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ABSTRACT BOOK

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Plenary Lectures and Hansch Session Abstracts

Toshio Fujita

Kyoto University, Japan

Education:
1948~1951: Kyoto University, Department of Agricultural Chemistry
1961~1963: Pomona College, Department of Chemistry, Postdoctoral Fellow (Professor Corwin Hansch)
1963~1964: