo / Postdoc
Zhenjun Si / Postdoc
Cyprien Lemouchi / Postdoc
Petr Vlček / Scientist
Pavle Močilac / Postdoc
Jason Perman / Postdoc

Structural Biology

Pavlína ŘEZÁČOVÁ

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Research topics

Our team's main interest is in the structural study of proteins having biological or medicinal interest. We use structural knowledge to understand and modulate the biological roles and functions of proteins.

We are interested in the *structure of transcription factors*, both prokaryotic and eukaryotic. To understand the mechanism of carbon catabolite repression in *B. subtilis* on a molecular level, we combine X-ray crystalography with other techniques to study the binding of small molecules to selected repressors and their modulation. Structural studies of human transcription factors focus on proteins interacting with LEDGF/ /p75, a prominent cellular cofactor for HIV integration. In our *structure-based drug discovery project,* targeting enzymes from pathogenic organisms (e.g. HIV protease, *Candida* proteases) as well as human enzymes (e.g. carbonic anhydrases), the knowledge of protein structures provides a platform for the rational design of specific inhibitors.

The *structural biology of metabolic pathways* topic is focused on the structural characterization of components of important metabolic pathways, which can contribute to the development of prospective therapeutics for insulin related diseases and obesity, such as analogues derived from insulin, insulin-like growth factors, food uptake-modulating neuropeptides and proteins stimulating energy expenditure in adipose tissue.

The team also maintains an X-ray diffraction station for macromolecular crystallography and provides small molecular crystallography services.

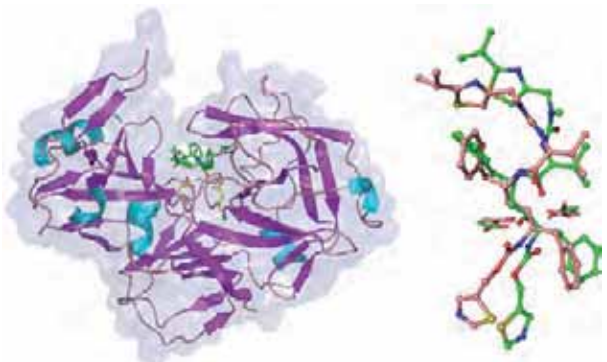
Current grant support

Rational drug design using NMR spectroscopy (LK11205 – Navrat), Ministry of Education of the Czech Republic

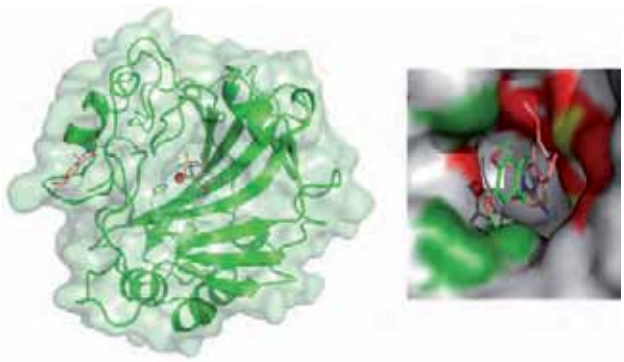
Center for development of original drugs (CDOD), Technology Agency of the Czech Republic

Selected recent papers

1. Krejcirikova, V., Pachl, P., Fabry, M., Maly, P., Rezacova, P. & Brynda, J. (2011). Structure of the mouse galectin-4 N-terminal carbohydrate-recognition domain reveals the mechanism of oligosaccharide recognition. *Acta Crystallogr D Biol Crystallogr* **67**, 204-11.
2. Mader, P., Brynda, J., Gitto, R., Agnello, S., Pachl, P., Supuran, C. T., Chimirri, A. & Rezacova, P. (2011). Structural basis for the interaction between carbonic anhydrase and 1,2,3,4-tetrahydroisoquinolin-2-ylsulfonamides. *J Med Chem* **54**, 2522-6.
3. Dostal, J., Brynda, J., Hruskova-Heidingsfeldova, O., Pachl, P., Pichova, I. & Rezacova, P. (2012). The crystal structure of protease Sapp1p from Candida parapsilosis in complex with the HIV protease inhibitor ritonavir. *J Enzyme Inhib Med Chem* **27**, 160-5.
4. Prochazkova, K., Cermakova, K., Pachl, P., Sieglova, I., Fabry, M., Otwinowski, Z. & Rezacova, P. (2012). Structure of the effector-binding domain of the arabinose repressor AraR from Bacillus subtilis. *Acta Crystallogr D Biol Crystallogr* **68**, 176-85.



Crystal structure of secreted aspartic protease 1 (Sapp1p) from *Candida parapsilosis* in complex with the anti-HIV drug ritonavir (see reference 3 for details). The right panel shows a comparison of ritonavir binding modes in Sapp1p (green) and HIV protease (pink).



Crystal structure of human carbonic anhydrase II in complex with isoquinoline inhibitor (see reference 2 for details). The right panel shows an unusual inhibitor binding mode (red) compared to a similar compound in canonical binding mode (green).

DIPLOMA THESES

Kateřina Čermáková	Preparation and characterization of human cellular cofactors of retroviral integration	Faculty of Sciences, Charles University in Prague
Kristýna Poncová	Preparation, characterization and crystallization of human carbonic anhydrase	Institute of Chemical Technology, Prague

TEACHING ACTIVITIES

Determination of 3D structure of biomolecules	Pavlína Řezáčová, Jiří Brynda	Faculty of Sciences, Charles University in Prague
Molecular Modeling and Bioinformatics	Jiří Brynda, Pavlína Řezáčová	Institute of Chemical Technology, Prague
Knowledge-based drug discovery	Václav Veverka	University of Leicester, UK

Pavlína Řezáčová / Head of the Group

Jiří Brynda / Staff Scientist
Václav Veverka / Staff Scientist
Jan Závada / Staff Scientist
Aleš Hnízda / Postdoc
Blanka Klepetářová / Research Assistant
Irena Sieglová / Research Assistant
Jitka Kredbová / Technician
Petr Pachl / Postgraduate Student
Jana Písačková / Postgraduate Student
Petr Těšina / Postgraduate Student
Kristýna Poncová / Undergraduate Student
Klára Pospíšilová / Undergraduate Student
Radka Skleničková / Undergraduate Student
Rozálie Litváková / Undergraduate Student

Helical Aromatics, Functional π-Electron Systems

Ivo STARÝ

Organic Synthesis
e-mail: stary@uochb.cas.cz

Research topics

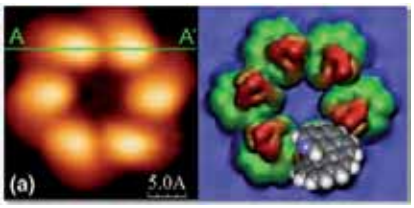
The team is focused on the synthesis and properties of new π-electron systems, which are attractive for enantioselective catalysis, supramolecular chemistry and molecular electronics. In particular, the attention is paid to helically chiral aromatics (helicenes) that are enantiopure and properly functionalised. Recently, the research is directed also towards self-assembly and chemical reactivity of π-electron systems on solid surfaces including nanoparticles, multiple D-A interactions and flow chemistry. The experimental approaches go hand in hand with computational ones in order to obtain deep insights into reactivity and physicochemical properties of target π-electron systems. Multidisciplinary research is performed in close collaboration with experts in scanning probe microscopy and electrochemistry.

Current grant support

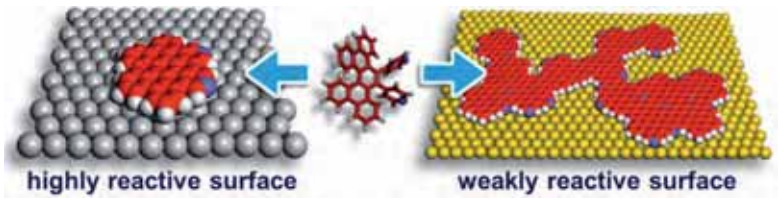
Czech Science Foundation (203/09/1766, P207/10/2214, P207/10/2207)

Selected recent papers

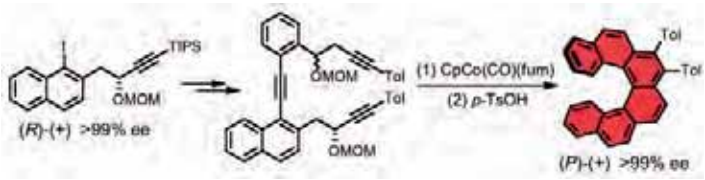
1. Lipnická, Š.; Bělohradský, M.; Kolivoška, K.; Pospíšil, L.; Hromadová, M.; Pohl, R.; Vacek Chocholoušová, J.; Vacek, J.; Fiedler, J.; Stará, I. G.; Starý, I. "Tetrathiafulvalene-Oligo(*p*-phenyleneethynylene) Conjugates: A Formation of Multiple Mixed-Valence Complexes upon Electrochemical Oxidation" *Chem. Eur. J.* **2013**, *19*, 6108–6121.
2. Pinardi, A. L.; Otero-Irurueta, G.; Palacio, I.; Martinez, J. I.; Sánchez-Sánchez, C.; Tello, M.; Roger, C.; Cossaro, A.; Preobrajenski, A.; Gomez-Lor, B.; Jančařík, A.; Stará, I. G.; Starý, I.; López, M. F.; Méndez, J.; Martín-Gago, J. A. "Tailored Formation of N-Doped Nanoarchitectures by Diffusion-Controlled On-Surface (Cyclo)dehydrogenation of Heteroaromatics" *ACS Nano* **2013**, *7*, 3676–3684.
3. Žádný, J.; Jančařík, A.; Andronova, A.; Šámal, M.; Vacek Chocholoušová, J.; Vacek, J.; Pohl, R.; Šaman, D.; Císařová, I.; Stará, I. G.; Starý, I. "A General Approach to Optically Pure [5]-, [6]-, and [7]Heterohelicenes" *Angew. Chem. Int. Ed.* **2012**, *51*, 5857–5861.
4. Jančařík, A.; Rybáček, J.; Cocq, K.; Vacek Chocholoušová, J.; Vacek, J.; Pohl, R.; Bednárová, L.; Fiedler, P.; Císařová, I.; Stará, I. G.; Starý I. "Rapid Access to Dibenzohelicenes and their Functionalized Derivatives" *Angew. Chem. Int. Ed.* **2013**, DOI: 10.1002/anie.201301739.



Experimental and calculated STM images of azahelicene cluster on Ag(111)



On-surface formation of N-doped nanographene or 2D network



Asymmetric synthesis of enantiopure helicenes

Three-to-six step synthesis of dibenzohelicenes

DIPLOMA THESES

Jan Holec	Amphiphilic tetrathiafulvalene derivatives	Institute of Chemical Technology, Prague
Jindřich Nejedlý	Derivatives of tetrathiafulvalene: Synthesis and study on their properties	Faculty of Sciences, Charles University in Prague
Tomáš Warzecha	The π-electron oligomers: Their synthesis and properties	Faculty of Sciences, Charles University in Prague
Ondřej Palata	Synthesis of thiophenohelicenes and their physico-chemical properties	Faculty of Sciences, Charles University in Prague
Jiří Klívar	Cyclotrimerization of alkynes and nitriles in the synthesis of helically chiral compounds	Faculty of Sciences, Charles University in Prague

PhD THESES

Angelina Andronova	Diastereoselective synthesis of helically chiral compounds for enantioselective catalysis	Faculty of Sciences, Charles University in Prague

POSTDOCTORAL PROJECTS

Serghei Chercheja	Moldova	Ivo Starý

TEACHING ACTIVITIES

Mechanisms of Organic Reactions	Ivo Starý	Faculty of Natural Sciences, Charles University in Prague

Ivo Starý / Head of the Group

Martin Bělohradský / Scientist
Petr Holý / Scientist
Jiří Rybáček / Scientist
Irena G. Stará / Scientist
Jaroslav Vacek / Scientist
Jana Vacek Chocholoušová / Scientist
Serghei Chercheja / Postdoc
Michal Buchta / Ph.D. Student
Jan Holec / Ph.D. Student
Andrej Jančařík / Ph.D. Student
Šárka Lipnická / Ph.D. Student
Jindřich Nejedlý / Ph.D. Student
Petr Polášek / Ph.D. Student
Arnošt Seidler / Ph.D. Student
Michal Šámal / Ph.D. Student
Tomáš Warzecha / Ph.D. Student
Jaroslav Žádný / Ph.D. Student
Václav Houska / Student
Jiří Janoušek / Student
Jiří Klívar / Ph.D. Student
Ondřej Palata / Student
Blanka Rejchrtová / Student
Jaroslava Perková / Technician
Kateřina Pokorná / Secretary

Bio-mimetic Reactions in Organic Synthesis

Jiří ŠROGL

Organic Synthesis
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Research topics

The main inspirations of our research are the chemistries and events we can see around us in everyday life. Consequently, our strategy involves expounding the core of natural processes and application of the resultant insights in such diverse fields as materials engineering on one side, and organic synthesis on the other, in the hope of obtaining a Nature-like quality in artificial settings.

The first of our interests is centered around the interactions of organosulfur moieties with transition and non-transition metals. Given the structural variety in sulfur based functional groups and their chemical functions, the whole research theme has been separated into several subprojects: sulfur based leaving groups in cross-coupling reactions, and disulfide/thiol dyad as a key factor in a bio-relevant metal transport and self-healing materials engineering.

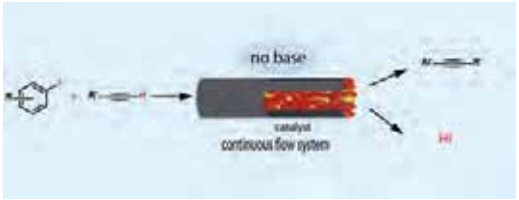
Our second research endeavor is focused on "non-chemical" control of chemical processes. Within this area we systematically study continuous flow regime as a paradigm in chemical equilibrium manipulation. Connected to this platform is also the last, fundamentally important theme of our research which examines a role of spatial arrangements on the reactivity of chemical entities.

Current grant support

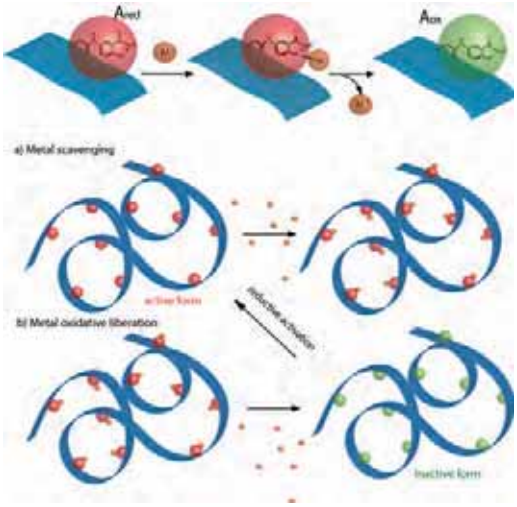
Ministry of Education LH12012
Grant Agency of the Czech Republic P207/12/0846
Ministry of Education LH12013
Academy of Sciences M200550907
Academy of Sciences M200550908

Selected recent papers

1. Voltrova, S., Hidasova, D., Genzer, J., Srogl, J. *Chem. Comm.*, 2011, *47*, 8067- 8069. Metallothionein-inspired prototype of molecular pincer.
2. Henke, A., Srogl, J. . *Chem. Comm.*, 2011, *47,* 4282- 4284. Pd2+ and Cu2+ Catalyzed Oxidative Cross-coupling of Mercaptoacetylenes and Arylboronic Acids.
3. S. Voltrova, Jiri Srogl. *Synlett,* 2013**,** *24*, 0394- 0396. Expedient Method for Samarium(II) Iodide Preparation Utilizing a Flow Approach.
4. Henke, A., Srogl, J. *Chem. Comm.* 2010**,** *46,* 6819-6821. Cu and Ag catalyzed arylthiation of terminal acetylenes.
5. Martinek, M., Korf, M., Srogl, J. *Chem. Comm.* 2010, ***46,*** 4387-4389. Ascorbate mediated copper catalyzed reductive cross–coupling of disulfides with aryl iodides .



Cross coupling reaction under non-basic condition



Metal capture and release

DIPLOMA THESES

Marek Martínek	Cross-coupling reactions of organosulfur compounds	Faculty of Sciences, Charles University in Prague
Denisa Hidasová	Transition metal catalyzed cross-coupling reactions of onium salts	Faculty of Sciences, Charles University in Prague
Iva Štibingerová	Study of behaviour of metal catalzyed reactions of sulfilimines and sulfoxides	Institute of Chemical Technology, Prague

PhD THESES

Adam Henke	Reactivity of organosulfur compounds and their interactions with transition metals	Institute of Chemical Technology, Prague
Jakub Hývl	Study of reactivity of organosulfur compounds and transition metals	Institute of Chemical Technology, Prague

Jiří Šrogl / Head of the Group

Svatava Voltrová / Scientist
Isabel Gay Sanchez / Ph.D. Student
Iva Štibingerová / Ph.D. Student
Erik Andris / Student
Šárka Kočová / Student
Annamarie Nemethová / Student
Petr Novotný / Student

Organic Chemistry of Fluorine, Phosphorus, Sulfur and Silicon
New Methodology Development and Synthesis

Petr BEIER

Organic Chemistry
email: beier@uochb.cas.cz

Research topics

Our research is focused on organic chemistry of fluorine, sulfur, phosphorus, and silicon elements. We are developing new synthetic methodologies towards selectively substituted fluorinated compounds. In particular, the research is focused on the chemistry of fluorinated phosphonates, novel reagents for the transfer of fluoroalkyl groups, synthesis and reactivity investigations of hypervalent sulfur fluorides such as sulfur pentafluorides and sulfur chlorotetrafluorides, and synthesis of butenolide germination promotors and inhibitors, determination of mechanism of their action and structure-activity relationship of their synthetic analogues. Properties and utilization of perfluorocarbons is also under investigation.

Current grant support

Grant Agency of the Czech Republic P207/11/0421.
Grant Agency of the Czech Republic P207/12/0072.
Deutsche Forschungsgemeinschaft. RO 362/54-1.
EU Initial Training Network Fluor 21.

Nucleophilic fluoroalkyl transfer using fluorinated phosphonates.

Selected recent papers

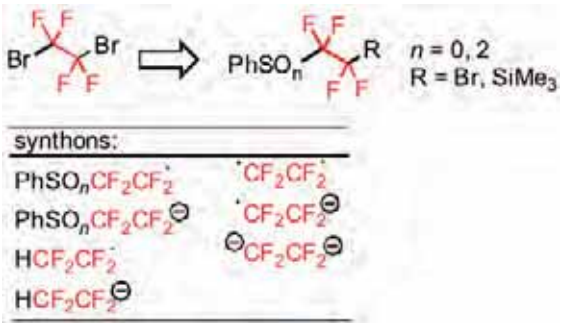
1. Pastýříková T., Iakobson G., Vida N., Pohl R., Beier P. "Direct Amination of Nitro(pentafluorosulfanyl)benzenes through Vicarious Nucleophilic Substitution of Hydrogen" *Eur. J. Org. Chem.* **2012**, 2123-2126.
2. Beier P., Pastýříková T., Vida N., Iakobson G. "S_NAr reactions of Nitro-(pentafluorosulfanyl)bnezenes to Generate SF_5 Aryl Ethers and Sulfides" *Org. Lett.* **2011**, *13*, 1466-1469.
3. Beier P., Pastýříková T., Iakobson G. "Preparation of SF_5 Aromatics by Vicarious Nucleophilic Substitution Reactions of Nitro(pentafluorosulfanyl)-benzenes with Carbanions" *J. Org. Chem.* **2011**, *76*, 4781-4786.
4. Chernykh Y., Hlat-Glembová K., Klepetářová B., Beier P. "Development of $PhSCF_2CF_2SiMe_3$ as a Tandem Anion and Radical Tetrafluoroethylene Equivalent: Preparation of Tetrafluoroethyl-Substituted Alcohols and Tetrafluorotetrahydropyrans" *Eur. J. Org. Chem.* **2011**, 4528-4531.
5. Beier P., Opekar S., Zibinsky M., Bychinskaya I., Prakash G.K.S. "A New Route to α-Alkyl-α-fluoromethylenebisphosphonates" *Org. Biomol. Chem.* **2011**, *9*, 4035-4038.

PhD THESES

Prabhakar Cherkupally	Synthesis and application of fluorophosphonates	Faculty of Sciences, Charles University in Prague

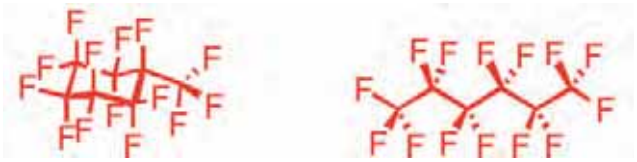
POSTDOCTORAL PROJECTS

Martin Pošta, Ph.D.	Czech Republic	Petr Beier



Sulfur-based reagents for CF_2CF_2 group transfer.

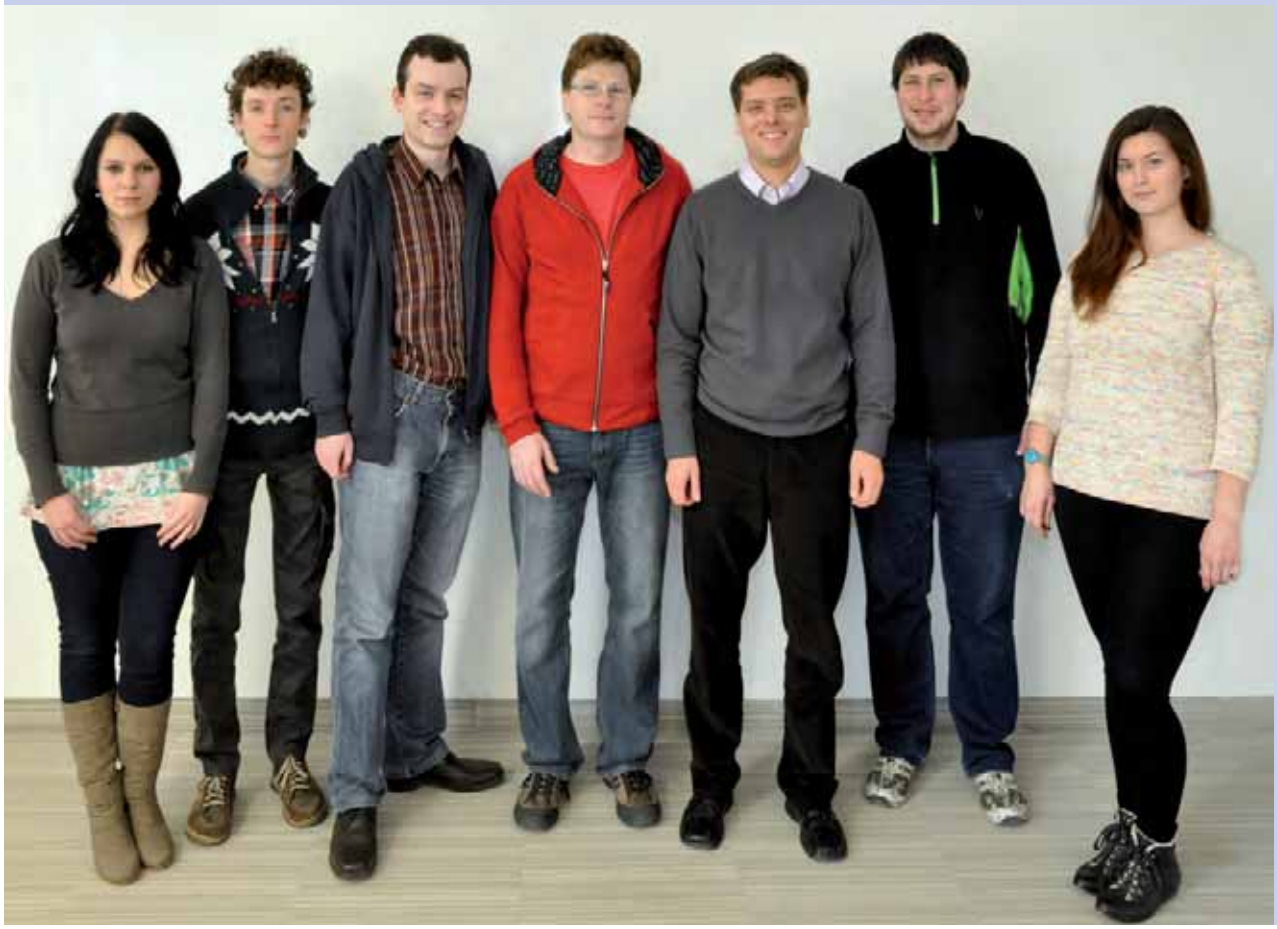
New methodologies towards arylsulfur pentafluorides.



Perfluorocarbons – novel reaction media.

Petr Beier / Head of the Group

Martin Pošta / Postdoc	Yana Chernykh / Ph.D. Student	Norbert Vida / Ph.D. Student
Stanislav Opekar / Ph.D. Student	George Iakobson / Ph.D. Student	Tereza Pastýříková / Student



Chemistry of Natural Products

Ullrich JAHN

Natural Products Chemistry
e-mail: jahn@uochb.cas.cz

Research topics

The research of the team centers around three major areas. Central to all is the aim of more time and resource efficient approaches to the total synthesis of natural products and their analogs. Members of the group work on the development of new domino or tandem reactions, which incorporate multiple intermediates of different redox state. These sequences are applied in approaches to the total synthesis of alkaloids, isoprostanes as major lipid metabolites of oxidative stress, lignans, β-amino acid derivatives and their analogs. In collaboration with other groups at the institute and abroad, the structure of natural products used in the communication of insects and the enzymes involved in their formation is elucidated. A third general direction consists of the exploration of new approaches for the generation of organometallic intermediates and their application for the synthesis of new ligands, transition metal complexes for catalysis and to the development of transition metal-catalyzed synthetic methodology.

Current grant support

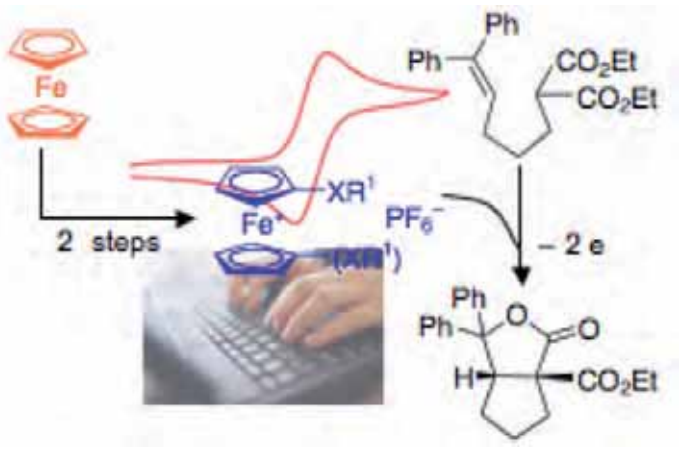
Academy of Sciences (RVO:61388963), Grant Agency of the Czech Republic (P207/11/1598, 13-40188S), COST (CM-1201), and Gilead Sciences, Inc. (Foster City, USA).

Selected recent papers

1. J. Cvačka, P. Jiroš, B. Kalinová, J. Straka, K. Černá, P. Šebesta, A. Tomčala, S. Vašíčková, U. Jahn, J. Šobotník Stylopsal: The first identified female sex pheromone of Strepsiptera, *J. Chem. Ecol.* **2012**, *38*, 1483-491.
2. D. A. Khobragade, S. G. Mahamulkar, L. Pospíšil, I. Cisařova, L. Rulíšek, U. Jahn, Acceptor-Substituted Ferrocenium Salts as New Strong Single-Electron Oxidants - Synthesis, Electrochemistry, Computational Investigations and Initial Synthetic Application, *Chem. Eur. J.* **2012**, *18*, 12267-12277.
3. E. Dinca, P. Hartmann, J. Smrček, I. Dix, P. G. Jones, U. Jahn, General and Efficient α-Oxygenation of Carbonyl Compounds by TEMPO Induced by Single Electron Transfer Oxidation of Their Enolates, *Eur. J. Org. Chem.* **2012**, 4461-4482.
4. Radicals in Transition Metal Catalyzed Reactions? Transition Metal Catalyzed Radical Reactions? A Fruitful Interplay Anyway. Part 1-3, U. Jahn, *Topics Curr. Chem.* **2012**, *320*, 121-190, 191-322, 323-452.
5. T. Amatov, U. Jahn, Perhaloalkylation of Metal Enolates - Unconventional and Versatile, *Angew. Chem. Int. Ed.* **2011**, *50*, 4542-4544.
6. B. Puget, U. Jahn β, β-Disilylated Sulfones as Versatile Building Blocks in Organic Chemistry - A New Sulfonyl Carbanion Transmetalation, *Synlett* **2010**, 2579-2582.

Reactive intermediate-directed chemistry.

Structure elucidation and total synthesis of the first identified sex pheromone of *Strepsiptera*.



New strong single electron oxidants, theory and applications.

DIPLOMA THESES

Martin Jának	Syntéza vicinálních derivátů β-amino-α-hydroxykyselin	Institute of Chemical Technology, Prague

PhD THESES

Roman Kunetskiy	1,3-Dialkyl-4,5-dimethylimidazol-2-ylidene Amines as a New Class of Strong Electron Donors in Design and Synthesis of Organosuperbases and Stable Cations	Faculty of Sciences, Charles University in Prague

POSTDOCTORAL PROJECTS

Bertrand Puget	France	Ullrich Jahn
Aude Vibert	France	Ullrich Jahn
Dushant Khobragade	India	Ullrich Jahn
Katarina Vazdar	Croatia	Ullrich Jahn
Roman Lagoutte	France	Ullrich Jahn

Ullrich Jahn / Head of the Group

Denisa Hidasová / Postdoc
Martin Holan / Ph.D. Student
Pratap Jagtap / Ph.D. Student
Emanuele Jahn / Research Assistant
František Kafka / Ph.D. Student
Vojtěch Kapras / Ph.D. Student
Lucie Řehová / Ph.D. Student
Shraddha Mahamulkar / Ph.D. Student
Jakub Smrček / Ph.D. Student
Petr Šebesta / Ph.D. Student
Martin Gebauer / Student
Tomaš Mašek / Student
Lucrece Pocquet / Exchange Student

Chemical Ecology of Social Insects

Irena VALTEROVÁ

Natural Products Chemistry
e-mail: valterova@uochb.cas.cz

Research topics

Research Team of Infochemicals groups together specialists in various fields of chemistry and biology with a common interest in chemical ecology and lipidomics of arthropods, namely in two groups of social insects of prime ecological and economic importance, bumblebees and termites. Our diversified approaches combine various methods of analytical and organic chemistry and biochemistry with complementary biological techniques, such as anatomy, behavioural analysis, and electrophysiology. The aspects of molecular biology underlying our topics are studied in collaboration with the IOCB team of I. Pichová.

The goal of the team is to obtain knowledge on chemistry, biochemistry and biological significance of arthropod semiochemicals and defensive compounds, including the biochemistry of lipids and its relation to the production of semiochemicals. Beside the general focus on basic research, we are aiming our projects at particular aspects of life history of pest species with a future prospect of their control. In this respect, we extend our field of interest to economically important solitary insects, such as pest species of Lepidoptera (leaf miners, bumblebee wax moths), Diptera (fruit flies), Coleoptera (bark beetles) and other insect orders.

Current grant support

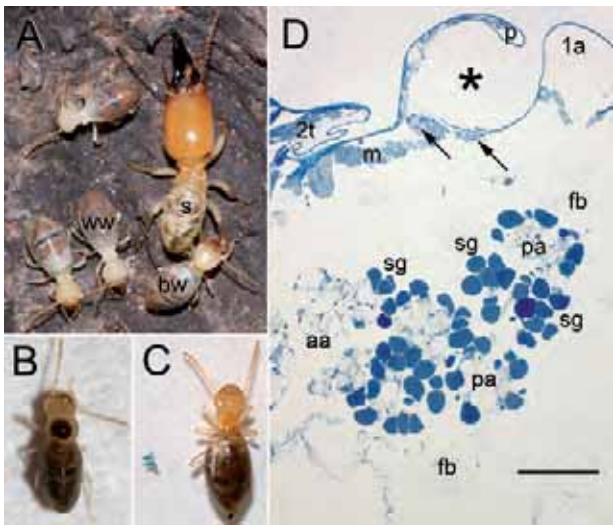
Academy of Sciences of CR (Z40550506), Ministry of Education, Youth and Sports (2B06007, KONTAKT ME 860), Czech Science Foundation (203/09/1446, 203/09/1327, 525/08/1179, P502/10/1734, P506/10/1570, P506/10/1466), Grant Agency of the ASCR (IAA600550614), Technological Agency of the Czech Republic (TA01020969), Ministry of Agriculture of the Czech Republic (QH81136), International Atomic Energy Agency (16106, 16965).

Selected recent papers

1. Hanus, R., Vrkoslav, V., Hrdý, I., Cvačka, J., Šobotník, J. "Beyond cuticular hydrocarbons: evidence of proteinaceous secretion specific to termite kings and queens." *Proc. R. Soc.* B **2010,** *277,* 995-1002.
2. Kindl, J., Kalinová, B., Červenka, M., Jílek, M., Valterová, I. "Male moth songs tempt females to accept mating: The role of acoustic and pheromonal communication in reproductive behaviour of *Aphomia sociella*." *PLoS One* **2011,** *6,* e26476.
3. Jiroš, P., Cvačka, J., Hanus, R, Kindl, J., Kofroňová, E., Valterová, I. "Changes in composition of triacylglycerols in the fat body of bumblebee males during their lifetime." *Lipids* **2011,** *46,* 863-871.
4. Vaníčková, L., Rufino do Nascimento, R., Hoskovec, M., Ježková, Z., Břízová, R., Tomčala, A., Kalinová, B. "Are the wild and laboratory insect populations different in semiochemical emission? The case of the medfly sex pheromone." *J. Agric. Food Chem.* **2012,** *60,* 7168-7176.
5. Šobotník, J., Bourguignon, T., Hanus, R., Demianová, Z., Pytelková, J., Mareš, M., Foltýnová, P., Preisler, J., Cvačka, J., Krasulová, J,. Roisin, Y. "Explosive backpacks in old termite workers." *Science* **2012,** *337,* 436.

Prorhinotermes simplex soldier

Bombus lucorum males



Anatomy of the defensive apparatus of *Neocapritermes taracua.* (A) Soldier (s) with two blue (bw) and two white workers (ww). (B) Blue worker after autothysis triggered by grasping it with tweezers. (C) Blue worker after removal of the blue crystals (placed next to it). (D) Section of anterior abdomen of a blue worker. Asteriskmarks crystal-bearing pouch (crystal dissolved); arrowsmark crystal gland cells. Scale bar, 200 μm. 1a, first abdominal segment; 2t, mesothorax; aa, anterior acini; fb, fat body; m, muscles; p, dorsal part of the crystal-bearing pouch; pa, posterior acini; sg, aggregates of secretion granules budding off posterior acini.

DIPLOMA THESES

Michaela Kudzejová	Analysis of bumblebee lipids using chromatographic methods	Faculty of Sciences, Charles University in Prague
Ivana Schneedorferová	Essential fatty acid diagnostics using modern analytical methods for nutrition studies	Czech Technical University in Prague
Klára Dolejšová	Specific behaviour of soldiers towards reproductives of termite genus Prorhinotermes (Isoptera: Rhinotermitidae)	Faculty of Sciences, Charles University in Prague
Michaela Slušná	Determinantion of volatile isoprenoids as indicators of water stress and the spruce resistence towards bark beetles	Faculty of Sciences, Charles University in Prague
Zuzana Ježková	Analysis of the sexual pheromone of a tropical fruitfly Ceratitis capitata (Tephritidae)	Faculty of Sciences, Charles University in Prague

PhD THESES

Pavel Jiroš	Lipid compounds in bumble bees	Institute of Chemical Technology, Prague
Lucie Vaníčková	Chemical ecology of fruit flies genera Ceratitis and Anastrepha	Institute of Chemical Technology, Prague

POSTDOCTORAL PROJECTS

David Sillam-Dusses	France	Infochemicals
Audrey Coppée	Belgium	Infochemicals

SIGNIFICANT AWARDS

Petr Žáček	Student Award from the Internation Society of Chemical Ecology	poster at 26th Annual Meeting of the ISCE	Internation Society of Chemical Ecology
Jana Krasulová	Student Award from the Internation Society of Chemical Ecology	lecture at 28th Annual Meeting of the ISCE	Internation Society of Chemical Ecology
Aleš Tomčala + Irena Valterová	Prize for the best poster at the 11th International Conference on Nutrition and Diagnostics	best poster	INDC Organizing Committee

TEACHING ACTIVITIES

Natural Products	Irena Valterová	Faculty of Sciences, Charles University in Prague
Chemoecology	Irena Valterová	Czech University of Life Sciences Prague
Biology of Social Insects	Jan Šobotník	Faculty of Sciences, Charles University in Prague
Biology of Social Insects	Jan Šobotník	University of South Bohemia
Sensoric Physiology and Ethology of insect	Robert Hanus	Faculty of Sciences, Charles University in Prague
Sensoric Physiology and Ethology of insect	Robert Hanus	University of South Bohemia
Chemical Ecology	Michal Hoskovec	Czech University of Life Sciences Prague
Sensoric Physiology and Neurophysiology	Blanka Kalinová	University of South Bohemia

Irena Valterová / Head of the Group

Robert Hanus / Scientist
Michal Hoskovec / Scientist
Oldřich Hovorka / Scientist
Anna Jirošová / Scientist
Blanka Kalinová / Scientist
Jiří Kindl / Scientist
Pavlína Kyjaková / Scientist
Jan Šobotník / Scientist
Klára Urbanová / Scientist
Marie Zarevúcka / Scientist
Aleš Tomčala / Postdoc
Pavel Jiroš / Postdoc
Jana Brabcová / Ph.D. Student
Radka Břízová / Ph.D. Student
Edita Kofroňová / Ph.D. Student
Jana Krasulová / Ph.D. Student
Kateřina Kutalová / Ph.D. Student
Lucie Vaníčková / Ph.D. Student
Petr Žáček / Ph.D. Student
Martina Kojecká / Research Assistant

Undergraduate students
Eva Havelková
Michaela Kudzejová
Ivana Schneedorferová
Lenka Tomešová

Technitians
Pavlína Hovorková
Anna Nekolová
Jarmila Titzenthalerová

Secretary
Lenka Valentová

Theoretical Bioinorganic Chemistry

Lubomír RULÍŠEK

Computational Chemistry
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Research topics

For many decades, metalloenzymes have inspired and fascinated chemists as some of the most efficient catalysts in nature. Many fundamental and difficult reactions, such as C–H activations, O=O and N≡N bond cleavages, are carried out under mild (often physiological) conditions at the metal centres in metalloenzyme active sites. Therefore, understanding their reaction mechanisms (or catalytic action) is of key importance for the progress in catalysis in general.

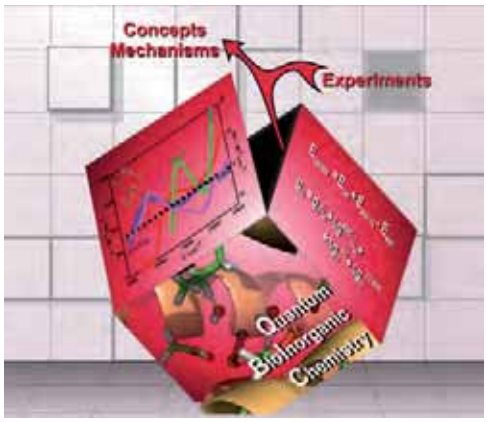
The aim of the research in our group is to link the experience acquired in ***theoretical studies of reaction mechanisms of metalloproteins*** (e.g., multicopper oxidases (MCOs), dinuclear non-heme iron Δ^9-desaturase (Δ^9D), dinuclear zinc glutamate carboxypeptidase II (GCPII), and mononuclear manganese super-oxide dismutase, MnSOD) with our recent applications of state-of-the-art quantum chemical methods and solvation models in areas of ***metal-ion coordination in biomolecules***, ***organic reactivity***, and ***computational electrochemistry***. This may bring us closer to fulfilling the long-term vision of our research which is the ***in silico design of smaller artificial metalloenzymes*** and answering one of fundamental questions of bioinorganic chemistry: ***"Does nature, indeed, have to use large complex proteins of several hundred amino acids to carry out the catalysis confined to a relatively small active site?"***

Current grant support

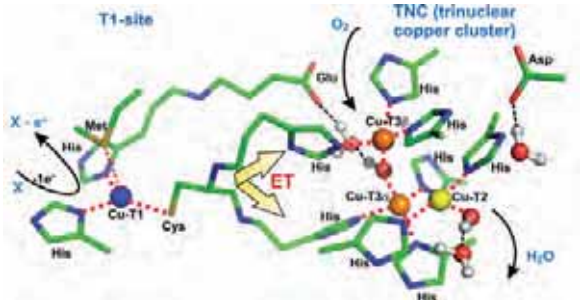
Gilead Sciences Research Centre in Prague II (GSRCP), Gilead Sciences, Inc. (Foster City, U.S.A.), 2011-2016

Selected recent papers

1. Rulíšek, L.*; Ryde, U.*: Theoretical Studies of the Active-Site Structure, Spectroscopic, and Thermodynamic Properties, and Reaction Mechanism of Multicopper Oxidases. *Coord. Chem. Rev.* **2013**, *257*, 445. *Invited Review.*
2. Rokob, T. A.; Srnec, M.; Rulíšek, L.*: Theoretical Calculations of Physico-Chemical and Spectroscopic Properties of Bioinorganic Systems: Current Limits and Perspectives. *Dalton Trans.* **2012**, *41*, 5754. *Invited Perspective.*
3. Srnec, M.; Rokob, T. A.; Schwartz, J. K.; Kwak, Y.; Rulíšek, L.*; Solomon, E. I.*: Structural and Spectroscopic Properties of the Peroxodiferric Intermediate of *Ricinus Communis* Soluble Δ^9 Desaturase. *Inorg. Chem.* **2012**, *51,* 2806.
4. Gutten, O.; Beššeová, I.; Rulíšek, L.* Interaction of Metal Ions with Biomolecular Ligands: How Accurate Are Calculated Free Energies Associated with Metal Ion Complexation? *J. Phys. Chem. A* **2011**, *115*, 11394.
5. Srnec, M.; Ryde, U.; Rulíšek, L.*: Reductive Cleavage of the O–O Bond in Multicopper Oxidases: QM/MM and QM Study. *Faraday Discuss.* **2011**, *148*, 41.
6. Vancoillie, S.; Chalupský, J.; Ryde, U.; Solomon, E. I.; Pierloot, K.; Neese, F.*; Rulíšek, L.*: Multireference *Ab Initio* Calculations of g tensors for Trinuclear Copper Clusters in Multicopper Oxidases. *J. Phys. Chem. B* **2010**, *114,* 7692.



Theoretical Bioinorganic Chemistry



The general architecture of the trinuclear copper cluster site (the site of the four-electron O2 → H2O reduction) and of the Cu-T1 site (the site of one-electron oxidations of organic substrates or metal ions). All steps in the MCO reaction mechanism were characterized by correlating spectroscopy with theoretical (QM, QM/MM) calculations.

DIPLOMA THESES

Ondrej Gutten	Modelling of the interaction of proteins and peptides with metal ions	Faculty of Sciences, Charles University in Prague

PhD THESES

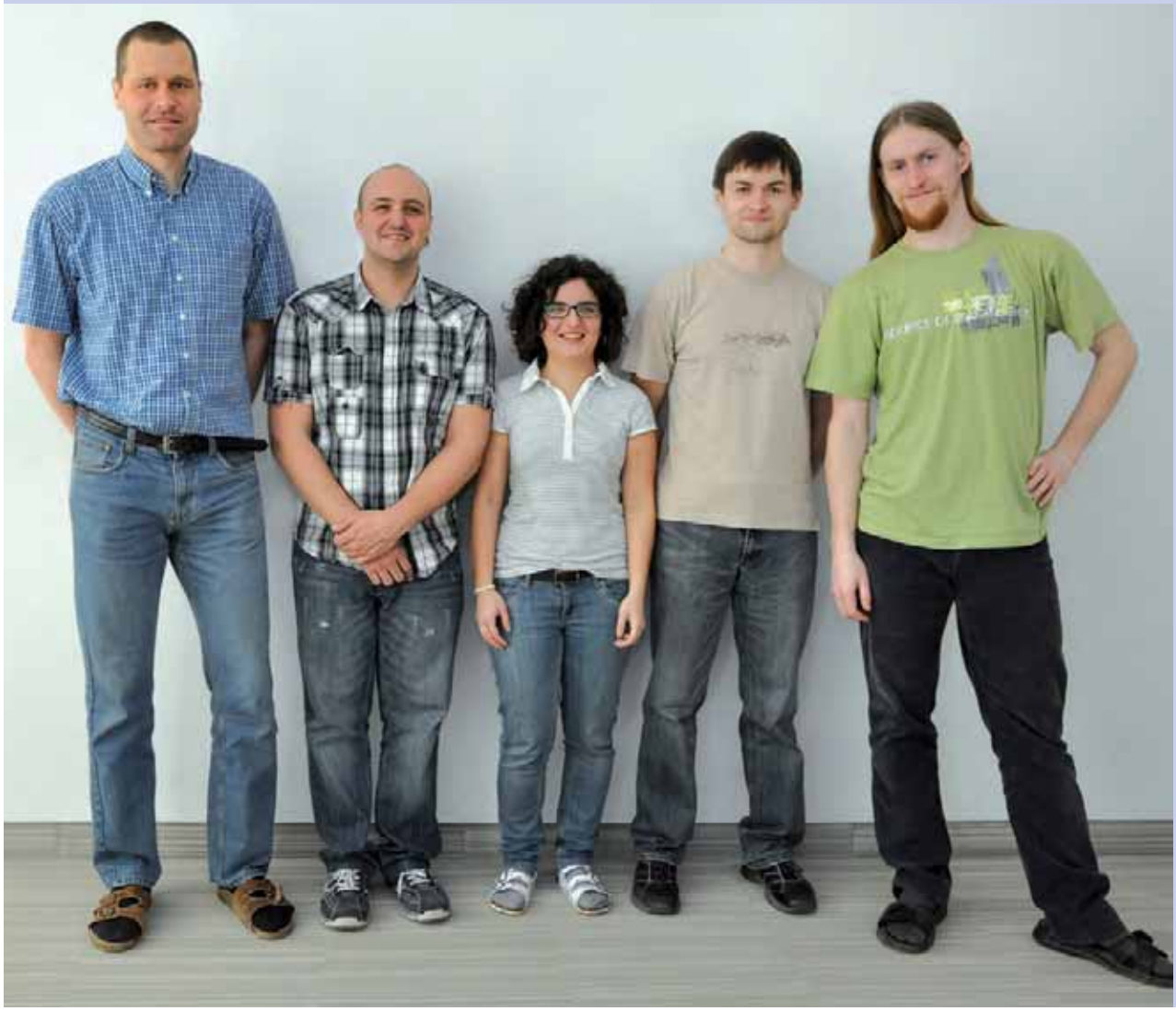
Martin Srnec	Catalytic and Electronic Properties of Redox-Active Metalloenzymes and Transition-Metal Complexes: Insight from Computational Chemistry	Faculty of Sciences, Charles University in Prague
Vojtěch Klusák	Non-covalent interactions in fundamental biological processes	Faculty of Sciences, Charles University in Prague

POSTDOCTORAL PROJECTS

Tibor András Rokob	Hungary	Lubomír Rulíšek
Goar Sánchez-Sanz	Spain	Lubomír Rulíšek

Lubomír Rulíšek / Head of the Group

Goar Sánchez-Sanz / Postdoc
Cristina Trujillo / Postdoc
Mgr. Ondrej Gutten / Ph.D. Student
Pavel Beran / Diploma Student



Computational Chemistry

Pavel JUNGWIRTH

Computational Chemistry
e-mail: jungwirth@uochb.cas.cz

Research topics

Binding of ions to proteins, polypeptides, and amino acids –Hofmeister effects.

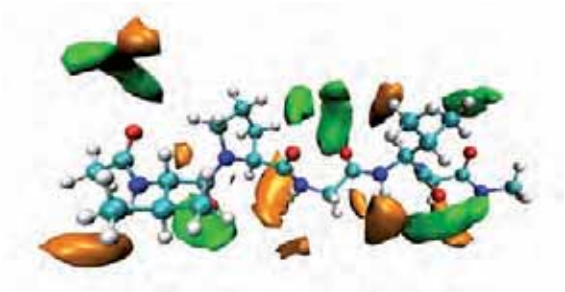


Fig. 1: Distribution of NaCl around aqueous VPGVG peptide.

Oxidative processes in cellular membranes and ion-membrane interactions.

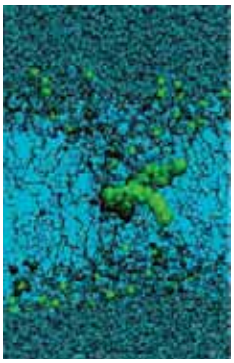


Fig. 2: Translocation of phosphatidylserine across a membrane.

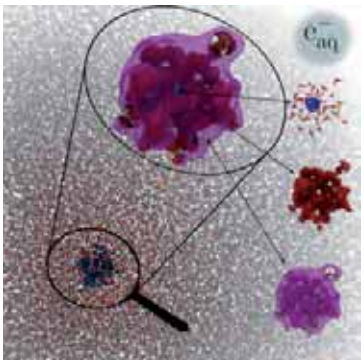


Fig. 3: Detailed structure of a hydrated electron.

Direct and indirect radiation damage to DNA in aqueous solutions.

We model with molecular resolution structure and chemical dynamics of biologically relevant molecules in aqueous solutions. In particular, we put a lot of effort into unraveling fundamental aspects of ion solvation in anisotropic and inhomogeneous environments. These range from the surfaces of aqueous droplets to solution/protein and solution/membrane interfaces. Using molecular dynamics simulations and quantum chemical methods and in close contact with experiments we are trying to figure out what drives ions to these interfaces and to one another. These specific ion effects have been observed since late 1800s, but only now it is becoming feasible to investigate the molecular mechanisms involved with atomic detail. Not only are we thrilled by the basic science we are discovering but also by applications our results are finding, which range from controlling enzymatic activity to translocation of potential drugs across cellular membranes. Our related research activities concern modeling of aerosol processes relevant for atmospheric chemistry and physics, and electron solvation, pertinent to radiation chemistry and DNA damage.

Current grant support

Czech Science Foundation (grant no. 203/08/0114, Eurocores grant no. MEM/09/E006, and Excellence in Basic Research grant no. P208/12/G016)
Czech Ministry of Education (Centrum grant no. LC512 and KONTAKT grants no. LH12001 and ME09064)
US NSF (Collaborative Research in Chemistry grants no. CHE0431312 and CHE0909227)
Academy of Sciences of the Czech Republic (Praemium Academie award)
Academy of Finland (Finland Distinguished Professor award)

Selected recent papers

1. Heyda, J.; Mason, P. E.; Jungwirth, P.: Attractive interactions between sidechains of histidine-histidine and histidine-arginine based cationic dipeptides in water. Journal of Physical Chemistry B, **2010**, 114 8744.
2. Volinski, R.; Cwiklik, L.; Jurkiewicz, P.; Hof., M.; Jungwirth, P.; Kinnunen, P. K. J.: Oxidized Phosphatidylcholines Facilitate Phospholipid Flip-Flop in Liposomes. Biophysical Journal, **2011**, 101 1376.
3. Kubickova, A.; Krizek, T.; Coufal, P.; Vazdar, M.; Wernersson, E.; Jungwirth, P.: Overcharging in Biological Systems: Reversal of Electrophoretic Mobility of Aqueous Polyaspartate by Multivalent Cations. Physical Review Letters, **2012**, 108, 186101.
4. Rembert, K.; Paterova, J.; Heyda, J.; Hilty, C.; Jungwirth, P.; Cremer, P. S.: The Molecular Mechanisms of Ion-Specific Effects on Proteins. Journal of the American Chemical Society, **2012**, 134,10039.
5. Uhlig, F.; Marsalek, O.; Jungwirth, P.: Unraveling the Complex Nature of the Hydrated Electron. Journal of Physical Chemistry Letters, **2012**, 3, 3071.

PhD THESES

Jan Heyda	Interactions of ions with proteins, 2011	Faculty of Sciences, Charles University in Prague
Ondřej Maršálek	Structure and dynamics of electronic charge defects in liquid water, 2012	Faculty of Mathematics and Physics, Charles University in Prague

POSTDOCTORAL PROJECTS

Erik Wernersson	Sweden	Pavel Jungwirth
Mario Vazdar	Croatia	Pavel Jungwirth
Ivan Gladich	Italy	Martina Roeselová

SIGNIFICANT AWARDS

Pavel Jungwirth	Finland Distinguished Professor	Research on Cellular Membranes	Academy of Finland, 2012
Pavel Jungwirth	Praemium Academie	Research on Aqueous Ions	AV Czech Republic, 2010
Pavel Jungwirth	Professeur Invité	Research on Aqueous Ions	École Normale Supérieure, Paris, 2010

TEACHING ACTIVITIES

Classical Molecular Dynamics and Monte Carlo	Martina Roeselová, Pavel Jungwirth	Faculty of Mathematics and Physics, Charles University in Prague
Advanced Methods of Molecular Dynamics	Pavel Jungwirth	Faculty of Mathematics and Physics, Charles University in Prague

Pavel Jungwirth / Head of the Group

Lukasz Cwiklik / Scientist
Phil Mason / Scientist
Martina Roeselová / Scientist
Miriam Kohagen / Postdoc
Jiří Brabec / Postdoc
Alena Habartová / Ph.D. Student
Jana Paterová / Ph.D. Student
Eva Pluhařová / Ph.D. Student
Frank Uhlig / Ph.D. Student
Barbara Jagoda-Cwiklik / Research Assistant
Jiří Polách / System Administrator
Alexei Chevko / Student
Denisa Kubániová / Student
Tomáš Martínek / Student
Josef Melcr / Student
Vladimír Palivec / Student
Kamila Riedlová / Student
Štěpán Timr / Student
Helena Černá / Secretary

Biomolecular Spectroscopy

Petr BOUŘ

Spectroscopy and Physical Chemistry
e-mail: bour@uochb.cas.cz

Research topics

We develop modern spectroscopic techniques used for molecular structural studies. Typically, complex simulations are used to extract structural information from the spectra. Understanding molecular structure and behaviour is important for future applications in medicine and industry.

Studied systems involve small molecules as well as fullerenes, proteins, and nucleic acids.

A major part of the effort is dedicated to optical activity. This phenomenon is related to interaction of molecules with circularly polarized light, and brings precious information about electronic and vibrational properties.

As a last example, research employing Raman and NMR spectroscopy is focused on chemically modified nucleic acids for nanotechnological application and on catalytic mechanisms in enzymes.

Current grant support

The Czech Science Foundation (grants Nos. 13-27676S, 13-03978S, 203/09/0237), the Academy of Sciences (M200551205), Ministry of Education (LH11033), and grant of Japan Society for the Promotion of Science.

Selected recent papers

1. Šebera, J.; Trantírek, L.; Tanaka, Y.; Sychrovský, V. *J. Phys. Chem. B,* **2012**, *116*, 12535. Pyramidalization of the Glycosidic Nitrogen Provides the Way for Efficient Cleavage of the N-Glycosidic Bond of 8-OxoG with the hOGG1 DNA Repair Protein.
2. Kessler, J.; Dračínský, M.; Bouř, P. *J. Comput. Chem.* **2013**, *34*, 366. Parallel Variable Selection of Molecular Dynamics Clusters as a Tool for Calculation of Spectroscopic Properties.
3. Yamamoto, S.; Bouř, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 11058. "Molecular Chirality Detection of Molecular Chirality by Induced Resonance Raman Optical Activity in Europium Complexes."

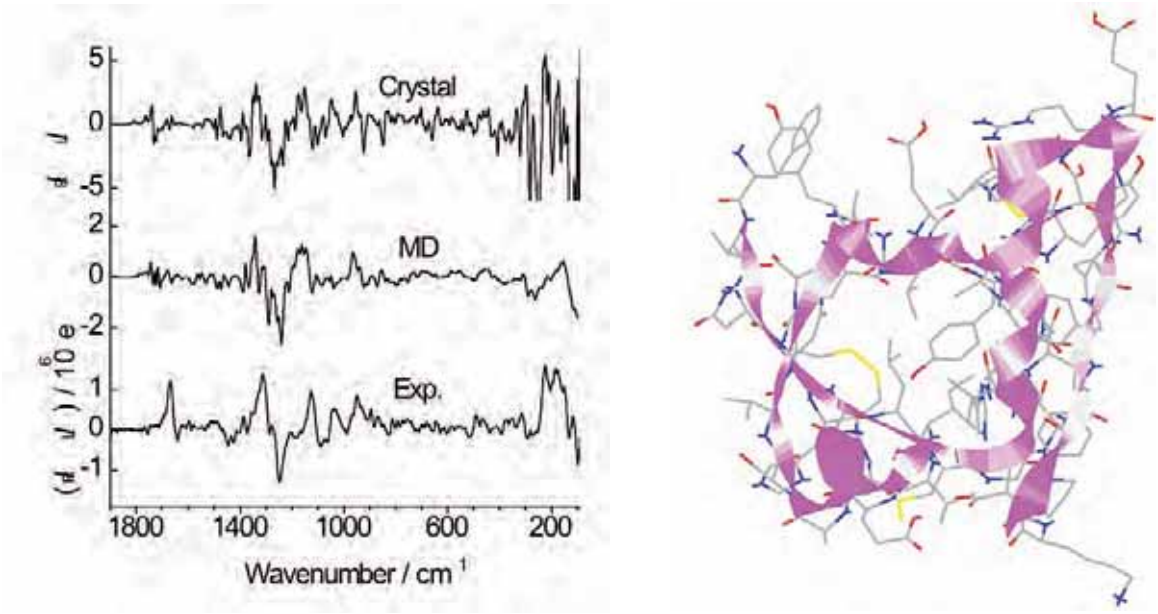


Figure: Calculated and experimental Raman optical activity spectra of insulin, and its derived structure in solution.

DIPLOMA THESES

Jiří Kessler	Development and application of molecular dynamics for chiral systems	Faculty of Sciences, Charles University in Prague

POSTDOCTORAL PROJECTS

Daniele Padula	Italy	Petr Bouř

TEACHING ACTIVITIES

Quantum chemistry and spectroscopy	Vladimír Sychrovský	Faculty of Mathematics and Physics, Charles University in Prague
Computations of molecular properties	Petr Bouř	Institute of Chemical Technology, Prague
General chemistry	Petr Štěpánek	Faculty of Mathematics and Physics, Charles University in Prague
Analytical chemistry	Vít Novák	Institute of Chemical Technology, Prague

Petr Bouř / Head of the Group

Valery Andrushchenko / Scientist
Ladislav Benda / Postdoc
Jiří Bufka / Student
Jana Hudecová / Ph.D. Student
Jan Ježek / Scientist
Jakub Kaminský / Scientist
Jiří Kessler / Ph.D. Student
Monika Krupová / Student
Vít Novák / Ph.D. Student
Daniele Padula / Postdoc
Václav Parchaňský / Ph.D. Student
Stanislav Standara / Ph.D. Student
Michal Straka / Scientist
Vladimír Sychrovský / Scientist
Martin Šafařík / Technician
Jakub Šebera / Scientist
Jaroslav Šebestík / Scientist
Petr Štěpánek / Ph.D. Student

Electromigration Methods

Václav KAŠIČKA

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Research topics

The team is engaged in the research and development of advanced capillary electrophoretic (CE) and capillary electrochromatographic (CEC) methods and their application to separation, analysis, isolation and physico-chemical and biochemical characterization of (bio)molecules.

Instrumentation

A new device for two-dimensional CE (2D-CE) is being constructed. 2-D separation will be implemented by on-line combination of orthogonal CE methods in two in-series connected capillaries with a cross-shaped interface for independent filling of the capillaries by different separation media. The device will be equipped with high-sensitive fluorescence or mass spectrometric detection.

Methodology

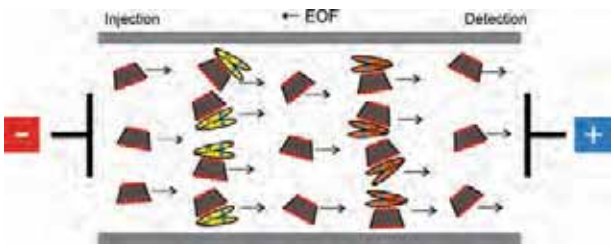
The work is focused on the development of new procedures for affinity CE and CEC methods allowing investigation of non-covalent interactions of (bio)-molecules (amino acids, peptides, proteins, nucleotides, polyaromatic receptors) with various ligands, such as helquats, oligopyrrole macrocycles, cyclodextrins and metal ions. In addition, new background electrolytes (strongly acidic, basic and isoelectric buffers) and (pseudo)stationary phases (chiral selectors, nanoparticles) are being developed in order to increase selectivity and separation efficiency of CE and CEC methods.

Current grant support

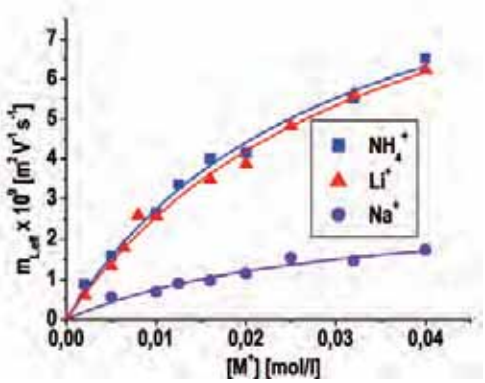
Academy of Sciences of CR (RVO 61388963, M200551207, ASCR-BAS-12)
Czech Science Foundation (P206/12/0453, 13-17224S, 13-32974S)
Ministry of Education, Youth & Sports of CR (7AMB-12FR012-Barrande)
Grant Agency of Charles University (629412)

Selected recent papers

1. Kašička V.*: Recent advances in CE and CEC of peptides (2007-2009). *Electrophoresis* **2010**, *31*, 122-146.
2. Ehala S., Toman P., Makrlík E., Rathore R., Kašička V.*: Affinity capillary electrophoresis and density functional theory applied to binding constant determination and structure elucidation of hexaarylbenzene-based receptor complex with ammonium cation. *J. Chromatogr. A* **2011**, *1218*, 4982-4987.
3. Koval D., Severa L., Adrianssens L., Vávra J., Teplý F., Kašička V.*: Chiral analysis of helquats by capillary electrophoresis: resolution of helical N-heteroaromatic dications using randomly sulfated cyclodextrins. *Electrophoresis* **2011**, *32*, 2683-2692.
4. Sázelová P., Kašička V.*, Leon C., Ibañez E., Cifuentes A.: Capillary electrophoretic profiling of tryptic digests of water soluble proteins from *Bacillus thuringiensis* transgenic and non-transgenic maize species. *Food Chem.* **2012**, *134*, 1607-1615.
5. Šolínová V., Poitevin M., Koval D., Busnel J.-M., Peltre G., Kašička V.*: Capillary electrophoresis in classical and carrier ampholytes-based background electrolytes applied to separation and characterization of gonadotropin-releasing hormones. *J. Chromatogr. A* **2012**, *1267*, 231-238.



Scheme of CE separation of *P*- and *M*-enantiomers of helquats using sulfated cyclodextrins as chiral selectors.



CE measured dependence of effective electrophoretic mobility of valinomycin, m_{Leff}, on the concentration of Na^+, Li^+ and NH_4^+ ions in the background electrolyte, [M+], for the determination of stability constants of valinomycin complexes with these ions.

DIPLOMA THESES

Hana Mikysková	Chiral separation of acyclic nucleoside phosphonates and determination of association constants of their complexes with cyclodextrins by capillary electrophoresis	Faculty of Sciences, Charles University in Prague
Miloslava Vítovcová	Analysis, characterization and separation of derivatives of 2,6-diaminopimelic acid by capillary zone electrophoresis and micellar electrokinetic chromatography	Faculty of Sciences, Charles University in Prague
Tereza Hlavsová	Analysis, characterization and separation of antimicrobial peptides by capillary zone electrophoresis	Faculty of Sciences, Charles University in Prague
Martina Brandejsová	Characterization of low-molecular-mass synthetic markers of isoelectric points by capillary zone electrophoresis and capillary isoelectric focusing	Faculty of Sciences, Charles University in Prague

SIGNIFICANT AWARDS

Dušan Koval	Otto Wichterle Premium Award	Contribution to the development of electromigration methods	Academy of Sciences of the Czech Republic

Václav Kašička / Head of the Group

Dušan Koval / Scientist
Petra Sázelová / Scientist
Veronika Šolínová / Scientist
Sille Štěpánová / Scientist
Martin Růžička / Ph.D. Student
Renáta Norková / Ph.D. Student

Synthetic Nanochemistry

Petr CÍGLER

Synthetic Chemistry
e-mail: cigler@uochb.cas.cz

Research topics

In our laboratory we find new approaches for synthesis of nanoparticles for diagnostic and therapeutic medical applications. Currently, we work on either inorganic or bioorganic structures. Using these nanoparticles we construct targeted multimodal imaging nanoprobes and particles for so-called theranostics (THERApeutic and diagNOSTICS).

The first type core structure is ***fluorescent nanodiamond***, a material with unique optical and magnetic properties. It is the only known non-protobleachable fluorophore. Using synthetic approach we build up on its surface new molecular architectures enabling use of the particles as fluorescent nanolabels and multimodal nanosensors.

Another type of particles we study are ***viral capsides*** – a versatile biomaterial inspired by Nature. The proteins of capsides spontanously self-assemble to compact pseudospheric particles. These building nanoblocks can be easily chemically modified. With atomic precision we attache to surfaces or to inner space of capsides new molecularly designed architectures. Viral capsides serve us as platform for polyvalent display of ligands that can target the cancer cells and simultaneously deliver the therapeutic molecules to the right place. Polyvalency brings us a new quality: strong co-operativity of ligands which can not be reached with small molecules.

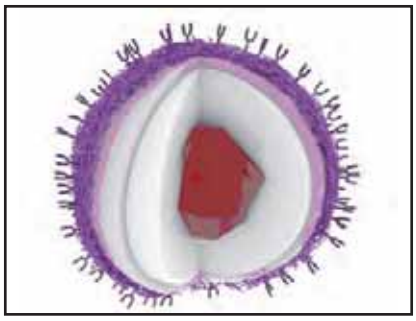
For all the projects we design and synthesize novel linkers, fluorescent dyes, ligands and (in collaboration) polymers and enzyme inhibitors.

Current grant support

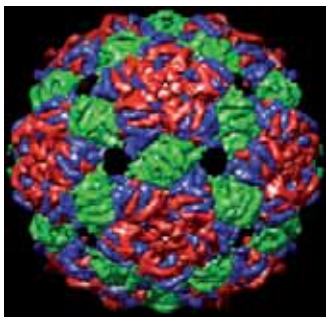
Grant Agency of the CR (P108/12/0640), Ministry of Education, Youth and Sports (LH11027).

Selected recent papers

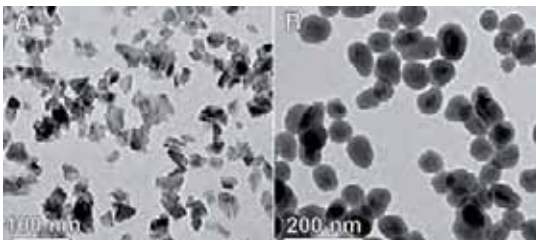
1. Cigler, P., Lytton-Jean, A.K.R., Anderson, D.G., Finn, M.G. & Park, S.Y. "DNA-controlled assembly of a NaTl lattice structure from gold nanoparticles and protein nanoparticles". *Nature Materials*, **2010**, *9*, 918–922.
2. Petrakova, V., Taylor, A., Kratochvilova, I., Fendrych, F., Vacik, J., Kucka, J., Stursa, J., Cigler, P., Ledvina, M., Fiserova, A., Kneppo, P. & Nesladek, M. "Luminescence of Nanodiamond Driven by Atomic Functionalization: Towards Novel Detection Principles." *Adv. Funct. Mater.*, **2012**, *22*, 812–819.
3. Havlik, J., Petrakova, V., Rehor, I., Petrak, V., Gulka, M., Stursa, J., Kucka, J., Ralis, J., Rendler, T., Lee, S.-Y., Reuter, R., Wrachtrup, J., Ledvina, M., Nesladek, M., & Cigler P. "Boosting Nanodiamond Fluorescence: Towards Development of Brighter Probes." *Nanoscale*, **2013**, *5*, 3208–3211.



Nanocrystal of fluorescent diamond coated by a biocompatible composite multilayer.



Bacteriophage Qβ – a building block for bionanotechnology



Transmission electron microphotographs of fluorescent nanodiamonds. (A) Unmodified material, (B) shape-normalized particles coated by a biocompatible nanolayer.

PhD THESIS

Jan Havlík	Design and synthesis of surface architectures on fluorescent nanodiamonds	Faculty of Natural Sciences, Charles University in Prague
Jitka Šlegerová	Targeted biocompatible nanoparticles for cancer therapy and diagnostics	First Faculty od Medicine, Charles University in Prague
Helena Raabová	Fluorescence diamond nanosensors	Faculty of Chemical Technology, in Prague

POSTDOCTORAL PROJECTS

Jakub Hývl	Czech Republic	Petr Cígler

SIGNIFICANT AWARDS

Petr Cígler	2012 Scopus Awards (1st place)	The prize for the top scientific work published by a Czech scientist younger 35 years; the awarded work: Cigler et al. (2010) Nat. Mater., 9, 918.	Scopus
Petr Cígler	2012 Prize of The Learned Society of the Czech Republic for pedagogues	For mentoring of Chemistry Olympiad and for continuous work with talented high school students	The Learned Society of the Czech Republic
Petr Cígler	2011 Alfred Bader Prize for Bioorganic and Bioinorganic Chemistry	An award for a top Czech chemist younger 35 years working in bioorganic and/or bioinorganic chemistry	Czech Chemical Society
Petr Cígler	2011 Carl and Gerty Cori Prize for Chemistry	Prize for the best talk at Sigma-Aldrich Conference for Young Chemists and Biologists	Sigma-Aldrich
Ivan Řehoř	2010 Rhodia Price for Chemistry (2nd place)	A price for a top Czech Ph.D. student working in chemical sciences	French Embassy in Prague, under the auspices of Nobel Prize winner, Professor Jean-Marie Lehn
Jitka Šlegerová	2012 Jaroslav Heyrovsky price	For best bachelor thesis in natural sciences	Rector of Charles University in Prague

Petr Cígler / Head of the Group

Ivan Řehoř / Scientist
Jakub Hývl / Postdoc
Eva Muchová / Research Assistant
Jan Havlík / Ph.D. Student
Jitka Šlegerová / Ph.D. Student
Helena Raabová / Ph.D. Student

Targeted Analogs of Nucleic Acid Components

Zlatko JANEBA

Medicinal Chemistry
e-mail: janeba@uochb.cas.cz

Research topics

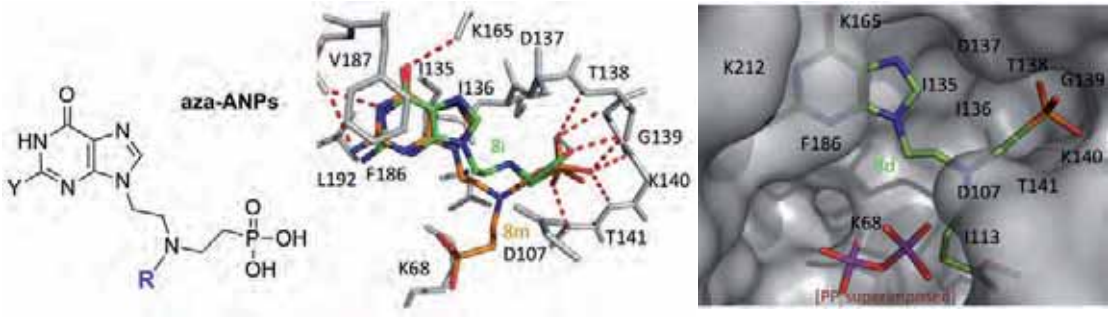
The current research of the group is mainly targeted at design, development, and synthesis of biologically active antimetabolites, namely analogues of nucleic acids components. Such compounds are able to act as inhibitors of various enzymes of nucleos(t)ide metabolism. Acyclic nucleoside phosphonates (ANPs) represent the key class of antimetabolites for their potential antiviral, cytostatic, and antiparasitic properties. Efficient methodologies for the synthesis of new types of ANPs are being developed and the biological properties of prepared ANPs are studied in collaboration with several scientific teams from the Czech Republic, as well as abroad. A special attention has recently been devoted to both aza-ANPs containing a nitrogen atom in the branched side chain and to bisphosphonate analogues for their significant antimalarial propeties. These analogues are potent inhibitors of HG(X)PRTase, an essential enzyme of the plasmodial purine salvage pathway. Another current project deals with efficient inhibitors of adenylate cyclase that have the potential to be used in treatment of diseases caused by the patogens *Bordetella pertussis* (whooping cough) and *Bacillus anthracis* (anthrax). Substantial effort is continuously directed to novel ANPs with antiviral properties and also to development of polysubstituted pyrimidines with significant immunomodulatory and antiphlogistic properties. These compounds have a promising potential in the treatment of colitis, inflamations, and colon cancer.

Current grant support

Institute of Organic Chemistry and Biochemistry AS CR (RVO:61388963), Ministry of Interior of the CR (VG20102015046), Technology Agency of the CR (TE01020028), Grant Agency of the CR (P207/11/0108, P303/12/0172), National Health and Medical Research Council, Australia (569703, 1030353), Zentiva (Prague), and Gilead Sciences, Inc. (Foster City, U.S.A.).

Selected recent papers

1. Hocková, D., Keough, D. T., Janeba, Z., Wang, T. H., de Jersey, J., Guddat, L. W.: Synthesis of novel *N*-branched acyclic nucleoside phosphonates as potent and selective inhibitors of human, *Plasmodium falciparum* and *Plasmodium vivax* 6-oxopurine phosphoribosyltransferases. *J. Med. Chem.* **2012**, *55*, 6209-6223.
2. Jansa, P., Baszczyňski, O., Procházková, E., Dračínský, M., Janeba, Z.: Microwave-assisted hydrolysis of phosphonate diesters: An efficient protocol for the preparation of phosphonic acids. *Green Chem.* **2012**, *14*, 2282-2288.
3. Baszczyňski, O., Jansa, P., Dračínský, M., Kaiser, M. M., Špaček, P., Janeba, Z.: An efficient oxa-Michael addition to diethyl vinylphosphonate under mild reaction conditions. *RSC Adv.* **2012**, *2*, 1282-1284.
4. Jansa, P., Baszczyňski, O., Dračínský, M., Votruba, I., Zídek, Z., Bahador, G., Stepan, G., Cihlar, T., Mackman, R., Holý, A., Janeba, Z.: A novel and efficient one-pot synthesis of symmetrical diamide (bis-amidate) prodrugs of acyclic nucleoside phosphonates and evaluation of their biological activities. *Eur. J. Med. Chem.* **2011**, *46*, 3748-3754.
5. Keough, D. T., Hocková, D., Krečmerová, M., Česnek, M., Holý, A., Naesens, L., Brereton, I. M., Winzor, D. J., de Jersey, J., Guddat, L. W.: Plasmodium vivax hypoxanthine-guanine phosphoribosyltransferase: A target for anti-malarial chemotherapy. *Mol. Biochem. Parasitol.* **2010**, *173*, 165-169.



A general structure of antimalarial aza-ANPs and examples of the docked structures to the active site of HGPRTase.

PhD THESES

Ondřej Baszczyňski	New synthetic approaches to acyclic nucleoside phosphonates with potential biological activity	Institute of Chemical Technology Prague
Petr Jansa	Synthesis of purine and pyrimidine derivates with potential biological activities	Faculty of Sciences, Charles University in Prague

POSTDOCTORAL PROJECTS

Petra Břehová	Czech Republic	Zlatko Janeba
Viktor Kolman	Czech Republic	Zlatko Janeba
Miloš Lukáč	Slovak Republic	Zlatko Janeba
Jiří Žurek	Czech Republic	Zlatko Janeba
Šimon Petr	Czech Republic	Zlatko Janeba

SIGNIFICANT AWARDS

Petr Jansa	Best Oral Presentation	lecture – 10th Conference of Young Scientists	Sigma-Aldrich CZ
Petr Jansa	Prix Sanofi de pharmacie 2011	research in pharmaceutical chemistry	Sanofi-Aventis

TEACHING ACTIVITIES

Bioorganic chemistry	Zlatko Janeba	Faculty of Sciences, Palacky University Olomouc

Zlatko Janeba / Head of the Group

Michal Česnek / Scientist
Dana Hocková / Scientist
Ondřej Baszczyňski / Ph.D. Student
Martin M. Kaiser / Ph.D. Student
Petr Jansa / Ph.D. Student
Lucie Čechová / Student

Petra Břehová / Postdoc
Viktor Kolman / Postdoc
Petr Šimon / Postdoc
Běla Nováková / Technician
Hana Hulačová / Technician
Barbara Česneková / Secretary

Former members:
Miloš Lukáč / Postdoc
Jiří Žurek / Postdoc

Medicinal Chemistry of Antimetabolites

Radim NENCKA

Bioorganic & Medicinal Chemistry
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Research topics

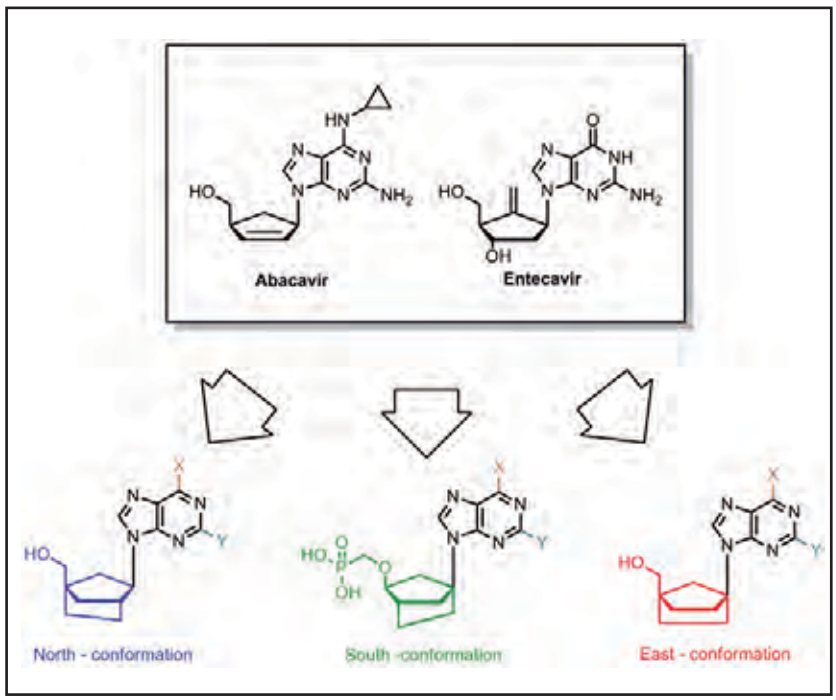
The main scientific direction of our group is medicinal chemistry oriented on the design and synthesis of novel antiviral agents, with a special respect to the compounds against RNA viruses. The current research area of our interest can be divided into two parts. Our first project deals with the synthesis of novel conformationally locked nucleoside and nucleotide derivatives. Its main objective is the investigation of novel structural patterns, which allow stabilization of nucleoside and nucleotide analogues in the desired conformations in order to enhance their interaction with target enzymes involved in viral replication. The second major research topic is connected with non-nucleoside compounds with antiviral properties. Recently, we have performed an extensive structure-activity relationship study of novel purine derivatives, which exerted significant inhibition of Coxsackieviruses, important human pathogens from the Picornaviridae family. Our latest non-nucleoside project focuses on the development of novel inhibitors of host-cell enzymes, which are involved in the replication of various RNA viruses. This specific type of inhibitors brings a promise of broad-spectrum antiviral therapeutics. Throughout all of our projects we have been developing novel synthetic methodologies with special focus on the synthesis of heterocycles and the preparation of novel bicyclic and polycyclic systems.

Current grant support

Czech Science Foundation (GAČR P303/11/1297, GAČR P207/11/0108, GAČR P207/12/P237), Ministry of Interior of the Czech Republic (VG20102015046), and Gilead Sciences, Inc.

Selected recent papers

1. Šála, M.; De Palma, A.M.; Hřebabecký, H.; Nencka, R.; Dračínský, M.; Leyssen, P.; Neyts, J.; Holý, A. "Design, synthesis, and biological evaluation of novel coxsackievirus B3 inhibitors" *Bioorg. Med. Chem.* **2010**, *18*, 4374-4384.
2. Šála, M.; De Palma, A. M.; Hřebabecký, H.; Dejmek, M.; Dračínský, M.; Leyssen, P.; Neyts, J.; Mertlíková-Kaiserová, H.; Nencka, R. "SAR studies of 9-norbornylpurines as Coxsackievirus B3 inhibitors" *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4271-4275.
3. Hřebabecký, H.; Dejmek, M.; Dračínský, M.; Šála, M.; Leyssen, P.; Neyts, J.; Kaniaková, M.; Krůšek, J.; Nencka, R. "Synthesis of novel azanorbornylpurine derivatives" *Tetrahedron* **2012**, *68*, 1286-1298.
4. Dejmek, M.; Kovačková, S.; Zborníková, E.; Hřebabecký, H.; Šála, M.; Dračínský M.; Nencka, R. "One-pot build-up procedure for the synthesis of variously substituted purine derivatives" *RSC Advances* **2012**, *2*, 6970-6980.



DIPLOMA THESES

Laura Mascarell	Locked nucleosides as potential antiviral agents	Institute of Chemical Technology, Prague / University of Valencia (Erasmus)

PhD THESES

Milan Dejmek	Conformationally locked carbocyclic nucleoside analogues	Faculty of Sciences, Charles University in Prague

POSTDOCTORAL PROJECTS

Michal Šála	Czech Republic	Radim Nencka
Martin Kögler	Austria	Radim Nencka
Rémi Guillon	France	Radim Nencka

TEACHING ACTIVITIES

Basic principles of drug discovery	Radim Nencka	Faculty of Sciences, Palacky University Olomouc

Radim Nencka / Head of the Group

Hubert Hřebabecký / Scientist
Rémi Guillon / Postdoc
Martin Kögler / Postdoc
Michal Šála / Postdoc
Milan Dejmek / Ph.D. Student
Barbara Česneková / Secretary
Jaroslava Sklenářová / Technician

Nucleoside and Nucleotide Analogues for Biomedical Applications

Marcela KREČMEROVÁ

Medicinal Chemistry
e-mail: krecmerova@uochb.cas.cz

Research topics

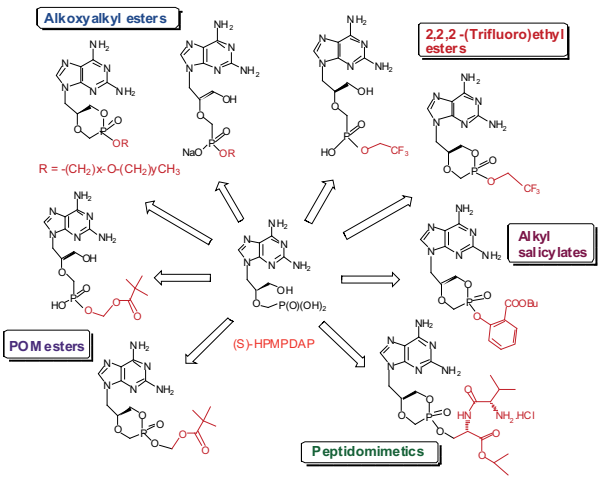
Our research is targeted to design and synthesis of novel bioactive molecules from the family of nucleoside and nucleotide analogs with the aim to find new drug candidates for antiviral, cancer or antiparasitic therapy. A special attention is paid to improvement of biological activities and pharmacokinetic profile of acyclic nucleoside phosphonates by increasing their cellular uptake *via* transformation to diverse types of prodrugs. Significant results were obtained in development of prodrugs derived from 2,6-diaminopurine derivative (S)-HPMPDAP as antipoxvirus agents or peptidomimetic phosphonate prodrugs – highly active, nontoxic and very perspective compounds with a good bioavailability. An important part of our research is also chemistry of triazine compounds, particularly 5-azacytosine and 5,6-dihydro-5-azacytosine derivatives as potential hypomethylating agents for epigenetic therapy of cancer.

Current grant support

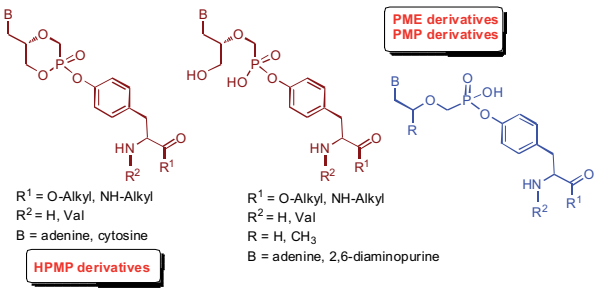
Ministry of Industry and Trade of the Czech Republic (FR-TI4/625), Ministry of Education, Youth and Sports (ME10040) and Academy of Sciences (M200551201).

Selected recent papers

1. Krečmerová M.; Holý A.; Andrei G.; Pomeisl K.; Tichý T.; *et al.* Synthesis of ester prodrugs of 9-(S)-[3-hydroxy-2-(phosphonomethoxy) propyl]-2,6-diaminopurine (HPMPDAP) as anti-poxvirus agents. *J. Med. Chem.* **2010**, *53*, 6825-6837.
2. Topalis D.; Lebeau I.; Krečmerová M.; Andrei G.; Snoeck R. Activity of different classes of acyclic nucleoside phosphonates against BK virus in primary human renal cells. *Antimicrob. Agents Chemother.* **2011**, *55*, 1961-1967.
3. Tichý T.; Andrei G.; Dračínský M.; Holý A.; Balzarini J.; Snoeck R.; Krečmerová M. New Prodrugs of Adefovir and Cidofovir. *Bioorg. & Med. Chem.* **2011**, *19*, 3527-3539.
4. Krečmerová, M.; Otmar, M. 5-Azacytosine compounds in medicinal chemistry: current stage and future perspectives. *Future Med. Chem.* **2012**, *4*, 991-1005.
5. Holý, A.; Krečmerová, M.; Pískala, A.; Andrei, G.; Snoeck, R.; De Clercq, E.; Neyts, J.; Naesens, L. Azacytosine Derivatives Useful as Antiviral Agents. EP 1966226 B1 (Date of the Patent: 10/11/2010).



Ester prodrugs of (*S*)-HPMPDAP developed as antipox-virus agents



Tyrosine prodrugs of acyclic nucleoside phosphonates – efficient antivirals with no toxicity

TEACHING ACTIVITIES

Chemistry	Jiří Blažek	Secondary Technical School of Building and Business, Kladno

Marcela Krečmerová / Head of the Group

Miroslav Otmar / Scientist
Karel Pomeisl / Scientist
Tomáš Tichý / Postdoc
Jiří Blažek / Ph.D. Student
Alice Chupíková / Student
Lucie Janská / Student
Nikola Lamatová / Technician
David Mařák / Technician

Intramembrane Proteolysis and Biological Regulation

Kvido STŘÍŠOVSKÝ

Biochemistry and Molecular Biology
e-mail: strisovsky@uochb.cas.cz

Research topics

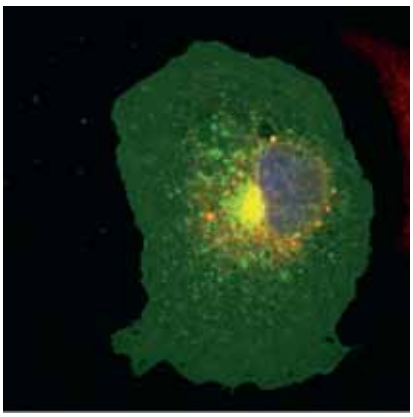
Cellular lipid membranes and the physical and chemical processes associated with them are essential for life. Many functions of cellular membranes are mediated by membrane integrated proteins, and their dysfunction causes disease. Our research is focussed on enzymatic catalysis in biological membranes, particularly on the intramembrane proteases of the rhomboid family. These evolutionarily nearly ubiquitous enzymes control growth factor and cytokine signalling, membrane protein trafficking, mitochondrial dynamics and are essential for the malaria parasite, but many aspects of their functions are still poorly understood. In our research we integrate membrane biochemistry, enzymology and structural biology to understand how rhomboids recognise substrates, and employ the methods of quantitative proteomics, cell biology and genetics to understand the molecular details of their biological functions in model bacteria and in mammals. We are primarily interested in the basic biological aspects of intramembrane proteolysis relevant for cellular signalling and membrane protein biogenesis and homeostasis, but we also exploit the acquired mechanistic insight practically in developing rhomboid inhibitors.

Current grant support

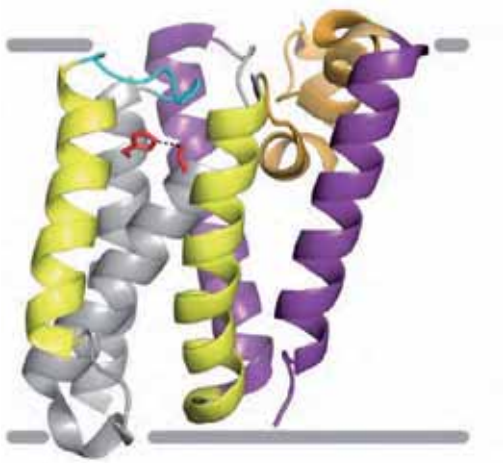
European Molecular Biology Organisation (project N° 2329)
Research Executive Agency of the European Commission (project N° 304154)
Czech Ministry of Education, Youth and Sports (project N° LK11206)
Czech Science Foundation (project N° P305-11-1886)

Selected recent papers

1. **Strisovsky, K**. (2013) Structural and mechanistic principles of intramembrane proteolysis - lessons from rhomboids, *FEBS J.* **280**, 1579-603. **(Cover page)**
2. Adrain C., **Strisovsky K.**, Zettl M., Hu L.D.A., Lemberg M.K. & Freeman M.: Mammalian EGF receptor activation by the rhomboid protease RHBDL2. *EMBO Reports* **12**: 421-427 (2011).
3. *Pierrat O.A., ***Strisovsky K.**, Christova Y., Large J., Ansell K., Bouloc N., Smiljanic E. & Freeman M.: Monocyclic beta-lactams are selective, mechanism-based inhibitors of rhomboid intramembrane proteases. *ACS Chemical Biology* **6**: 325-335 (2011). (*equal contribution)
4. Zettl M., Adrain C., **Strisovsky K.**, Lastun V. & Freeman M.: Rhomboid family pseudoproteases use the ER quality control machinery to regulate intercellular signaling. *Cell* **145**: 79-91 (2011).
5. **Strisovsky K.**, Sharpe H.J. & Freeman M.: Sequence-specific intramembrane proteolysis: identification of a recognition motif in rhomboid substrates. *Molecular Cell* **36**: 1048-1059 (2009). **(Issue highlight)**



COS7 cells overexpressing the mouse rhomboid protease RHBDL2 (green). Nucleus is coloured blue and BAP31 marker of the endoplasmic reticulum is in red. Collocalisation of BAP31 and RHBDL2 displays in yellow. The bulk of RHBDL2 localises to the cell surface.



The X-ray structure of *E.coli* rhomboid protease GlpG and its approximate position in the lipid membrane. The catalytic serine-histidine dyad is shown in red.

DIPLOMA THESES

Lucie Peclinovská	Analysis of substrate specificity and mechanism of Escherichia coli GlpG, an intramembrane protease of the rhomboid family	Faculty of Sciences, Charles University in Prague

PhD THESES

Jan Škerle	Analysis of the substrate repertoire of Escherichia coli rhomboid intramembrane protease GlpG and investigation of its biological function	Faculty of Sciences, Charles University in Prague
Jakub Began	Substrate repertoires, specificity and biological roles of rhomboid proteases in model Gram-positive bacterium Bacillus subtilis	Faculty of Sciences, Charles University in Prague

POSTDOCTORAL PROJECTS

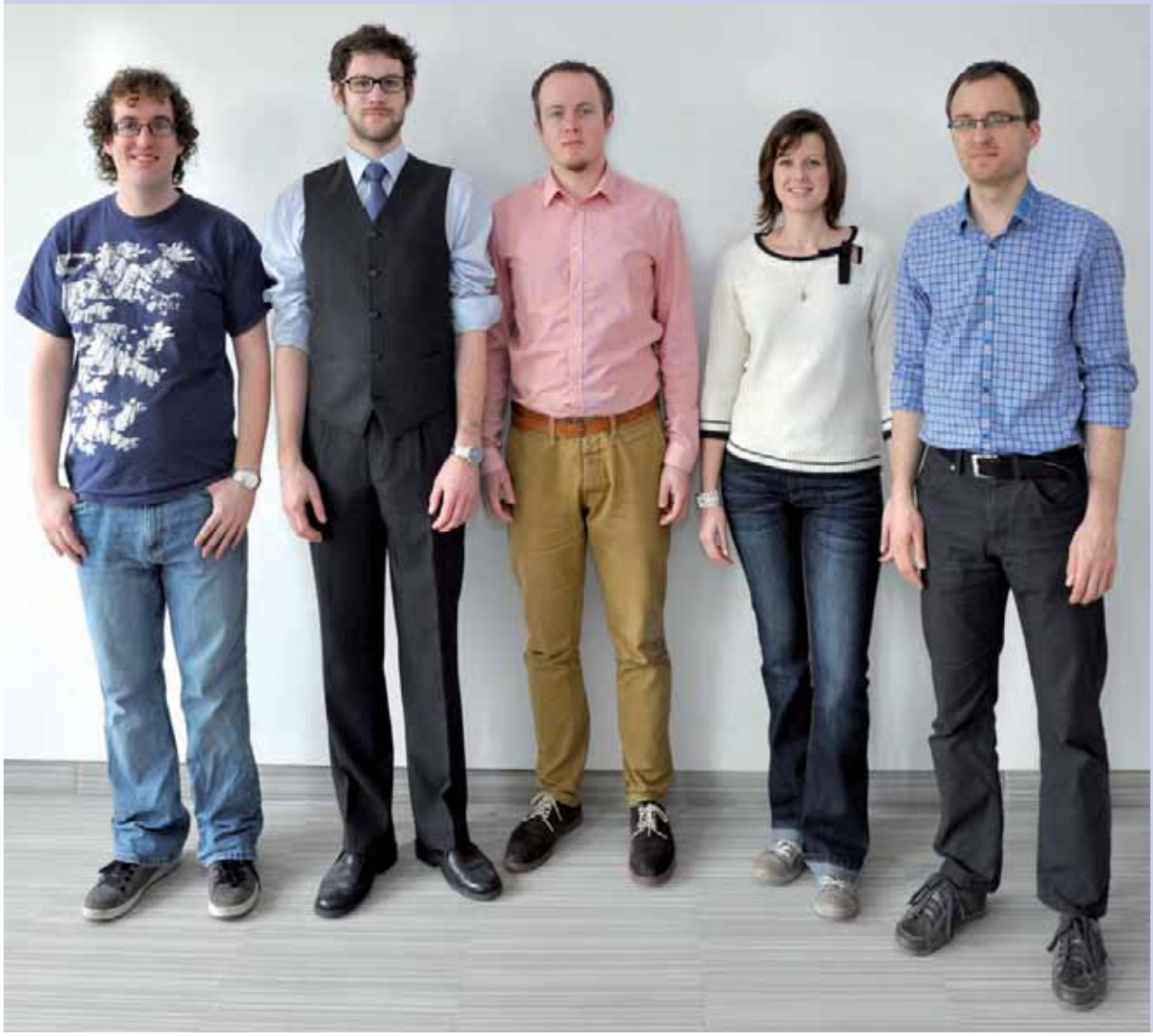
Sebastian Zoll	Germany	Kvido Stříšovský

SIGNIFICANT AWARDS

Kvido Stříšovský	Fellowship J. E. Purkyně	scientific research	Academy of Sciences of the Czech Republic
Kvido Stříšovský	EMBO Installation Grant	scientific reserach	European Molecular Biology Organisation (EMBO)

Kvido Stříšovský / Head of the Group

Sebastian Zoll / Postdoc
Nicholas Johnson / Postdoc
Stancho Stanchev / Postdoc
Jakub Began / Ph.D. Student
Jan Škerle / Ph.D. Student
Lucie Peclinovská / Student



Structure, Function and Regulation of PI4 Kinases

Evžen BOUŘA

Biochemistry and Molecular Biology
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Research topics

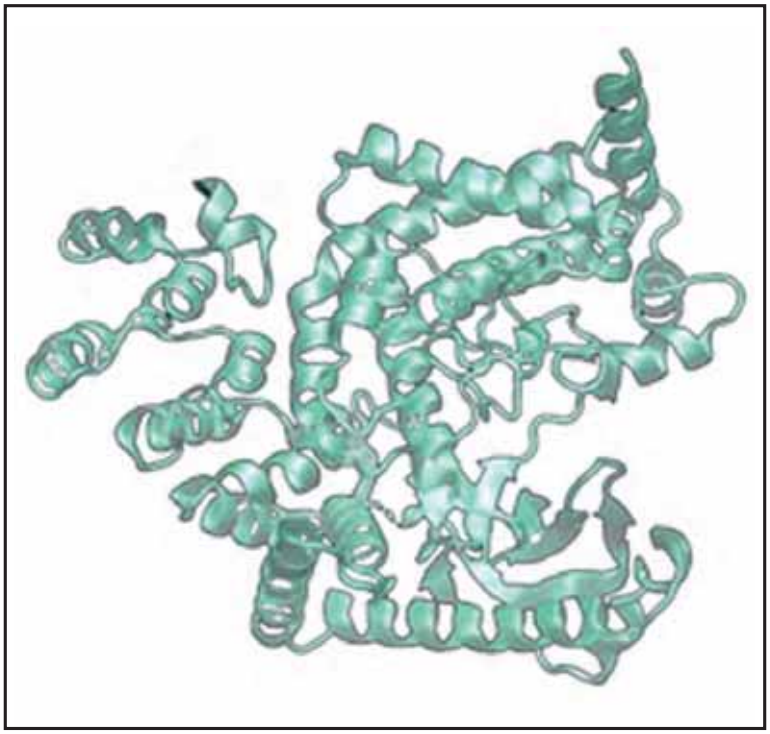
Phosphatidyl inositol phosphates (PIPs) are universal markers of intracellular membranes. Their precise spatial and temporal control enables various protein machineries to operate in the correct location at the right time. PI(4)P is the main marker of the Golgi and the trans-Golgi network (TGN). Its biosynthesis is carried out by phosphatidylinositol 4-kinases (PI4Ks). Two major classes of PI4Ks are known in humans, the type-II PI4Ks are small (50 kDa) palmitoylated proteins that are stably associated with membranes; the type-III PI4Ks are on the other hand soluble proteins that are highly conserved among higher eukaryotes and share homology to PI3Ks. PI4Ks have been reported to play a key role in membrane biogenesis, vesicular transport, lipid dynamics, and protein and lipid sorting in the TGN. Recently, it has been shown that they play role in the regulation of autophagy. Importantly, the replication of several RNA viruses such as poliovirus (PV), Hepatitis C virus (HCV), rhinovirus, West Nile virus (WNV), severe acute respiratory syndrome (SARS) virus and Chikungunya virus depends on type III PI4Ks. HCV hijacks PI4KIIIα to generate endoplasmic reticulum (ER) derived membranous webs that are enriched in PI(4)P and where the replication of HCV takes place. Our laboratory is focused on: 1) understanding the biosynthesis of PI(4)P on the structural level 2) design of small molecule inhibitors to combat plus stranded RNA viruses 3) understanding the regulation of PI4Ks (phosphorylation dependent activation, Arf1 regulation, attenuation by 14-3-3 proteins) on the structural level. We use a multidisciplinary approach employing molecular biology, biochemistry, X-ray crystallography and organic chemistry to reach our goals.

Current grant support

P333916: "StarPI4K– Structural targeting of PI4 kinases", Marie Curie Actions, FP7-PEOPLE-2012-CIG

Selected recent papers

1. **Boura E**, Ivanov V, Carlson LA, Mizuuchi K, Hurley JH. *Endosomal Sorting Complex Required for Transport (ESCRT) Complexes Induce Phase-separated Microdomains in Supported Lipid Bilayers.* **J Biol Chem.** 2012 Aug 10;287(33):28144-51.
2. Baskaran S, Ragusa MJ, **Boura E**, Hurley JH. *Two-Site Recognition of Phosphatidylinositol 3-Phosphate by PROPPINs in Autophagy.* **Mol Cell**. 2012 Aug 10;47(3):339-48.
3. **Boura E**, Rozycki B, Chung HS, Herrick DZ, Canagarajah B, Cafiso DS, Eaton WA, Hummer G, Hurley JH. *Solution Structure of the ESCRT-I and -II Supercomplex: Implications for Membrane Budding and Scission.* **Structure**. 2012 May 9;20(5): 874-86.
4. Noinaj N, Easley NC, Oke M, Mizuno N, Gumbart J, **Boura E**, Steere AN, Zak O, Aisen P, Tajkhorshid E, Evans RW, Gorringe AR, Mason AB, Steven AC, Buchanan SK. *Structural basis for iron piracy by pathogenic Neisseria.* **Nature**. 2012 Feb 12;483(7387):53-8. doi: 10.1038/nature10823.
5. **Boura E,** Hurley JH. *Structural basis for membrane targeting by the MVB12-associated β-prism domain of the human ESCRT-I MVB12 subunit.* **PNAS** 2012 Feb 7;109(6):1901-6
6. **Boura E**, Rozycki B, Herrick D, Chung HS, Vecer J, Eaton W, Cafiso D, Hummer G, and Hurley JH. *Solution structure of the ESCRT-I complex by small angle x-ray scattering, EPR, and FRET spectroscopy* **PNAS** 2011 Jun 7;108(23):9437-42



Model of phosphatidyl inositol 4-kinase III α

Evžen Bouřa /Head of the Group

Dominika Chalupská / Scientist
Adriana Bäumlová / Ph.D. Student

TARGETED RESEARCH GROUPS

Transport and Diagnostic Nanosystems

Miroslav LEDVINA

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Research topics

The principal topic of our research interest is nanochemistry focused on development of transport and diagnostic nanosystems based on luminescent nanodiamond particles (NDPs) modified with biomolecules. Project employs the prominent physical, chemical and biological attributes of NDPs. The internal structure of nanodiamonds allows the incorporation of defects such as NV centres (pairs of nitrogen and vacancy) that produce stable and strong luminescence, showing no photobleaching or photoblinking in comparison to QDs or fluorescent labels. Additionally, the proportion of NV^0/NV^- photoluminescence can be driven, by alternating of the surface chemical potential induced by interacting atoms and molecules near the diamond surface. This phenomenon allows construction of optical chemo-biosensors operable on molecular level. The unique surface bonding architecture can be used for grafting of therapeutic and target biomolecules (saccharides, peptides, proteins and oligonucleotides). Another important property of NDPs is low polydispersity and ability to penetrate into intracellular compartments without cytotoxic side-effects. This project deals with fabrication of NDPs having high density of NV^- centres, their surface functionalization suited for employing common ligation techniques, preparation of properly functionalized biomolecules and their grafting onto NDPs. The fabrication of NDPs with high population of NV^- centres that produce intensive luminescence with emission wave length at 637 nm, which is essential for bioimaging, is solved in collaboration with Dr. Jan Štursa's team from Nuclear Physics Institute AS CR. The other subjects of our scientific interest are self-assembly lipid nanostructures surface modified with molecular vectors and their applications in targeted chemo- and immunotherapy. Our team is also engaged in the process of transfer research results achieved in the field of non-pyrogenic normuramyl glycopeptides having significant immunostimulatory activities to clinical practice. This task is solved in collaboration with commercial partners.

Current grant support

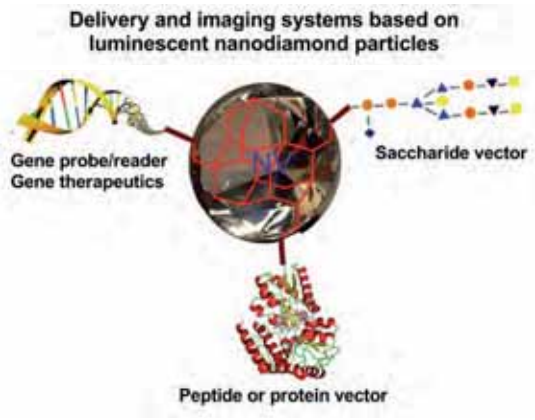
Academy of Sciences (RVO 61388963), European FP7 DINAMO (245122), Ministry of Education, Youth and Sport of the CR (7E11070 and OPVK CZ.1.07/2.3.00/20.0306) and Technology Agency of the CR (TA01011165 and TA02010760)

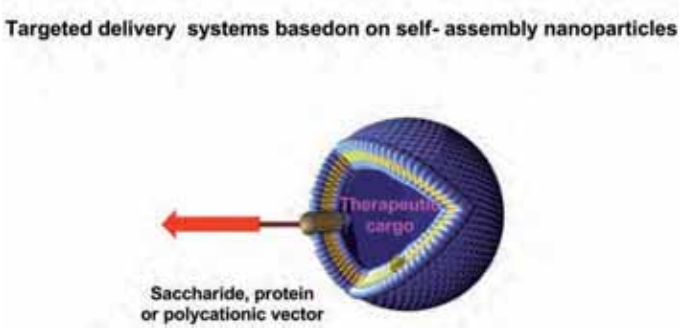
Selected recent papers

1. Petráková V., Taylor A., Kratochvílová I., Fendrych F., Vacík J., Kučka J., Štursa J., Cígler P., Ledvina M., Fišerová A., Kneppo P., Nesládek M.: Luminescence of Nanodiamond Driven by Atomic Functionalization: Towards Novel Detection Principles, *Adv. Funct. Mater.* **2012**, *22*, 812-819.
2. Korvasová Z., Drašar L., Mašek J., Knotigová P.T., Kulich P., Matiasovic J., Kovarčik K., Bartheldyová E., Koudelka S., Škrábalová M., Miller A.D., Holý A., Ledvina M., Turánek J.: Antiviral effect of HPMPC (Cidofovir (R)), entrapped in cationic liposomes: In vitro study on MDBK cell and BHV-1 virus, *J. Controll. Release* **2012**, *160*, 330-338.
3. Ledvina M., Turánek J., Miller A.D., Hipler K.: Derivatives of muramyl peptide, EP 2271 661 B1, **2013**.
4. Havlík J., Petráková V., Řehoř I., Petrák V., Gulka M., Štursa J., Kučka J., Ráliš J., Rendler T., Lee S.Y., Reuter R., Ledvina M., Nesládek M., Cígler P.A.: Boosting Nanodiamond Fluorescence: Towards Development of Brighter Probes, *Nanoscale* **2013**, 5, 3208–3211
5. Ledvina M., Drašar L., Turánek J., Korvasová Z.: Lipopolyamines of spermine type for construction of liposomal transfection systems, PCTCZ2013000004, **2013**.

PhD THESES

Lukáš Drašar	Preparation of polycationic lipids of hexosamine and polyamine type with potential transfection activity	Institute of Chemical Technology, Prague
Martina Wermerová	Synthesis of Saccharide Building Units of D-Hexosamine Type and Their Application in the Oligosaccharide Synthesis	Faculty of Sciences, Charles University in Prague





Miroslav Ledvina / Head of the Group

Daniel Zyka / Scientist
Jan Štursa / Scientist
Jana Lokajová / Postdoc
Júlia Mičová / Postdoc
Lukáš Drašar / Postdoc
Roman Effenberg / Ph.D. Student

Innovative Research of Steroids for Brain

Eva KUDOVÁ

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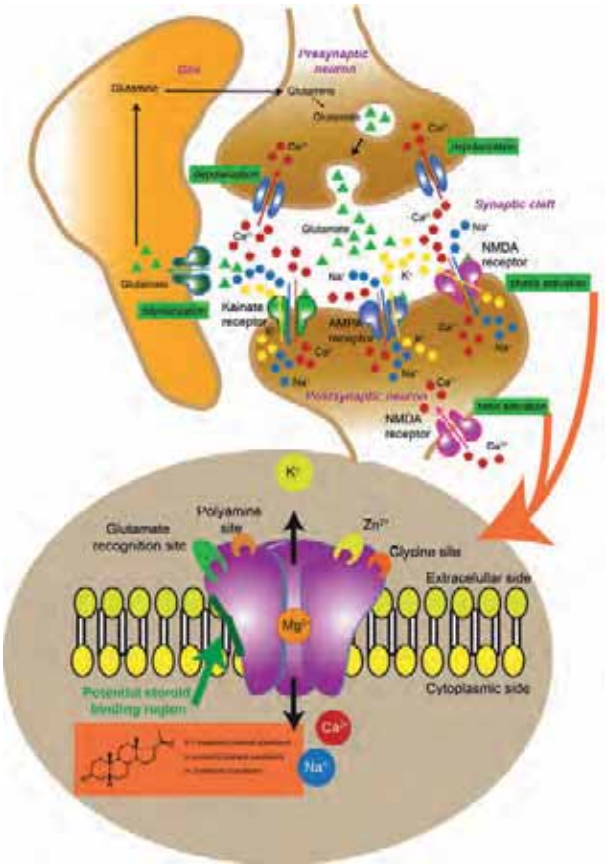
Research topics

The fundamental goal of our research group is design, synthesis and structure-activity relationship evaluation of novel steroid ligands that are able to modulate the most common excitatory receptor in CNS – the NMDA receptor. This receptor plays a significant role in the process of learning and memory; however its overactivation under pathological conditions is connected with various neurodegenerative diseases. The ability of our steroidal compounds to affect the activity of such overactivated NMDA receptors provides attractive opportunity for the design of novel drug entities that could be used for the treatment of some pathological conditions of CNS and act as neuroprotectives. Nevertheless, these novel drugs should have favourable physical-chemical, pharmacokinetic, and pharmacodynamic properties. To explore such pharmacological and physiological diversity, we closely collaborate with behavioural scientists (*in vivo* models) as well as experts with *in vitro* electrophysiological techniques and we have already successfully prepared and tested promising structures that do serve as a leading platform for the design of additional molecules. Also, we focussed upon finding binding site for neurosteroids on NMDA receptors. Identifying neurosteroid binding site may enable to specify pathophysiological role of neurosteroids in the CNS as well as establish more complex knowledge about structural properties of NMDA pharmacophore.



Current grant support

Grant Agency of the Czech Republic (303/12/1464), Technology Agency of the Czech Republic – Center for Development of Original Drugs (TE01020028).

Selected recent papers

1. Borovská J., Vyklický V., Šťastná E., Kapras V., Slavíková B., Horák M., Chodounská H., Vyklický L.Jr.: "Access of inhibitory neurosteroids to the NMDA receptor." *Brit. J. Pharmacol.* 166: 1069-1083, **2012**.
2. Kapras V., Slavíčková A., Šťastná E., Vyklický L.Jr., Valeš K., Chodounská H.: "Synthesis of deuterium labelled NMDA receptor inhibitor – 20-Oxo--5β-[9,12,12-$^2H_3$] pregnan--3α-yl-L-glutamyl 1-ester." *Steroids* 77: 282-287, **2012**.
3. Kapras V., Rambousek L., Holubová K., Svoboda J., Bubeníková-Valešová V., Chodounská H., Vyklický L. Jr., Stuchlík A.: "3α,5β-Pregnanolone glutamate, a use-dependent NMDA antagonist, reversed spatial learning deficit in an animal model of schizophrenia." *Behav. Brain Res.* 235: 82-88, **2012**.
4. Kořínek M., Kapras V., Vyklický V., Adamusová E., Borovská J., Valeš K., Stuchlík A., Horák M.,Chodounská H., Vyklický L.Jr.: "Neurosteroid modulation of N-methyl-D-aspartate receptors: Molecular mechanism and behavioural effects." *Steroids* 76: 1409-1418, **2011**.

TEACHING ACTIVITIES

Natural Products I. Hana Chodounská Faculty of Sciences, Charles University in Prague

Eva Kudová / Head of the Group

Hana Chodounská / Scientist
Barbora Slavíková / Research Assistant
Kateřina Kouřilová / Student
Kamila Riedlová / Student
Daďka Hybšová / Technician
Michaela Sedláčková / Technician

Antiobesity Peptides

Lenka MALETÍNSKÁ

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Research topics

The research of our group is focused on the study of **food intake regulation** with aim to develop possible pharmacologic interventions for food intake disorders such as **obesity** or **cachexia**. Our research has multidisciplinary character, it involves peptide chemistry, biochemistry, physiology and pharmacology.

Food intake regulating peptides not only affect hunger or satiety but also energy homeostasis and affect metabolic disturbances such as leptin and insulin resistance resulting in so called metabolic syndrome. **Metabolic syndrome** includes metabolic changes leading to obesity, type 2 diabetes and hypertension and is nowadays a major public health problem associated with morbidity and mortality and continues to increase worldwide. Recently discovered anorexigenic neuropeptides involved in food intake regulation such as **prolactin-releasing peptide (PrRP)** and **cocaine- and amphetamine-regulated transcript (CART) peptides**, as well as antagonists of orexigenic **ghrelin** represent new possibilities in the development of future **anti-obesity agents**. We study the above mentioned peptides both ***in vitro*** in physiologically relevant cell lines expressing respective peptide receptors and ***in vivo*** in mouse models of obesity and leptin and insulin resistance. Recently, we designed **stable analogs of neuropeptide PrRP** with agonistic effect capable to cross the blood brain barrier and therefore to be administered peripherally.

Ghrelin is the only orexigenic peptide of gut origin acting in the brain containing octanoyl group bound to its Ser^3 necessary for its biological activity. Its agonists are promising agents for **treatment of cachexia**. To stabilize the ghrelin molecule, we designed ghrelin analogs acylated through an amide bond at Ser^3 and non-coded amino acids in the peptide chain. These ghrelin agonists have high affinity to the ghrelin receptor and an orexigenic effect similar to ghrelin but with a substantially higher stability.

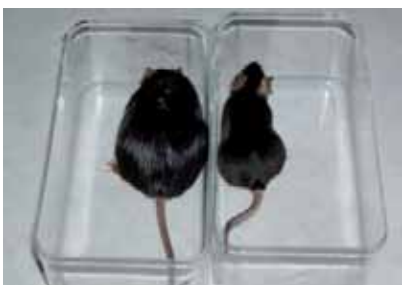
The most common chronic disorders in elderly people are insulin resistance and obesity that result in type 2 diabetes. Recently, central insulin resistance was linked to neurodegenerative changes in the brain, namely **Alzheimer disease** that could be characterized as **type 3 diabetes**. We investigate the connection between central insulin resistance and pathological **phosphorylation of Tau protein** – one of the main players in Alzheimer disease development – in very different **models of insulin resistance**: lipodystrophic A-ZIP mice lacking fat tissue and mouse MSG model with obesity caused by neonatal monosodium glutamate treatment.

Current grant support

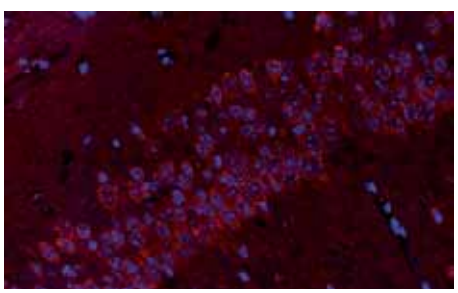
Grant Czech Science Foundation P303/10/1368
Grant Agency of Charles University 560112 (M.Holubová)
Grant Czech Science Foundation P303/12/0576

Selected recent papers

1. Maletínská L, Pýchová M, Holubová M, Blechová M, Demianová Z, Elbert T, Železná B. J Pharmacol Exp Ther. 2012, 340(3):781-6.
2. Maletínská L, Špolcová A, Maixnerová J, Blechová M, Železná B. Peptides. 2011, 32(9):1887-92.
3. Maletínská L, Matyšková R, Maixnerová J, Sýkora D, Pýchová M, Špolcová A, Blechová M, Drápalová J, Lacinová Z, Haluzík M, Železná B. Mol Cell Endocrinol. 2011; 343(1-2):55-62.
4. Maixnerová J, Špolcová A, Pýchová M, Blechová M, Elbert T, Řezáčová M, Železná B, Maletínská L. Peptides. 2011, 32(4):811-7.
5. Matyšková R, Železná B, Maixnerová J, Koutová D, Haluzík M, Maletínská L. Horm Metab Res. 2010, 42(3):182-6.



Obese and lean C57BL mice



Immunohistochemical fluorescent staining of hippocampal neurons with phospho-Tau[Thr212] and DAPI

DIPLOMA THESES

Andrea Špolcová	New pharmacological interventions affecting food intake	Faculty of Sciences, Charles University in Prague
Miroslava Pýchová	Ghrelin analogs in food intake regulation	Faculty of Sciences, Charles University in Prague
Veronika Nagelová	Characterization of CART peptide analogs in in vitro and in vivo tests	Faculty of Sciences, Charles University in Prague

PhD THESES

Resha Matyšková	Impact of leptin and ghrelin on food intake and metabolic parameters in obese ovariectomized female mice.	First Faculty of Medicine, Charles University in Prague
Jana Maixnerová	New pharmacological interventions influencing food intake focused on effects of CART peptide and PrRP	First Faculty of Medicine, Charles University in Prague

Lenka Maletínská / Head of the Group

Blanka Železná / Scientist
Martina Holubová / Ph.D. Student
Andrea Špolcová / Ph.D. Student
Veronika Nagelová / Ph.D. Student
Barbora Mikulášková / Student
Anežka Tichá / Student
Hedvika Vysušilová / Technician

Antimicrobial Peptides for Treatment of Osteomyelitis

Václav ČEŘOVSKÝ

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Research topics

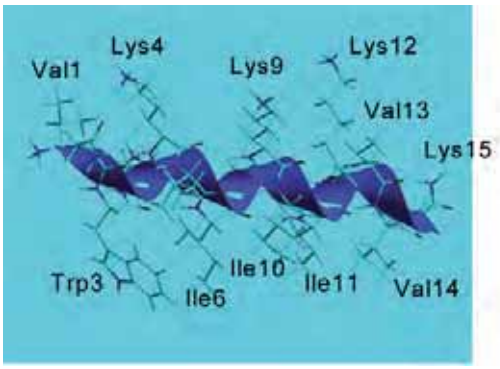
Osteomyelitis, the infection of the bones represents one of the most serious complications in orthopedics which may lead to the limb amputation or death. The reason is growing resistance of causative microorganisms such as *Staphylococcus aureus, Enterobacter*, *Streptococcus species* or *Pseudomonas aeruginosa* against conventional antibiotics. Existing treatment of osteomyelitis is based on antibiotic therapy combined with surgical treatment and adjuvant therapy. A key problem is the treatment of the "dead space" after debridement and removal of sequester formation which is colonized by bacterial biofilm. The proposed way of increasing the therapeutic potential is filling the cavity in the infected bone with local carriers loaded with antimicrobial peptide (AMP). AMPs exhibit activities comparable to those of conventional antibiotics but the physical nature of their action implies a faster killing process. The advantage resides in their mechanism of action, which is markedly different from that of conventional antibiotics and is assumed not to develop bacterial resistance. It consists in the disruption of bacterial cell membrane (see the figure below). Our discoveries of novel potent AMP challenge us to apply these synthetically available AMP for eradication of the bone infections. We will select the most effective one, incorporate it into various local carriers and test it against bone infection in the *in vitro* experiments and in animal models. The design of potent analog is aiming to the improvement of its antimicrobial potency against bacterial biofilm and to the elimination of its side effects. This includes chemical modifications of native peptide structure resulting to the alteration of the structural parameters such as net charge, helicity, hydrophobicity, amphipathicity and stability against degradation in biological fluids. The final goal is to find out suitable combination of selected AMP with a local carrier for the treatment of osteomyelitis finally leading to the promising formula that can enter into preclinical and clinical development.

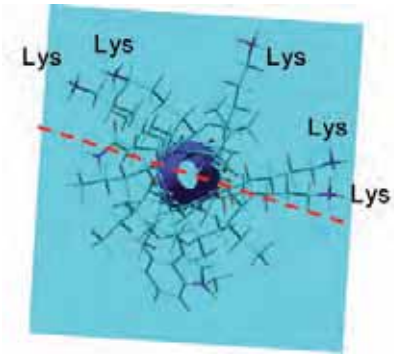
Current grant support

Grant No. P302/11/1901 of the Czech Science Foundation and Project of Targeted Research Groups

Selected recent papers

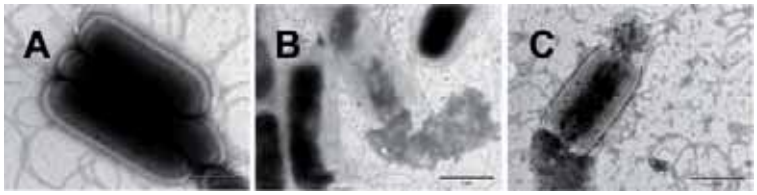
1. Monincová L., Slaninová J., Fučík V., Hovorka O., Voburka Z., Bednárová L., Maloň P., Štokrová J., Čeřovský V. Lasiocepsin, a novel cyclic antimicrobial peptide from the venom of eusocial bee *Lasioglossum laticeps* (Hymenoptera: Halictidae). *Amino Acids* **2012**, 43, 751-761
2. Chapuis H., Slaninová J., Bednárová, L., Monincová, L., Buděšínský, M., Čeřovský V. Effect of hydrocarbon stapling on the properties of α-helical antimicrobial peptides isolated from the venom of hymenoptera. *Amino Acids* **2012**, 43, 2047-2058





In a front view lasioglossin III shows a hydrophobic sector with aliphatic amino acid residues on one side of the helix (down the red line) and hydrophilic sector dominated by five cationic Lys residues on the opposite side. Lassioglossin III adopts such a secondary structure within the bacterial cell membrane which is essential for its antimicrobial action.

α-helical structure of lasioglossin III, the antimicrobial peptide which we isolated from the venom of the wild bee *Lasioglossum laticeps* (lateral view).



Electron micrographs of *Bacillus subtilis* either untreated (A) or treated with antimicrobial peptide lasiocepsin for 60 min showing disruption of cell envelope (B, C). Scale bars 1 μm

DIPLOMA THESES

Tereza Tůmová	The effect of arthropod´s antimicrobial peptides on proliferation and migration of mammalian cells	Institute of Chemical Technology, Prague

PhD THESES

Ondřej Nešuta	Antimicrobial peptides – study of the action mechanism	Institute of Chemical Technology, Prague
Sabína Čujová	Novel insect antimicrobial peptides and the study of their action mechanism	Faculty of Sciences, Charles University in Prague
Lenka Monincová	Novel antimicrobial peptides isolated from the venom of Hymenoptera	Faculty of Sciences, Charles University in Prague

Václav Čeřovský, Assoc. Prof. / Head of the Group

Vladimír Fučík / Scientist
Sabina Čujová / Ph.D. Student
Lenka Monincová / Ph.D. Student
Ondřej Nešuta / Ph.D. Student
Lenka Borovičková / Technician

Helquat Chemistry and Biology

Filip TEPLÝ

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Research topics

Helquats are doubly positive helical systems. Our group has recently introduced these compounds as a novel structural class and has demonstrated that these helical dications are easily accessible and exhibit range of exciting properties.

Our efforts have been driven by a hypothesis that crossbreeding rich fields of viologens and helicenes leading to helquats opens a large and unexplored territory with many attractive applications.*

In the broadest sense, our current work explores supramolecular chemistry of helquats. We pursue identification of biologically interesting molecules interacting with our helical dications which will be key to cultivation of helquat chemistry for its future applications.

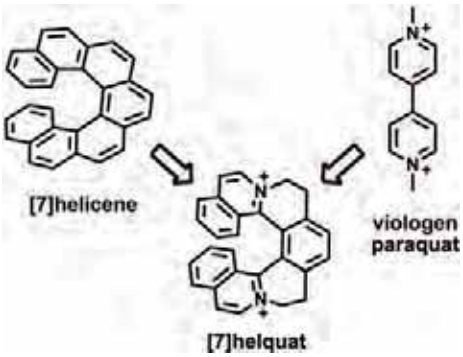
Current grant support

Academy of Sciences of the Czech Republic (RVO: 61388963, M200551208), Czech Science Foundation (13-19213S, 203/09/0705).

*Viologens and helicenes have been in focus of many research laboratories due to their rich and applicable chemistry. This interest centers mainly around electrochemistry, supramolecular self-assembly, optical properties, chirality, catalysis, and biological activity.

Selected recent papers

1. Adriaenssens, L.; Severa, L.; Koval, D.; Císařová, I.; Martínez Belmonte, M.; Escudero-Adán, E.C.; Novotná, P.; Sázelová, P.; Vávra, J.; Pohl, R.; Šaman, D.; Urbanová, M.; Kašička, V.; Teplý, F. "[6]Saddlequat: A [6]helquat captured on its racemization pathway." *Chem. Sci.* **2011**, *2*, 2314-2320.
2. Severa, L.; Ončák, M.; Koval, D.; Pohl, R.; Šaman, D.; Císařová, I.; Reyes-Gutiérrez, P.E.; Sázelová, P.; Kašička, V.; Teplý, F.; Slavíček, P. "Chiral Dicationic [8]Circulenoid: Photochemical Origin of Circulene-Like Species and its Facile Thermal Conversion into Helicene Congener." *Angew. Chem. Int. Ed.* **2012**, *51*, 11972-11976.
3. Balogh, D.; Zhang, Z.; Cecconello, A.; Vávra, J.; Severa, L.; Teplý, F.; Willner, I. "Helquat-Induced Chiroselective Aggregation of Au NPs." *Nano Letters* **2012**,*12*, 5835-5839.
4. Vávra, J.; Severa, L.; Švec, P.; Císařová, I.; Koval, D.; Sázelová, P.; Kašička, V.; Teplý, F. "Preferential Crystallization of a Helicene-Viologen Hybrid - An Efficient Method to Resolve [5]Helquat Enantiomers on a 20 g Scale." *Eur. J. Org. Chem.* **2012**, 489-499.
5. Vávra, J.; Severa, L.; Císařová, I.; Klepetářová, B.; Šaman, D.; Koval, D.; Kašička, V.; Teplý, F. "Search for Conglomerate in Set of [7]Helquat Salts: Multigram Resolution of Helicene-Viologen Hybrid by Preferential Crystallization." *J. Org. Chem.* **2013**, 78,1329-1342.



The privileged pedigree of helquats arising from a combination of structural features of dicationic viologens and helically chiral helicenes.

Solutions of example helquat derivatives.

Fluorescence of various helquat derivatives.

DIPLOMA THESES

Lukáš Severa	Helquats: synthesis and properties	Institute of Chemical Technology, Prague

PhD THESES

Jan Vávra	Helquats - Modular synthesis and properties of novel helical dications	Faculty of Sciences, Charles University in Prague
Martina Čížková	Modular synthesis of N-heteroaromatic cations by [2+2+2] cycloaddition	Faculty of Sciences, Charles University in Prague

POSTDOCTORAL PROJECTS

Paul E. Reyes Gutiérrez	Mexico	Filip Teplý

SIGNIFICANT AWARDS

Pavel Švec	Orion special prize at the 23rd EU Contest for Young Scientists, Helsinki, Finland.	For his work entitled „Synthesis And Testing Of Tetramethyl[5] helquat“	The Jury for EUCYS 2011
Filip Teplý and team of authors	Miloš Hudlický Award	For significant work published in the journals of ChemPubSoc Europe consortium.	Czech Chemical Society

Filip Teplý / Head of the Group

Paul E. Reyes Gutiérrez / Postdoc
Pradeep Devadig / Ph.D. Student
Vishwas Joshi / Ph.D. Student
Lukáš Severa / Ph.D. Student
Manoj Sonawane / Ph.D. Student
Michael Jirásek / Student
Pavel Švec / Student

Drug Delivery Systems

Tomáš KRAUS

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Research topics

Macrocycles are an important class of compounds found in natural products as well as in fully synthetic constructs. Cyclodextrin macrocycles are of special interest due to their capabilities of a forming inclusion complexes with other molecules. Our group is involved in projects that exploit the use of cyclodextrin building blocks for the construction of larger molecular scaffolds.

We have developed synthetic methods for the preparation of tubular cyclodextrin duplexes as potent host molecules for the complexation of shape-compatible organic compounds with high affinity. Dynamic covalent bonds – in particular disulfide linkages – are used as „chemical glue“ holding the building blocks together. The inclusion complexes with guest compounds can be cleaved by reducing thiols in order to facilitate the release of the guest to surrounding medium. Currently, we explore this system as a molecular transporter capable of delivery of anionic compounds (drugs) across cell membrane.

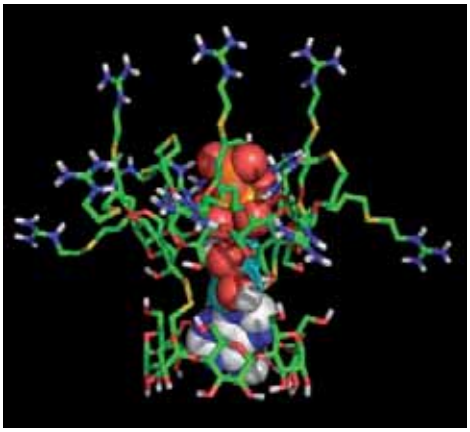
In collaboration with Institute of Chemical Technology (Dr. R. Cibulka), cyclodextrin macrocycles have been used as chiral scaffolds for the synthesis of cyclodextrin-flavinium conjugates as organocatalysts for enantioselective sulfoxidation. We have prepared several conjugates that proved to be very active catalysts of sulfoxidations performed with hydrogen peroxide as the oxidant allowing enantioselectivities up to 90% ee.

Current grant support

Ministry of Education, Youth and Sports (LD12019).

Selected recent papers

1. L. Kumprecht, M. Buděšínský, J. Vondrášek, J. Vymětal, J. Černý, I. Císařová, J. Brynda, V. Herzig, P. Koutník, J. Závada, T. Kraus: “Rigid Duplex –Cyclodextrin Reversibly Connected With Disulfide Bonds. Synthesis and Inclusion Complexes.“ *J. Org. Chem.* **2009**, *74*, 1082-1092.
2. L. Krejčí, M. Buděšínský, I. Císařová, T. Kraus: “Tubular duplex α-cyclodextrin triply bridged with disulfide bonds: synthesis, crystal structure and inclusion complexes.” *Chem. Commun.* **2009**, 3557-3559.
3. V. Mojr, V. Herzig, M. Buděšínský, R. Cibulka and T. Kraus. “Flavin-cyclodextrin conjugates as catalysts of enantioselective sulfoxidations with hydrogen peroxide in aqueous media. “ *Chem. Commun.* **2010**, *46*, 7599-7601.
4. V. Mojr, M. Buděšínský, R. Cibulka and T. Kraus. “Alloxazine-cyclodextrin conjugates for organocatalytic enantioselective sulfoxidations.“ *Org. Biomol. Chem.*, **2011**, 9, 7318-7326.
5. A. Grishina, S. Stanchev, L. Kumprecht, M. Buděšínský, M. Pojarová, M. Dušek, M. Rumlová, I. Křížová, L. Rulíšek, T. Kraus: “Beta-Cyclodextrin Duplexes That Are Connected through Two Disulfide Bonds: Potent Hosts for the Complexation of Organic Molecules. “ *Chem. Eur. J.* **2012**, *18*, 12292-12304.



An inclusion complex of ATP and guanidinylated β-cyclodextrin duplex.

A cyclodextrin-flavin conjugate for enantioselective sulfoxidations with hydrogen peroxide in aqueous media.

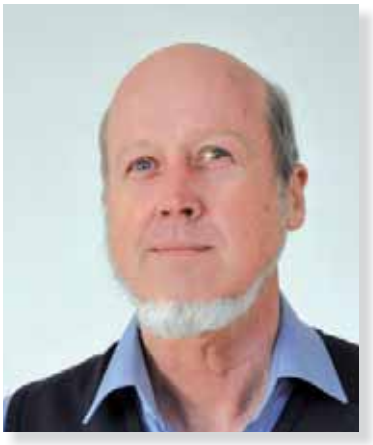
DIPLOMA THESES

Lucie Krejčí	Synthesis of rigid alpha-cyclodextrin duplexes connected with three disulfide bridges	Charles University in Prague
Petr Koutník	Alpha-beta cyclodextrin heteroduplex: synthesis and application as a molecular connector for anchoring multivalent ligands onto alkyl-silyl monolayers on glass surfaces	Institute of Chemical Technology Prague
Vladimír Herzig	Synthesis of cyclodextrin-isoalloxazine conjugates and their use as catalysts for enantioselective oxidation of sulfides	Institute of Chemical Technology Prague

Tomáš Kraus / Head of the Group

Anastasia Grishina / Ph.D. Student
Ameneh Tatar / Postdoc
Pavle Močilac / Postdoc

RESEARCH SERVICE GROUPS



Nuclear Magnetic Resonance

David ŠAMAN

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Research topics

NMR is a unique spectroscopic method for structure elucidation and provides information about the constitution, configuration and conformation of studied compounds. Our research is focused on structural study of both synthetic compounds originating in laboratories of the IOCB and those isolated from natural sources. We utilize modern onedimensional and multidimensional NMR techniques and then obtained NMR parameters are subsequently used for structure elucidation of nucleosides, nucleotides, peptides, steroids, saccharides, pheromones, helicenes and other classes of compounds. Chirality is an important property of many biologically signifiant compounds and knowledge of absolute configuration is necessary for structure--activity relationship evaluation. NMR enables determination of enantiomeric purity, enantiomeric excess and absolute configuration using chiral shift reagents and chiral derivatizing reagents for *in-situ* reactions in NMR tubes.

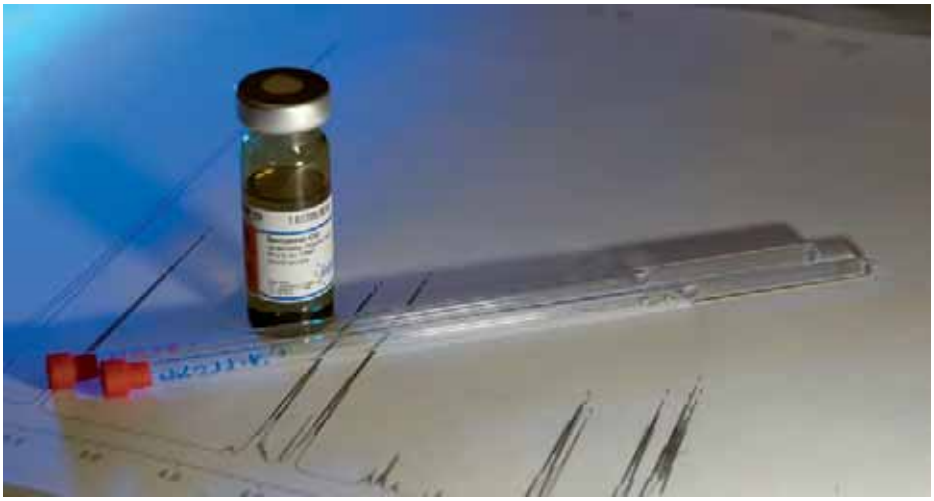
Our research is also focused on the study of nonbonding interactions of supramolecular systems, mechanism and kinetics of deuterium exchange of pyrimidine C(5)-H using NMR and *ab initio* quantum chemical calculations. Quantum chemical calculations of NMR parameters are found to be useful for prediction and interpretation of experimental NMR data. Our research is focused on calculation of these NMR parameters using *ab initio* methods for model compounds (peptides, nucleotides) and understanding and explaining of relationships between structural factors and calculated NMR parameters.

Current grant support

Grant Agency of the Czech Republic (13-24880S)

Selected recent papers

1. Pohl, R., Dracinsky, M., Slavetinska, L. & Budesinsky, M. (2011). The observed and calculated H-1 and C-13 chemical shifts of tertiary amines and their N-oxides. *Magnetic Resonance in Chemistry* 49, 320-327
2. Severa, L., Jirasek, M., Svec, P., Teply, F., Revesz, A., Schroder, D., Koval, D., Kasicka, V., Cisarova, I. & Saman, D. (2012). Counterion-Induced Inversion of Conformer Stability of a [5]Helquat Dication. *Chempluschem* 77, 624-635
3. Dracinsky, M., Jansa, P. & Bour, P. (2012). Computational and Experimental Evidence of Through-Space NMR Spectroscopic J Coupling of Hydrogen Atoms. *Chemistry-A European Journal* 18, 981-986
4. Pohl, R., Potmischil, F., Dracinsky, M., Vanek, V., Slavetinska, L. & Budesinsky, M. (2012). ^{13}C GIAO DFT calculation as a tool for configuration prediction of N-O group in saturated heterocyclic N-oxides. *Magnetic Resonance in Chemistry* 50, 415-423



PhD THESES

Eliška Procházková	Structure and properties of modified nucleic acid components	Faculty of Sciences, Charles University in Prague

TEACHING ACTIVITIES

Basic NMR I	Martin Dračinský	Faculty of Sciences, Charles University in Prague
Basic NMR II	Martin Dračinský	Faculty of Sciences, Charles University in Prague

David Šaman / Head of the Group

Miloš Buděšínský / Scientist
Martin Dračínský / Scientist
Radek Pohl / Scientist
Ján Tarábek / Scientist
Lenka Poštová Slavětínská / Postdoc
Eliška Procházková / Ph.D. Student
Marie Snopková / Technician
Vojtěch Svoboda / Undergraduate Student

Mass Spectrometry

Josef CVAČKA

e-mail: cvacka@uochb.cas.cz

Research topics

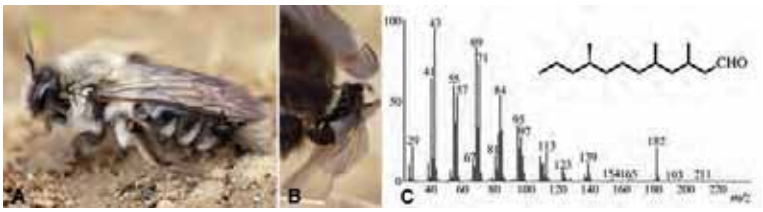
The team develops analytical and research methods based on mass spectrometry (MS) to be used in various areas of life sciences. MS is most frequently utilized for structure elucidation and identification of organic substances. The target compounds are typically natural products with known or expected biological functions, ranging from small volatiles to large biomolecules like proteins. The methods are based on direct sample analysis by MS or coupling of MS with thoroughly optimized chromatographic separations (GC/MS, LC/MS or TLC/MS). The recent projects are focused on detailed characterization of complex lipid mixtures and disclosing structures of new lipid classes. The compounds of interest are also being detected in situ, which allows visualization of their spatial distribution (MS imaging techniques). The team also performs routine MS analyses for the local scientific community, maintains open-access instruments and provides collaborative support.

Current grant support

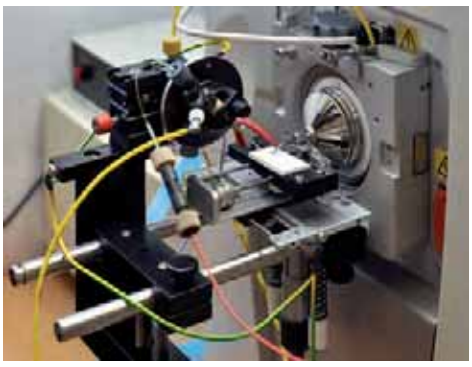
Academy of Sciences (RVO 61388963, M200551204), Czech Science Foundation (203/09/0139, P206/12/1093, P206/12/0750, P13 – 21409P).

Selected recent papers

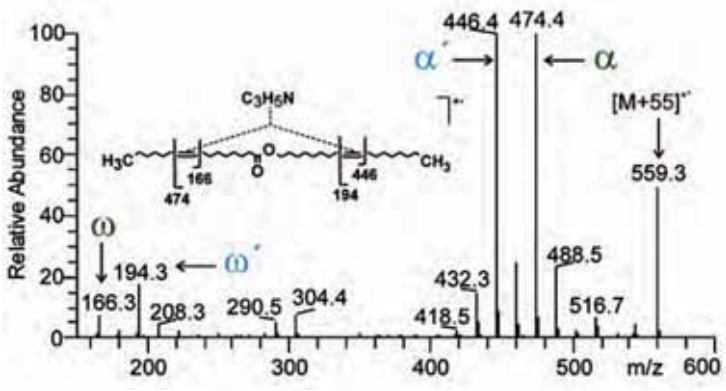
1. Šobotník, J., Bourguignon, T., Hanus, R., **Demianová, Z.**, Pytelková, J., Mareš, M., Foltýnová, P., Preisler, J., **Cvačka, J.**, Krasulová, J., Roisin, Y., Bourguignon, T., Roisin, Y., Lacey, M.J. & Sillam-Dusses, D. (2012). Explosive backpacks in old termite workers. *Science,* **337**, 436.
2. Urbanová, K., **Vrkoslav, V.**, Valterová, I., Háková, M. & **Cvačka, J.** (2012). Structural characterization of wax esters by electron ionization mass spectrometry. *J. Lipid. Res.,* **53**, 204-213.
3. **Vrkoslav, V.**, Háková, M., Pecková, K., Urbanová, K. & **Cvačka, J.** (2011). Localization of double bonds in wax esters by high-performance liquid chromatography/atmospheric pressure chemical ionization mass spectrometry utilizing fragmentation of acetonitrile-related adducts. *Anal. Chem.,* **83**, 2978–2986.
4. **Vrkoslav, V.**, Muck, A., **Cvačka, J.** & Svatoš, A. (2010). MALDI imaging of neutral cuticular lipids in insects and plants. *J. Am. Soc. Mass. Spectr.,* **21**, 220-231.
5. Raindlová, V., Pohl, R., **Šanda, M.** &Hocek M. (2010). Direct polymerase synthesis of reactive aldehyde-functionalized DNA and its conjugation and staining with hydrazines. *Angew. Chem. Int. Ed.*, **49**, 1064-1066.



Sex pheromone of Stylops muelleri identified with the help of mass spectrometry (A, B: parazite on the bee host; C: spectrum and structure).



In-house built motorized platform for ambient ionization mass spectrometry (DESI/DAPPI).



Localization of double bonds in lipids (MS/MS spectrum of a specific adduct).

DIPLOMA THESES

Václav Martinovský	Effect of pesticides on the nutriends arsitability	Faculty of Agrobiology, Food and Natural Resources, Czech University of Life Sciences Prague
Daniela Janechová	Analysis of antimicrobial peptides in venom glands of bumblebees	Faculty of Sciences, Charles University in Prague
Petra Macháčková	New matrices for MALDI-MS analysis of lipids	Faculty of Sciences, Charles University in Prague
Martina Háková	Determination of double bond position in wax esters by dimethyl disulfide derivatization and mass spectrometry	Faculty of Sciences, Charles University in Prague
Jana Jersáková	Determination of double bond positions in higher hydrocarbons	Faculty of Sciences, Charles University in Prague
Renáta Norková	Study of tebuconazali compless with methods	Faculty of Sciences, Charles University in Prague

TEACHING ACTIVITIES

Mass spectrometry detection in separation techniques	Josef Cvačka	Faculty of Sciences, Charles University in Prague
High-performance liquid chromatography	Josef Cvačka	Faculty of Sciences, Charles University in Prague
Academic Communication	Jana J. Dytrtová	Faculty of Sciences, J. E. Purkinje University in Ústí nad Labem

Josef Cvačka / Head of the Group

Vladimír Vrkoslav / Scientist
Jana Jaklová Dytrtová / Scientist
Zuzana Demianová / Postdoc
Filip Kaftan / Ph.D. Student
Radka Míková / Ph.D. Student
Marie Zábranská / Ph.D. Student
Petra Horká / Ph.D. Student
RNDr. Anna Březinová / Research Assistant
Jana Horáková / Research Assistant
Ing. Květa Kertisová / Research Assistant
Ing. Kateřina Nováková / Research Assistant
Eva Háková / Ph.D. Student
Jan Rejšek / Ph.D. Student
Lenka Šubčíková / Student
Martin Vít / Student
Eva Slabá / Technician-Specialist
Karel Rücker / Technician

Virology

Jan WEBER

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Research topics

Virology research-service team was established in September 2011 to aid in IOCB drug discovery program by providing in-house facility for screening of antiviral compounds against variety of viruses and to reinforce basic research of the institution in virology field.

In the service part we are currently testing compounds against HIV, influenza virus, Dengue virus, and coxsackie virus.

Our research is focused on HIV in particular exploring new strategies for HIV inhibition, HIV drug resistance, HIV tropism, viral fitness and its implication for HIV pathogenesis and disease progression.

HIV capsid plays two important roles: first early in infection during virus core uncoating and second late in infection during assembly of new virus. We investigate and search for compounds interfering with both of these roles.

Disease progression varies significantly in HIV-infected patients and is dependent on a number of host genetic, immune and virological factors. We investigate the role of HIV fitness in disease progression in the absence of antiretroviral treatment.

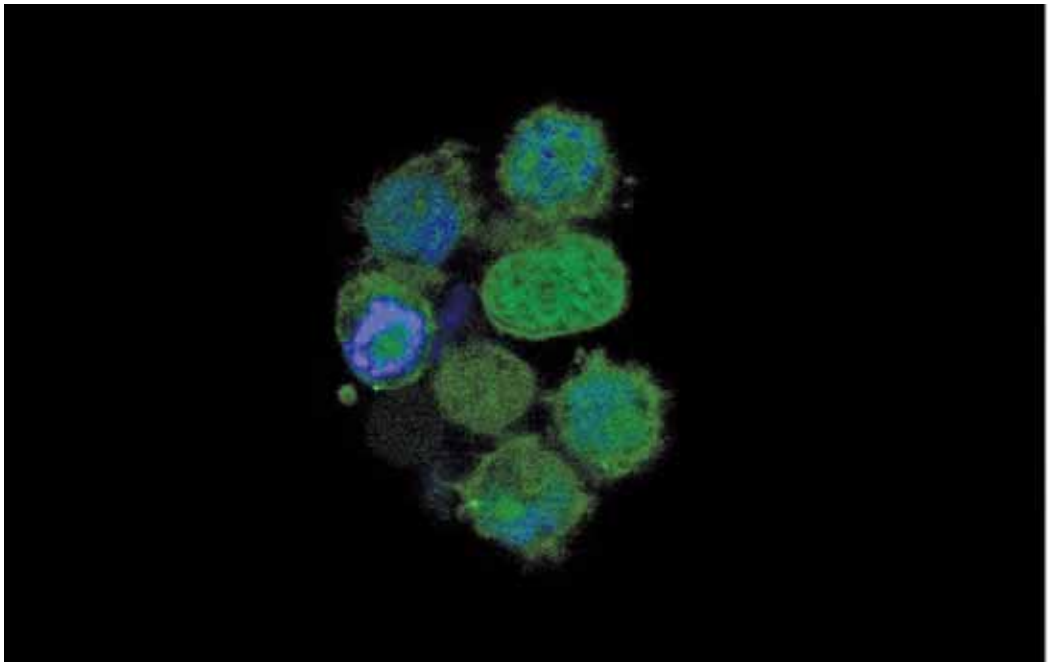
Current grant support

Ministry of Education, Youth and Sports of the Czech Republic (LK11207)

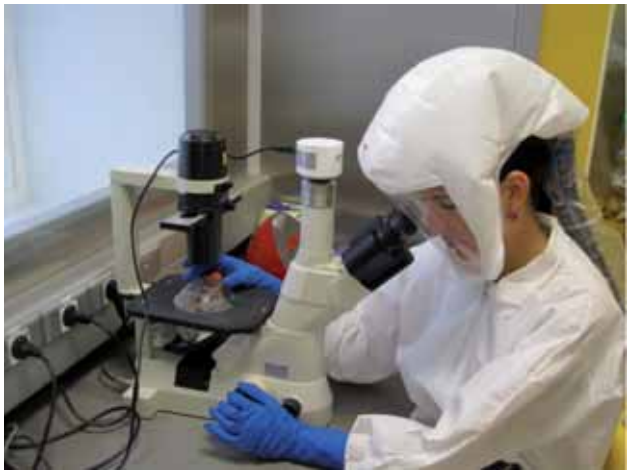
Grant Agency of the Czech Republic (13-19561S)

Selected recent papers

1. Archer J., Weber J., Henry K., Winner D., Gibson R., Lee L., Paxinos E., Arts E.J., Robertson D.L., Mimms L., Quinones-Mateu M.E. (2012) Use of Four Next-Generation Sequencing Platforms to Determine HIV-1 Coreceptor Tropism. PLoS ONE 7(11): e49602.
2. Weber J., Vazquez A., Winner D., Gibson R., Rhea A., Rose J., Wylie D., Henry K., Wright A., King K., Archer J., Poveda E., Soriano V., Robertson D., Olivo P., Arts E., and Quinones-Mateu, M. (2013) Sensitive Cell-based Assay to Determine Human Immunodeficiency Virus Type 1 Coreceptor Tropism" J Clin Microbiol 2013 Mar 13. [Epub ahead of print]

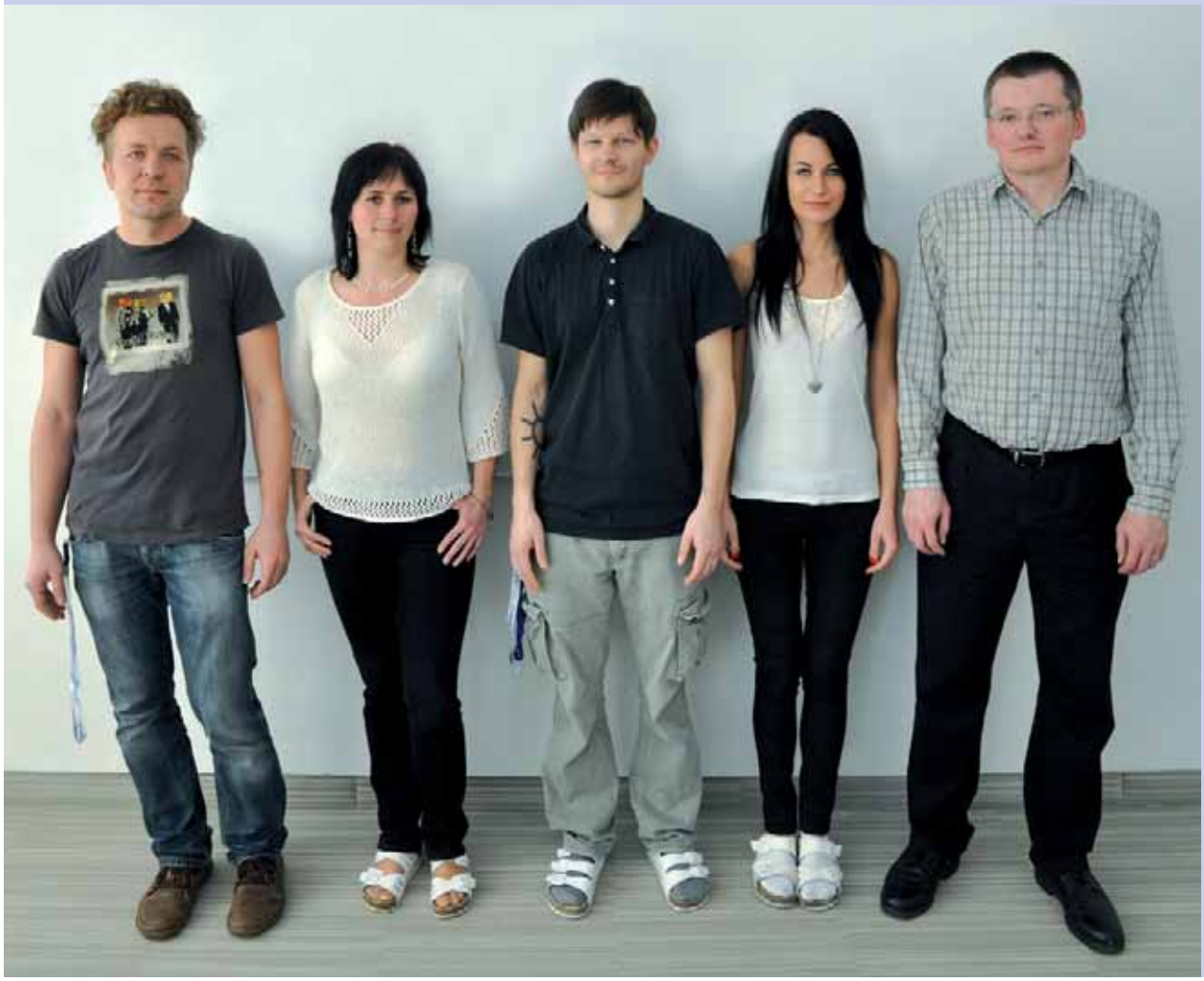


MT-4 cells infected with HIV-1 expressing green fluorescent protein



Jan Weber / Head of the Group

Marcela Pávová / Postdoc
Jan Hodek / Research Assistant
Dmytro Strunin / Research Assistant
Lenka Ptáčníková / Ph.D. Student
Hana Prouzová / Technician



Bioinformatics

Jiří VONDRÁŠEK

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Research topics

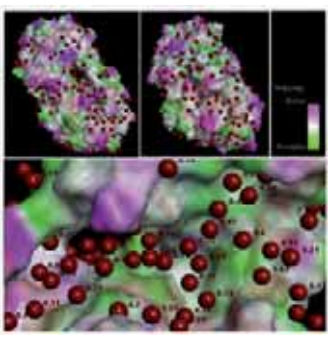
Primary subject of studies in group of Bioinformatics are Proteins, their structures, architectures, interactions, stabilities, processes of their folding/unfolding and evolutional pathways in which a function emerged and was further optimized. We are specifically interested in problems of local structure preferences along proteins main chain which are strongly dependent on a character of a side chain and define not only character of the folding process but more importantly they determine proteins behavior in different environments. Most of the methods we used are combinations of molecular modeling, molecular simulations, computational chemistry, bioinformatics analysis and mathematical statistics to establish a robust methodological background suitable to provide solution of various structural biology and life science related problems. We also offer professional support for institutional users in modeling of protein structures, prediction of protein-protein interactions and standard bioinformatics analysis and tools. Last but not least one of our goals is a setup of Integrated Database of Small Molecules which should serve as a national contribution to the pan-European ESFRI project ELIXIR.

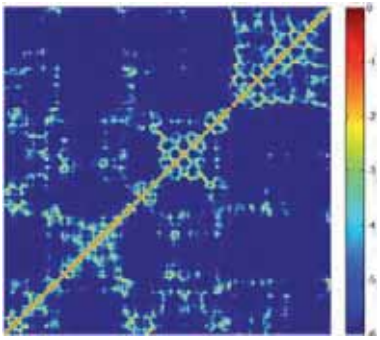
Current grant support

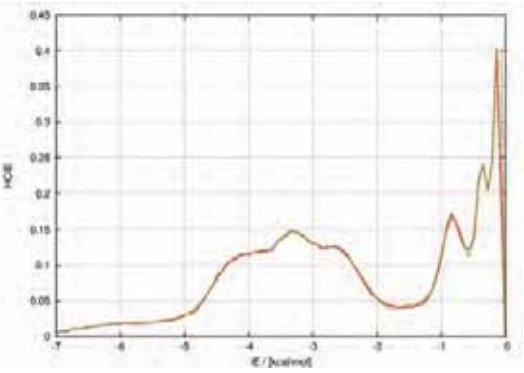
Ministry of Education, Youth and Sports g - No. LH11020, Ministry of Education, Youth and Sports g - No. LG13061 and Grant Agency of the Czech Republic P208/10/0725

Selected recent papers

1. **Berka, K. – Laskowski, R. A. – Hobza, P.[G] Vondrášek, Jiří** Energy Matrix of Structurally Important Side-Chain/Side-Chain Interactions in Proteins. *Journal of Chemical Theory and Computation*. Roč. 6, č. 7 (2010), s. 2191-2203. ISSN 1549-9618
2. **Vymětal, Jiří – Vondrášek, Jiří[G]** Metadynamics As a Tool for Mapping the Conformational and Free-Energy Space of Peptides – The Alanine Dipeptide Case Study. *Journal of Physical Chemistry B*. Roč. 114, č. 16 (2010), s. 5632-5642. ISSN 1520-6106
3. **Fačkovec, Boris – Vondrášek, Jiří[G]** Decomposition of Intramolecular Interactions Between Amino-Acids in Globular Proteins – A Consequence for Structural Classes of Proteins and Methods of Their Classification. *Systems and Computational Biology – Molecular and Cellular Experimental Systems*. Rijeka : InTech, 2011 – (Yang, N.), s. 69-82 ISBN 978-953-307-280-7
4. **Vymětal, Jiří – Vondrášek, Jiří[G]** Gyration- and Inertia-Tensor-Based Collective Coordinates for Metadynamics. Application on the Conformational Behavior of Polyalanine Peptides and Trp-Cage Folding. *Journal of Physical Chemistry A*. Roč. 115, č. 41 (2011), s. 11455-11465. ISSN 1089-5639
5. **Kysilka, Jiří – Vondrášek, Jiří[G]** Towards a better understanding of the specificity of protein-protein interaction. *Journal of Molecular Recognition*. Roč. 25, č. 11 (2012), s. 604-615. ISSN 0952-3499
6. **Ramis, J. M. – Rubert, M. – Vondrášek, Jiří[G] – Gaya, A. – Lyngstadaas, S. P. – Monjo, M.** Effect of Enamel Matrix Derivative and of Proline-Rich Synthetic Peptides on the Differentiation of Human Mesenchymal Stem Cells Toward the Osteogenic Lineage. *Tissue Engineering*. Roč. 18, 11-12 (2012), s. 1253-1263. ISSN 1937-3341







DIPLOMA THESES

Boric Fackovec	Intramolecular and intermolecular interactions in proteins 2012	Faculty of Sciences, Charles University in Prague
David Jakubec	Amino acids and their selectivity in protein-protein interactions 2015	Faculty of Sciences, Charles University in Prague

PhD THESES

Karel Berka	Side-chain Side-chain Interactions in Proteins 2010	Faculty of Sciences, Charles University in Prague
Jiří Kysilka	Intermolecular interactions in proteins 2013	Faculty of Sciences, Charles University in Prague
Jiří Vymetal	Theoretical Study of the Conformational Behavior and Structural Preferences of Amino Acids in Peptides by Metadynamics 2014	Faculty of Sciences, Charles University in Prague

Jiří Vondrášek / Head of the Group

Jakub Galgonek / Postdoc
Jiří Kysilka / Ph.D. Student
Jiří Vymetal / Ph.D. Student
Krati Sharma / Ph.D. Student
David Jakubec / Student
David Chena / Student

Biochemical Pharmacology

Helena MERTLÍKOVÁ-KAISEROVÁ

e-mail: kaiserova@uochb.cas.cz

Research topics

The primary goal of our group is to promote drug discovery process at IOCB. Our research is therefore multidisciplinary and based on collaboration with medicinal chemistry, structural biology and biochemistry groups. Our essential research tools are cell-based and *in vitro* assays. Apart from the routine screening activities, we provide and assist with new biochemical method development according to the actual needs.

Traditionally, we focus on the analogs of nucleic acid components i.e. variously modified nucleos(t)ides and purine or pyrimidine bases. However, other structural motifs have also been investigated lately. Our expertise is particularly found in the field of anticancer drug research.

Pharmacological potential of novel compounds is generally studied at the level of cellular uptake (intracellular, transcellular), metabolism and interactions with specific cellular targets such as e.g. telomeres/telomerase, thymidine phosphorylase, DNA polymerases, protein/lipid kinases, cell signaling molecules etc.

Currently we are engaged in the projects involving

1. identification and characterization of novel inhibitors of xanthine oxidase
2. identification and characterization of novel inhibitors bacterial adenylyl cyclase
3. biotransformation and mechanistic aspects of potential antivirals and antileukemic agents of 9-norbornyl-6-chloropurine class
4. anti-inflammatory and anti-angiogenic effects of substituted pyrimidines
5. development of novel G-quadruplex stabilizing ligands.

The team operates two high-end flow cytometers (one of them allowing cell sorting) which are actively employed for both research and service purposes.

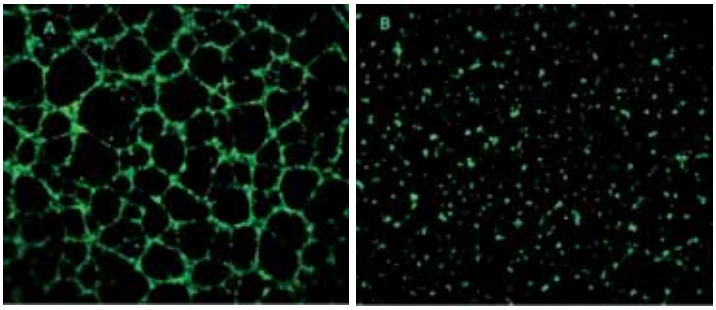
The provided services include cytotoxicity screening, cell cycle and apotosis analysis, assessment of DNA/RNA synthesis (BrdU, BrU incorporation) and cellular permeability assay (Caco-2).

Current grant support

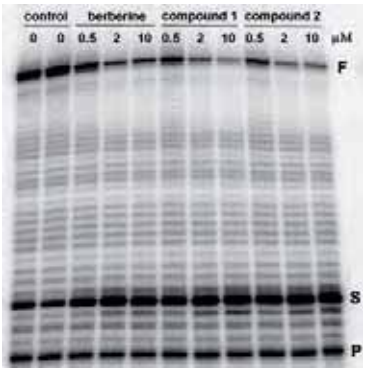
Academy of Sciences (RVO:61388963**)**, Czech Science Foundation (P303/11/1297), Czech Ministry of Interior (VG20102015046), Technology Agency of the Czech Republic (TE01020028)

Selected recent papers

1. Procházková, E.**,** Jansa, P., Dračínský, M., Holý, A., Mertlíková-Kaiserová, H. (2012) Determination of the antioxidative activity of substituted 5-aminopyrimidines. *Free Radic Res.* **46**, 61-67.
2. Mertlíková-Kaiserová, H., Nejedlá, M., Holý, A., Votruba, I. (2012) Involvement of MAP Kinases in the Cytotoxicity of Acyclic Nucleoside Phosphonates. *Anticancer Res.* **32,** 497-502.
3. Matoušová, M., Votruba, I., Otmar, M., Tloušťová, E., Günterová, J., Mertlíková-Kaiserová, H. (2011) 2'-deoxy-5,6-dihydro-5-azacytidine-a less toxic alternative of 2'-deoxy-5-azacytidine. A comparative study of hypomethylating potential. *Epigenetics.* **6**, 769-776.
4. Mertlíková-Kaiserová, H., Rumlová, M., Tloušťová, E., Procházková, E., Holý, A., Votruba, I. (2011) Point mutations in human guanylate kinase account for acquired resistance to anticancer nucleotide analogue PMEG. *BiochemPharmacol.* **82**, 131-138.
5. Šála, M., De Palma, A. M., Hřebabecký, H., Dejmek, M., Dračínský, M., Leyssen, P., Neyts, J., Mertlíková-Kaiserová, H., Nencka, R. (2011) SAR studies of 9-norbornylpurines as Coxsackievirus B3 inhibitors. *Bioorg Med Chem Lett.* 21, 4271-4275.



Endothelial cells (HUVEC) on Matrigel™ forming typical capillary-like structures. A-without treatment, B-10 μM test compound (substituted pyrimidine).



Autoradiogram of a sequencing gel showing enhanced DNA synthesis pausing at the G-quadruplex site (VEGF G-quadruplex, DNA polymerase stop assay).

DIPLOMA THESES

Michaela Nejedlá	Effects of acyclic nucleoside phosphonates PMEG and PMEDAP on p38-kinase signaling in human leukemia cells	Faculty of Sciences, Charles University in Prague
Eliška Procházková	Antioxidant effects of the analogs of nucleic acid components	Faculty of Sciences, Charles University in Prague
Nela Rozumová	Biotransformation aspects of novel carbocyclic nucleoside analogs	Faculty of Sciences, Charles University in Prague
Lenka Pohlová	Novel G-quadruplex stabilizers in regulation of oncogene expression	Faculty of Sciences, Charles University in Prague
Pavla Hubálková	Identification of novel G-quadruplex ligands interacting with the telomeres	Institute of Chemical Technology, Prague

PhD THESES

Pavla Plačková	Molecular aspects of the cytostatic and antiviral effects of new nucleoside/nucleotide analogs	Institute of Chemical Technology, Prague
Alexandra Dvořáková (Kostinová)	Interactions of nucleoside/nucleotide analogs with cAMP/cGMP-mediated signaling	Institute of Chemical Technology, Prague

Helena Mertlíková-Kaiserová / Head of the Group

Miroslav Hájek / Scientist
Marika Matoušová / Postdoc
Markéta Šmídková / Postdoc
Jaroslav Kozák / Postdoc
Alexandra Dvořáková / Ph.D. Student
Pavla Plačková / Ph.D. Student
Pavla Hubálková / Student
Lenka Pohlová / Student
Jana Günterová / Research Assistant
Eva Tloušťová / Research Assistant
Karolína Müllerová / Technician
Ludmila Tovchigrechko / Technician

Medicinal Chemistry

Pavel MAJER

e-mail: majer@uochb.cas.cz

Research topics

The mission of the service part of the group consists of:

- Solid phase synthesis of peptides up to 50 amino acid residues
- Synthesis of peptide derivatives containing e.g. fluorescent labels, hydrophobic modifications, PEG linkers, special amino acids, dendritic branching, multiple disulfide bridges etc.
- Synthesis of small molecules, mainly enzyme inhibitors with various warheads
- Qualitative and quantitative amino acid analysis of peptides and proteins
- Protein and peptide sequencing using Edman's method in the standard scale and micro scale
- Maintenance and standard service of LC-MS-TOF instrument and custom analysis of samples
- Quantitative amino acid analysis by fluorescent derivatization and HPLC

List of current scientific projects and collaborations:

1. **Controlling Structure and Function of Biomolecules at the Molecular Scale: Theory Meets Experiment** (Participation in a Center of Excellence – PI Prof. Pavel Hobza, IOCB)
2. **Cathepsin Proteases in Pathology** – Collaboration with Michael Mares' Group at IOCB and Center for Drug Discovery, University of California San Francisco, U.S.A.
3. **Glutamate Carboxypeptidase II (GCPII) a.k.a. Prostate Specific Membrane Antigen (PSMA) Related Projects**

3a. **Polymer Bound GCPII Ligands for Targeted Drug Delivery** – Collaboration with Jan Konvalinka, IOCB and Karel Ulbrich, Institute of Macromolecular Chemistry, Academy of Sciences of the Czech Republic

3b. **Prodrugs of 2-Phosphonomethyl Pentanedioic Acid (PMPA) a Potent yet Orally Non-Available Inhibitor of Glutamate Carboxypeptidase II (GCPII)** -Collaboration with Marcela Krečmerová, IOCB and Barbara Slusher, Brain Science Institute, Jonhs Hopkins University, Baltimore, U.S.A.

4. **Biogenesis Of (*E*)-1-Nitropentadec-1-ene In Soldiers Of The Termite Genus *Prorhinotermes* –** Collaboration with Irena Valterova's group at IOCB
5. **Development of Protein Delivery Systems Suitable for Cell Reprograming of Non-Endorine Pancreatic Cells into the Insulin Producing beta-Cells** – Collaborationwith with Tomáš Koblas and František Saudek, Institute for Clinical and Experimental Medicine (IKEM), Prague, Czech Republic
6. **Design, Characterization and Mechanism of Action of Novel Inhibitors of HIV Assembly** – Participation on collaborative project with Jan Konvalinka's group (IOCB) and Ales Machara (Dept. of Organic Chemistry, Faculty of Natural Sciences, Charles University, Prague, Czech republic
7. **Synthesis of Novel Biradicaloid Heterocycles Small Chromophores with Efficient Singlet Fission** – Collaboration with Josef Michl and Zdenek Havlas at IOCB

Current grant support

Design, Characterization and Mechanism of Action of Novel Inhibitors of HIV Assembly (PI – Jan Konvalinka)-GACR

New Pharmacological Interventions Influencing Energy Homeostasis and Development of Insulin Resistance in Type II Diabetes Mellitus (PI – Lenka Maletinska) –GACR

Controlling Structure and Function of Biomolecules at the Molecular Scale: Theory Meets Experiment – (Center of excellence, PI – Pavel Hobza) – GACR

Inter-membrane Proteases of the Rhomboid Family in Secretionary Pathways of Mamalian Cells: Their Substrate Specificity, Biological Role and Inhibition (Grant "Return" from Ministry of Education, PI – Kvido Strisovsky)-MSMT

Selected recent papers

1. Ferraris D.; Duvall B.; Ko Y.S.; Thomas AG.; Rojas C.; **Majer P.;** Hashimoto K.; Tsukamoto T. Synthesis and biological evaluation of D-amino acid oxidase inhibitors. Journal of Medicinal Chemistry (2008), 51(12), 3357-3359.
2. Barinka C.; Hlouchova K.; Rovenska M.; **Majer P.;** Dauter M.; Hin N.; Ko Y.S.; Tsukamoto T.; Slusher B.S.; Konvalinka J.; Lubkowski J. Structural basis of interactions between human glutamate carboxypeptidase II and its substrate analogs. Journal of Molecular Biology (2008), 376(5), 1438-1450.
3. Grella B, Adams J., Berry, J.F., Delahanty, G., Ferraris D.V., Majer**, P**., Ni, C., Shukla, K., Shuler S.A., Slusher, B.S., Stathis, M.,Tsukamoto, T., The discovery and structure-activity relationships of indole-based inhibitors of glutamate carboxypeptidase II. Bioorg. Med. Chem. Lett. (2010), 20(24), 7222-7225.
4. Čeřovský V., Hovorka, O., Cvačka, J., **Voburka, Z**., Bednárová, L., Borovičková, L., Slaninová, J. & Fučík, V. Melectin: A novel antimicrobial peptide from the venom of the cleptoparasitic bee Melecta albifrons. (2008) Chembiochem. 9(17), 2815-2821. [15]
5. Maixnerová J, Špolcová A, Pýchová M, **Blechová M.**, Elbert T, Řezáčová M, Zelezná B, Maletínská L. Characterization of prolactin-releasing peptide: binding, signaling and hormone secretion in rodent pituitary cell lines endogenously expressing its receptor. (2011) *Peptides*., 32(4), 811-817.
6. **Blechová M.,** Nagelová V, Záková L, Demianová Z, Zelezná B, Maletínská L. (2013). New analogs of the CART peptide with anorexigenic potency: The importance of individual disulfide bridges. *Peptides*., 39, 138-144.

Pavel Majer / Head of the Group

Aneta Kadlčíková / Postdoc
Andrej Jančařík / Postdoc
Jakub Hývl / Postdoc
Jitka Bařinková / Research Assistant
Miroslava Blechová / Research Assistant
Martin Hradilek / Research Assistant
Radko Souček / Research Assistant
Zdeněk Vobůrka / Research Assistant
Alexandrina Prichodko / Technician
Věra Himrová / Technician

SERVICE GROUPS

Waste Management

Petr ŠIMEK

e-mail: simek@uochb.cas.cz

The Waste Management Department deals mainly with the disposal of hazardous wastes. The wastes are prepared for transport and disposal in compliance with the legislation in force, in particular the Act on Waste and the European Agreement concerning the International Carriage of Dangerous Goods by Road (ADR). The department further performs statutory duties of an administrative nature, such as keeping records of the wastes produced, sending reports required by state institutions, granting permission for hazardous waste handling, preparing a waste producer's waste management plan and monitoring the legislative changes concerning waste disposal.

Petr Šimek / Head of the Group

Lukáš Rynda / Technician
Vladimír Strnad / Technician

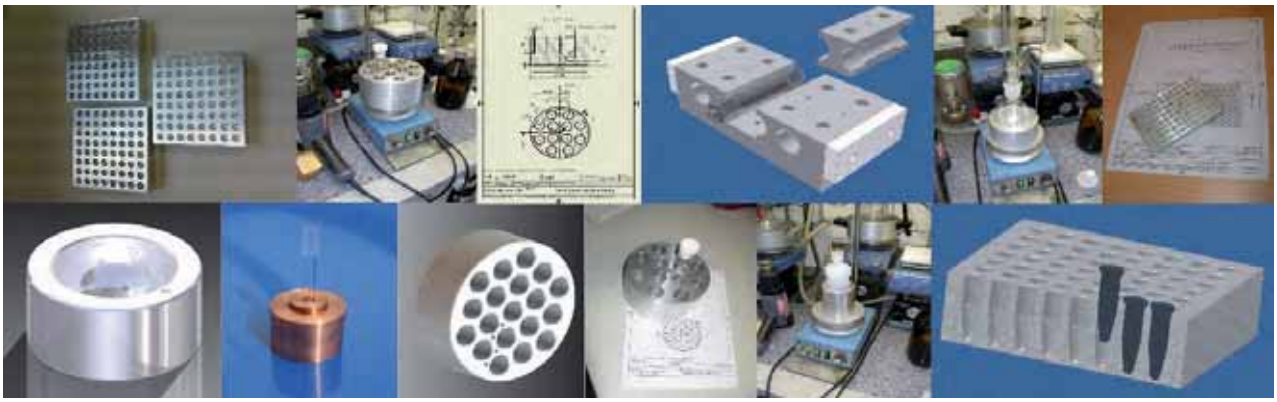
Development Workshops

Petr MUDRA

e-mail: mudra@uochb.cas.cz

Field of our work is rather wide. We provides simple electromechanical service and production of specific products which are not available on the market, inclu-ding custom holders, thermal blocks, movements, loaders, fittings and glass workshop. Our focus is developing complex systems to cover the range of activity of the IOCHB. Data measuring and collec-tin, engeneering and electronic proposals, software and hardware development. We can cooperate on your projects!

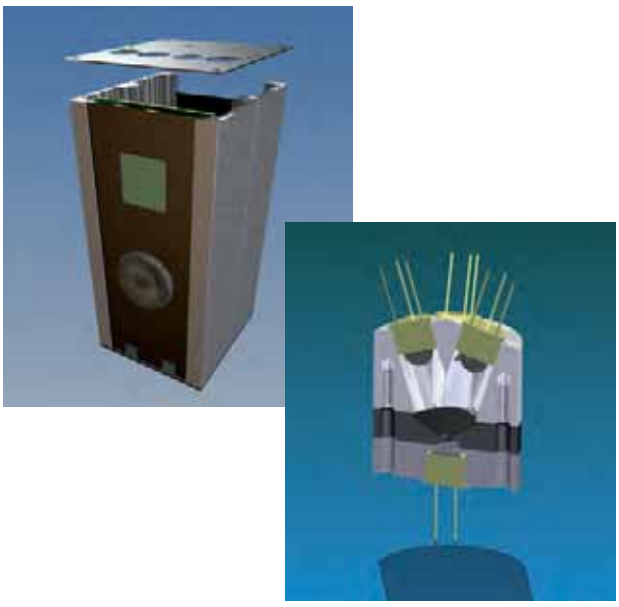
SAMPLES OF OUR WORK

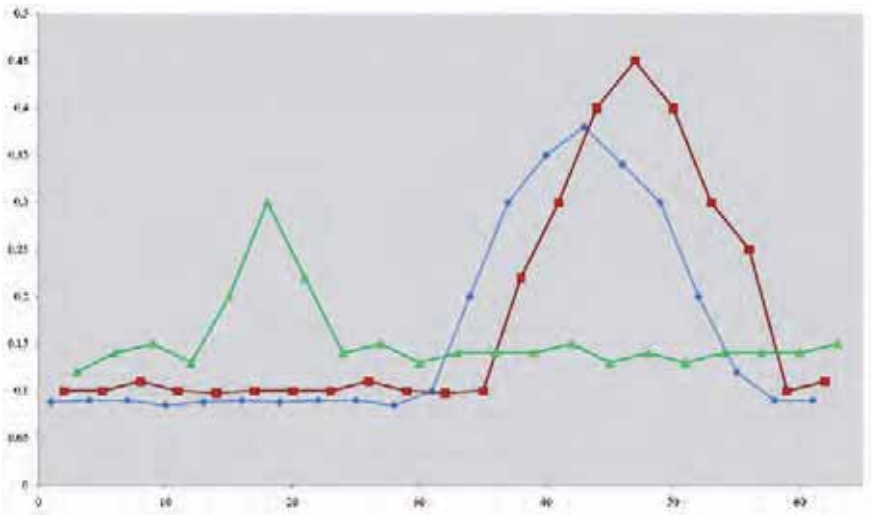


Thermal blocks
Simple thermal blocks to cool or heat your samp-les. They are custom made to your specifications. Use standard laboratory sources of tempering (hotplates, magnetic stirers, ice). They have better handling and thermal properties than standard oil bathes.

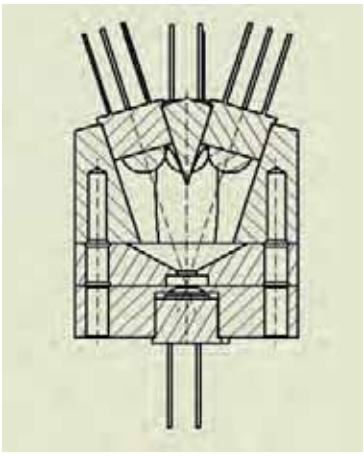
UV monitor innovations
We are in the process of rebuilding our preparative UV monitor. Rather than a standard mercury bulb (254 nm) as a UV source, we are developing wide spectrum LED source and detection (244 – 1100 nm). The heart of the new monitor is a multi-source flow cell. It has one detector and up to four LEDs as a light sour-ce. It would be possible create customer combinations of wave lengths to have a semi-diode array for specific compounds.
Other advantages of this UV monitor are Bluetooth or LAN connection to PC, integral memory, color display to see simple chromatograms and a user frien-dly control menu.

Finally, we are developing our own data collection software.
We `re looking forward to working with you.





LED sources work in pulse mode, significantly prolonging the live time of UV LEDs.



Multisource cells combine to four sources of light per one flow cell with one detector. It`s possible to detect targets without mobile phase collision.

Petr Mudra / Head of the Group

Pavel Poncar / Technician
Zdeněk Barták / Technician IT
Olga Karpíšková / Technician
Ondřej Pačes / Technician
Václav Pešek / Technician
Vít Pokorný / Technician
Vladimír Přibyl / Technician
Jiří Smrž / Technician
Věra Bláhová / Secretary

Qualified Workers:
Jaroslav Bárta
Miroslav Bílý
Daniel Kolaja
Vladimír Šprdlík
František Vávra
Jan Všetečka

Scientific Information Centre

Zuzana FORMANOVÁ

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The Scientific Information Centre of IOCB (library) was established with the foundation of IOCB. Since then, the library stock and the number of provided services have been enlarged significantly. Visitors of the library are mainly employees of IOCB. Since the library was opened to the public in 2002, it has also provided services to external visitors. The number of individual users is currently **424**.
Particularly, we cooperate with libraries of The Academy of Sciences of the Czech Republic, The National Library, The National Medical Library, The National Technical Library and with university libraries.

Currently, the existing department of SIC (Scientific Information Centre) is divided into three parts:
1/ Library
2/ Reprography
3/ Bindery

SIC Collections:
The library collection is comprised of **53 140** items (2012). With the advancement of modern technology, the structure of services provided has changed. In 2012, we offered only **61** print journals compared to **8 062** fulltext on-line journals. We purchase chemistry collections from major publishers (Elsevier, Wiley, Springer, ACS, Royal Society of Chemistry, ASM, IOP, etc.), many separately purchased journals from publishers like Nature Publishing, Thieme, AIP, APS, AACR, etc. Furthermore, we offer many bibliographic, factographic, video and other kinds of information from databases like Web of Knowledge, Scopus, Reaxys, Henry Steward Talks, etc.

Services:
- Purchase of books and journals on demand for employees of IOCB
- ISBN assignment
- Loan of books and journals in print
- Access to scientific information online
- Access to information through Wifi
- Remote access via EZproxy
- Inter-library journal exchange
- (International) inter-library loan services for library users – in paper form and through electronic document delivery system
- Inter-library loan services for libraries
- Collecting of information about publication activity of scientists of IOCB into the database ASEP (RIV)
- Reprography and print services, including poster printing and scanning
- Bindery services
- Organizing of annual sell exhibition of scientific literature, and exhibitions of interesting photos of IOCB employees.

All services are described on our library website – http://library.uochb.cas.cz/

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Lenka Haškovcová / Librarian
Miluše Kortusová / Book-binder
Marie Krahulcová / Librarian
Hana Pěknicová / Librarian
Jana Procházková / Librarian
Michaela Záluská / Librarian
Viktorie Tothová / Reprography

Information Technology

Ivan ČERNÝ

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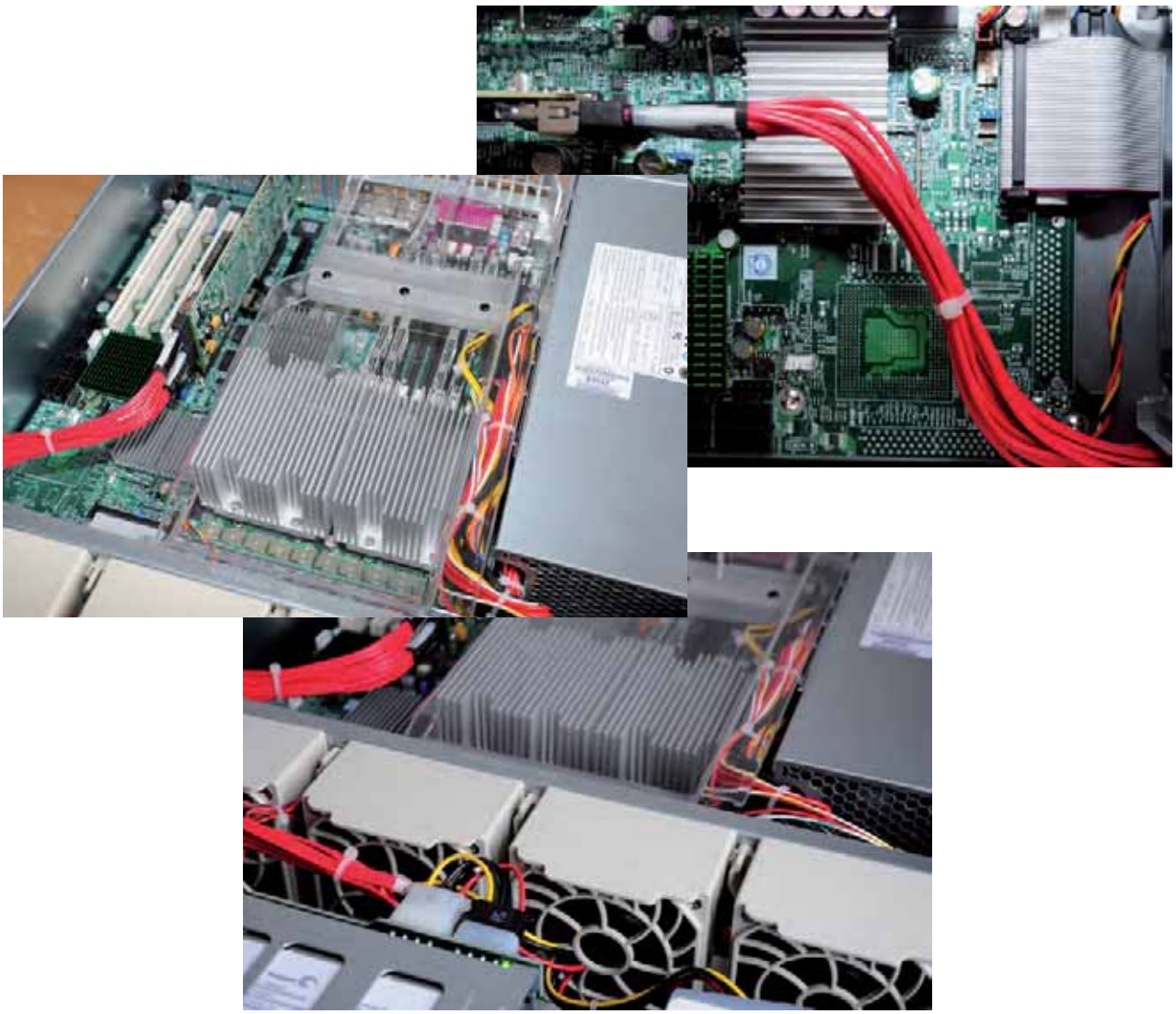
The main objective of the Department of Information Technology is to provide convenient and secure access to information sources and services for IOCB employees. Our team is responsible for the maintenance and development of a basic network infrastructure, for the management of institutional servers (network services and databases), and for assistance in a desktop computer related problems. We provide support for workstation installations, network configuration, multi-license software administration, security incidents handling, and network printing.

Network services at the Institute have been provided since 1992 by network administrators. In 2003, the IT group was formed as part of the Scientific Information Center of IOCB, and in 2007 the group became an independent department. During the year 2012, the team was expanded to provide better user support and to assist during the reconstruction of the Institute's buildings.



Ivan Černý / Head of the Group

Jiří Polách / IT Specialist
Vladimír Kulhavý / IT Specialist
Dušan Koval / IT Specialist
Radek Liboska / IT Specialist
Martin Sokol / IT Specialist
Tomáš Svoboda / IT Specialist

Analytical Laboratory

Stanislava MATĚJKOVÁ

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For complete characterization of synthetized and/or isolated organic substances and their systems the detailed and reliable elemental analysis is still an indispensable tool (optimally in combination with advanced methods of structural analysis, for example, MS, NMR and FTIR spectrometries). Recently, new methodologies and instrumental techniques have been introduced in our laboratory to supplement and/or to replace the classical chemical methods of analysis, e.g. titrimetry. The implementation of instrumental methods is aimed at improvement of detection limits sensitivity and other performance characteristics of analytical methods. Furthermore, the amount of sample required for analysis should be reduced and non-destructive techniques (if possible) could be applied. The range of elements determined has been expanded significantly.

Currently, the C, H, N determination is performed using the automatic PE-Analyzer in the CHN mode.

Fluorine is determined after mineralization potentiometrically by fluoride ion-selective electrode.

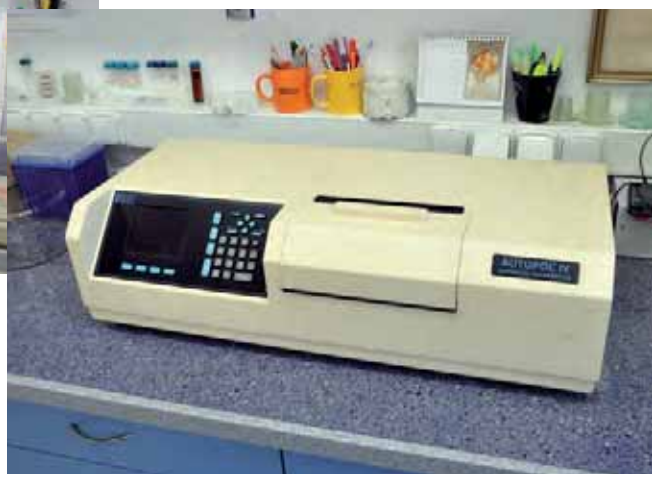
Energy dispersive X-ray fluorescence (ED-XRF) spectrometry is used in our laboratory predominantly for "routine" determination of various elements in newly synthesized organic compounds. The developed quantitative analytical methodology is based on measurements of solutions of studied samples in methanol (mostly), water or another appropriate solvent, the element range is Al – U. Qualitative or semiquantitative analyses in element range Na – U are feasible for diverse materials without calibration; the method is non-destructive.

Inductively coupled plasma – optical emission spectroscopy (ICP-OES) is used basically as a supplementary method to ED-XRF, for example for (i) the determination of lightest elements such as Li, B,..., (ii) analyses of very complex samples and nanoparticle systems and (iii) trace analysis e.g. in biochemical and/or biological samples.

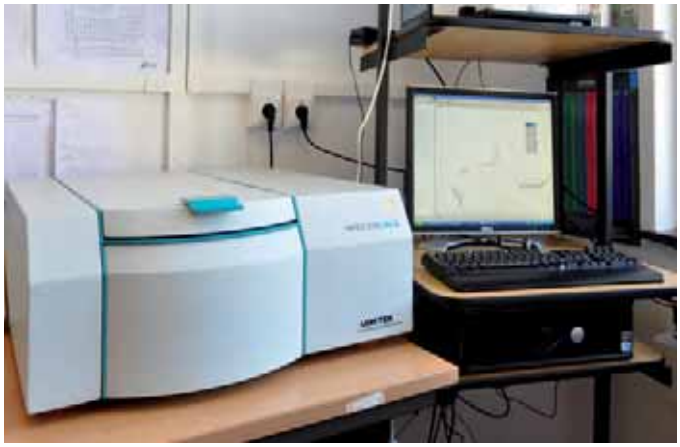
The optical activity measurement of organic compounds is a standard type of our services. Precise weighing of low amounts of samples for some experiments of scientific teams is also performed on our very precise analytical balance and microbalances.

The staff of Analytical Laboratory is involved in the project aimed at archivation of all relevant samples synthetized in the Antonin Holy Library (AHL).

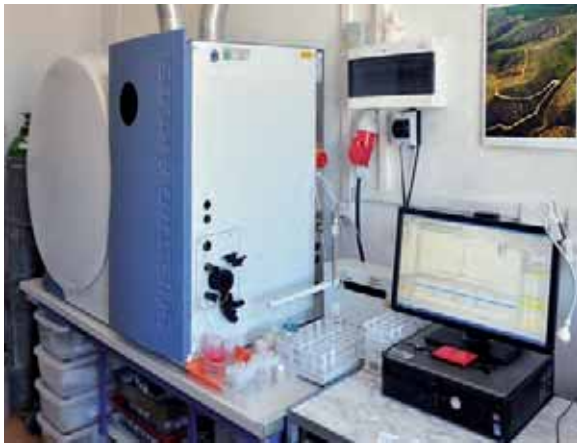
PE 2400 CHNS/O Analyzer (Perkin Elmer)



Optical polarimeter Autopol IV (Rudolph Research)



Energy-dispersive X-ray fluorescence (ED-XRF) spectrometer Spectro iQ II (Spectro A.I.)



Inductively coupled plasma optical emission spectrometer (ICP-OES) Spectro Arcos SOP (Spectro A.I.)

Stanislava Matějková / Head of the Group

Věra Bártová / Research Assistant
Jaroslava Hniličková / Research Assistant
Lucie Holasová / Research Assistant
Magdalena Hošková / Technician
Štefan Štanga / Technician

Molecular Spectroscopy

Lucie BEDNÁROVÁ

e-mail: bednarova@uochb.cas.cz

The molecular spectroscopy team carries out spectroscopic characterizations of various organic compounds synthesized by other teams at the IOCB. To this end we mostly use infrared spectroscopy, in some specific cases in combination with gas chromatography. If necessary, we also provide Raman spectroscopy measurements for full sample characterization, thanks to our collaboration with the other laboratories equipped with appropriate spectrometers. Circular dichroism spectroscopy allows us to characterize the chirality of various organic compounds prepared at the IOCB.

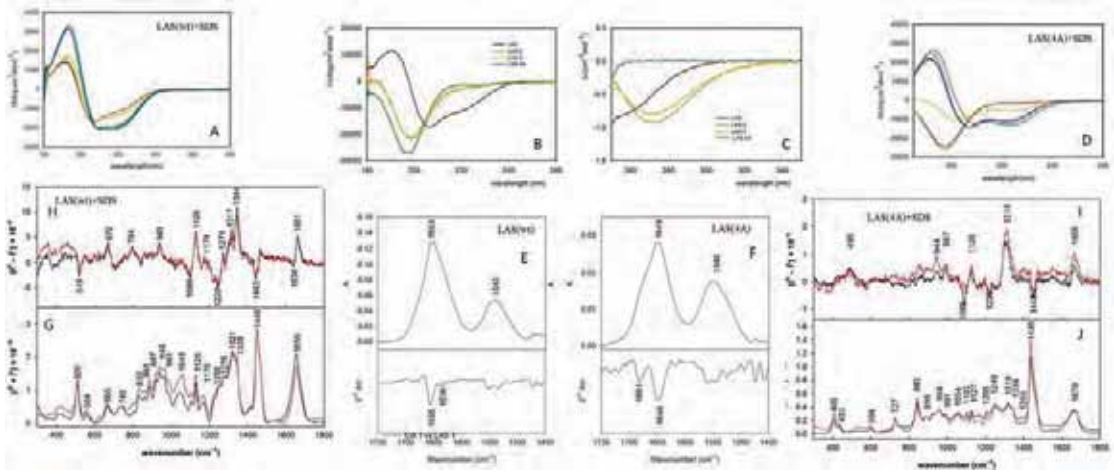
Particular attention is given to the study of secondary and eventually tertiary structure of peptides and proteins using circular dichrosim (CD) and vibrational (infrared and Raman) spectroscopies and their chiral variants (vibrational CD (VCD) and Raman optical activity (ROA)). Although we are a service team, we run research oriented on the study of structural changes and dynamics of biopolymers, mainly proteins. We focus on the structural changes of antibacterial peptides and their analogs in interaction with model membranes with the aim to clarify their specific mode of action. We are also interested in the possibility to characterize the nonplanarity of amide bonds in a way similar to what we showed with the possibility of assigning an absolute configuration of a disulfide bond using the aforementioned set of spectroscopic techniques.

The spectroscopic work is performed on a FTIR spectrometer Nicolet 6700, CD spectrometer Jasco-815 and ROA spectrometer ChiralRaman (Biotools).

We also deal with Raman microspectroscopy of live cells with the aim to be able to designate the chemical contents of specific cell's organelles (in collaboration with the Dept. of Biomolecules, Inst. of Physics, MFF, Charles Univ. Prague)

Selected recent papers

1) **Pazderková M., Bednárová L., Dlouhá** H., Flegel M., Lebl M., Hlaváček J., Setnická V., Urbanová M., Hynie S., Klenerová V., Baumruk V., **Maloň P.**: Electronic and vibrational optical activity of several peptides related to neurohypophyseal hormones: Disulfide group conformation. *Biopolymers* 97: 923-932, 2012.
2) **Pazderková M.**, Kočišová E., Pazderka T., **Maloň P.**, Kopecký V., Monincová L., Čeřovský V., **Bednárová L.**: Antimicrobial Peptide from the Eusocial Bee *Halictus sexcinctus* Interacting with Model Membranes., *Spectroscopy: An International Journal* **27**: 497-502, 2012.
3) Cvačka J., Jiroš P., Kalinová B., Straka J., Černá K., Šebesta P., Tomčala A., **Vašíčková S.**, Jahn U., Šobotník J.:Stylopsal: The First Identified Female-produced Sex Pheromone of Strepsiptera. *Journal of Chemical Ecology* 38: 1483-1491, 2012.
4) **Bednárová L**. Palacký J., Bauerová V., Hrušková-Heidingsfeldová O., Pichová I., Mojzes P.: Raman Microspectroscopy of the Yeast Vacuoles. *Spectroscopy: An International Journal* **27**: 503-507, 2012.



Disulfide bonds geometry assignment using circular dichroism and vibrational spectroscopies made for antibacterial peptide lasiocepsin and its analogs varying in disulfide bridge content

Lucie Bednárová / Head of the Group

Markéta Pazderková / Ph.D. Student
Pavel Fiedler / Research Assistant
Beáta Seidlerová / Research Assistant
Jana Hanzlíková / Research Assistant
Helena Dlouhá / Research Assistant
Miroslava Otrubová / Technician

External Members:
Petr Maloň
Soňa Vašíčková

Laboratory of Radioisotopes

Tomáš ELBERT

e-mail: elbert@uochb.cas.cz

Research topics

The tasks of the Laboratory of Radioisotopes are multiple:

- To provide commercialy nonavailable radioactively labeled compounds to biochemical research teams of the institute.
- Secure the radiometric service.
- Management of the radioactive waste.
- Management of the radiation safety on the institute.

The problems concerning the synthesis of compounds labeled by radionuclides are very specific for each of the radionuclide.

1. Labeling of peptides by radionuclide ^{125}I.
   We have optimized the labeling procedure of peptides with 5 to 35 amino acid residues with IODOGENE™ – Na[^{125}I]. The resulting mixture of the starting peptide and its monoiodinated and diiodinated derivatives is separated using radio-HPLC and thus the peptides with specific activities over 2 000 Ci/mmol are obtained. Lyophilized ^{125}I-labeled peptides can be stored at – 20 °C for period of two months.
2. Labeling of nucleoside and nucleotide analogs and study of the stability of ^{3}H label.
   New biologically active compounds developed in our institute are labeled by standard methods – Catalytic Exchange Solution Gas (CESG), catalytic reduction or catalytic dehalogenation under the carrier-free tritium gas. For handling of carrier-free tritium gas we use Tritium manifold from RC TRITEC AG, Switzerland. All ^{3}H-labeled compounds are fully characterised by ^{3}H and ^{1}H NMR and *radio*-HPLC.
3. Labeling of brassinosteroids by radionuclide ^{3}H.
   The work on syntheses of ^{3}H-labeled brassinosteroids and their applications in the Laboratory of Growth Regulators of University of Palacký, Olomouc, was supported by the grant of GAAV No. IAA400550801. 24-[^{3}H]Epicastasterone, 24-[^{3}H]epibrassinolide and 28-[^{3}H]homocastasterone were prepared. The precursors for the introduction of tritium – either chlorocarbonates or derivatives with double bond in the side chain were prepared from the starting non-labeled brassinosteroids.
4. Syntheses of ^{14}C-labeled compounds.
   Recently we prepared S-[*methyl*-^{14}C]methyl-L-methionine by the reaction of [^{14}C]methyl iodide with L-methionine. The specific activity of the product (54.2 mCi/mmol) was assayed by ^{13}C NMR.

Current grant support

Academy of Sciences (RVO 61388963), Ministry of Education (LG13002)

Selected recent papers

1. Elbert T., Veselá I.: Conditions for Succsesful Labeling of Oxidation Sensitive Peptides by Na[^{125}I] – IODO-GEN™ System. *Journal of Labelled Compounds & Radiopharmaceuticals* **2010**, *53*, 288-291.
2. Elbert T., Břehová P., Holý A.: The Preparation of ^{3}H-Labeled Acyclic Nucleoside Phosphonates and Study of Their Stability. *Collection of Czechoslovak Chemical Communications* **2010**, *75*, 757-766.
3. Marek A., Patil M. R., Klepetářová B., Kohout L., Elbert T.: A stereospecific pathway for the introduction of deuterium on the brassinosteroid skeleton by reductive dechlorination of chlorocarbonates. *Tetrahedron Letters* **2012**, *53*, 2048-2050.

Tritiation manifold

Vacuum manifold for syntheses with $^{14}CO_2$

radio-HPLC

PhD THESES

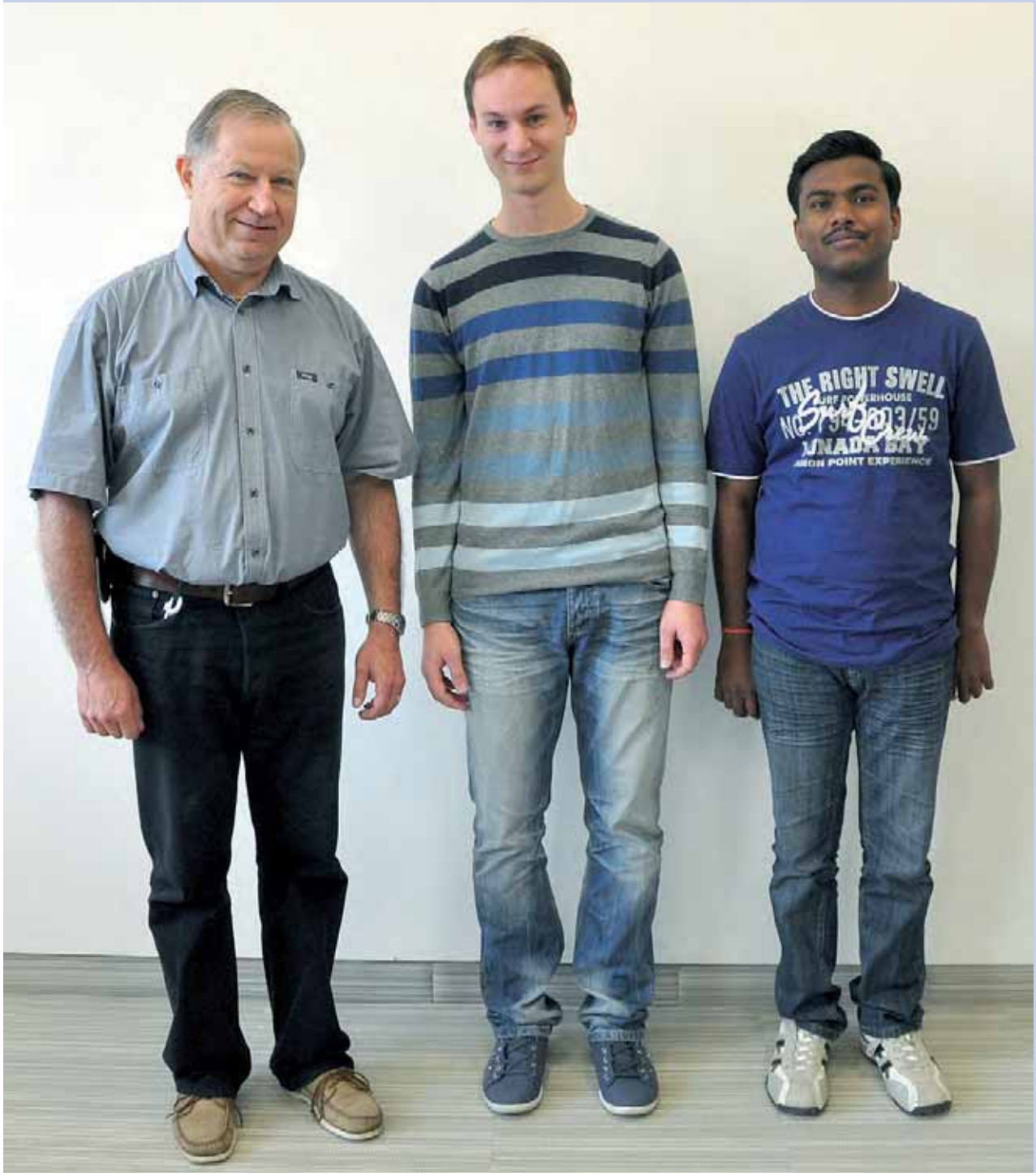
Mahadeo R. Patil	Syntheses of precursors for preparation of tritium-labeled biologically active compounds with steroid skeleton and modeling of tritiation reaction using deuterium gas.	Institute of Chemical Technology, Prague

SIGNIFICANT AWARDS

Tomáš Elbert	IIS-CED Award 2011	For many years of scientific accomplishments to International Isotope Society	Central European Division and Bad Soden conferences

Tomáš Elbert / Head of the Group

Aleš Marek / Scientist
Mahadeo R. Patil / Ph.D. Student
Martin Káčerik / Research Assistant



IOCB TTO – TECHNOLOGY TRANSFER OFFICE

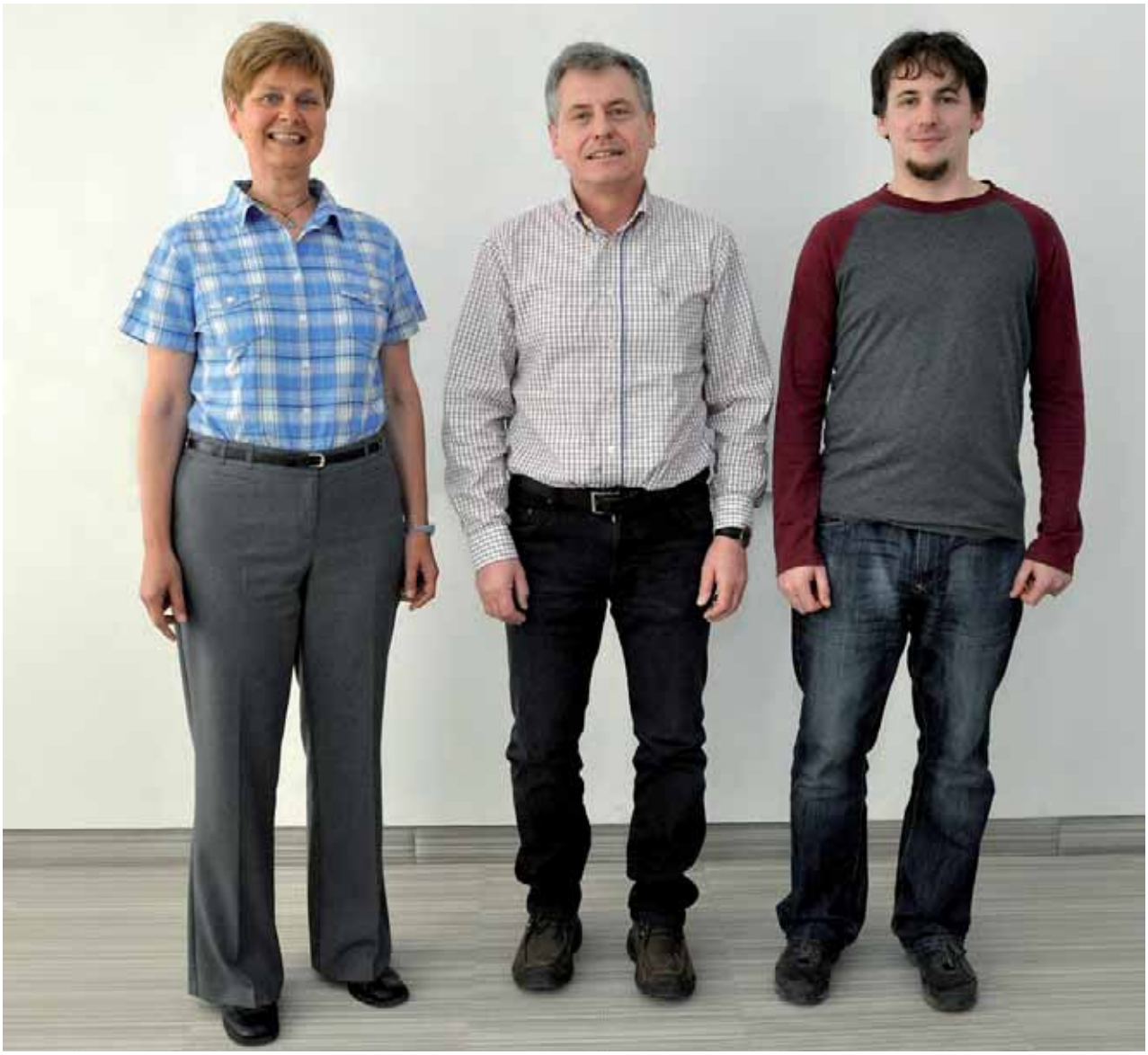
www.iocb-tto.cz

The IOCB TTO was established in the year 2009 to provide services for the Institute in the field of technology transfer. The office operates as a commercial unit which is 100 % owned by the institute. The IOCB TTO was created to help scientists transform their discoveries into commercial assets. Among the main responsibilities being the protection of intellectual properties, maintaining the existing patent portfolio, identifying the commercial value of scientific results, help with the project management (in the case of oriented research projects), identification of potential commercial partners and related areas. The main focus is aimed at the development of historically successful area of medicinal chemistry and chemical biology.

The office currently cares for more than 46 patents and patent applications. During 2010 – 2012 25 novel patent applications were submitted, many of them in collaboration with other scientific or commercial partners both in the Czech Republic and abroad. The Institute was awarded 24 patents from local and international patent agencies during the above mentioned period.

The office plays key managerial role within the Strategic Alliance of local scientific institutions and companies which is focused on the development of novel drugs as a part of a project *"Center for Development of Original Drugs"*. This project supported by the Technology Agency of the Czech Republic and the support is planned until 2019. The IOCB TTO provides management for this project and plays pivotal role in the development of vivid interactions between academia and industrial partners.

The IOCB TTO mission can be summarized as: *"By providing professional services in the area of technology transfer to help the institute to stay an excellent scientific institution".*



Ladislava Součková **Martin Fusek** **Jaromír Zahrádka**

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Janáčková Ivana
Juzlová Simona
Klímová Jana
Mlejnková Jarmila
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Administration
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Binková Eva
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Hroník Přemysl
Hrubý Zdeněk
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Kracík Radoslav
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The Reconstruction and New Construction of the IOCB Complex in Dejvice

The central part of the complex of the Institute of Organic Chemistry and Biochemistry of the AS CR is being reconstructed and completed, which includes the reconstruction of the old historical building and the construction of new buildings with the aim of creating a clearly organized, functionally divided complex of the IOCB in compliance with the requirements of a modern research workplace.

The following picture provides a view of Building B from Zelená Street.

Another view from the Architecture Building.

DEVELOPMENT OF THE IOCB CAMPUS

The reconstruction of the old, historical main building ('A') and the completion of a new laboratory building of organic chemistry ('B') will result in the creation of an interconnected complex of research workplaces, whose basic structural unit is the space for the research team, including mainly laboratories with the related evaluation workplaces and the necessary facilities. This essential scheme in Building 'A' is complemented with the spaces for the institute's management, the library, research workplaces of theoretical chemistry, the lecture hall etc. Building 'B' contains, besides the laboratory workplaces of organic chemistry, also storage areas, the data center of theoretical chemistry, book storage room, garages and the technological base for both buildings comprising mainly the HVAC and refrigeration system.
The reconstruction of the building from the second half of the 1950s ('C'), containing the research workplaces of biochemistry, screening and virology, was completed in 2011. The independently functioning building of biochemistry further comprises the necessary administrative, sanitary and technological facilities. A civil protection shelter has been preserved in the basement.

The Institute of Organic Chemistry and Biochemistry also runs a lodging house, which has recently been completely reconstructed. It is one part of a semi-detached house in Prague-Břevnov, which is fully equipped for the needs of our researchers.
The construction of the first stage of the hall in Papírenská Street in Prague 6 which is intended for the operation of the development workshops of the IOCB (the machinery and electronics development for laboratory equipment and machines) has been finished.

Lodging House

Papírenská Facility

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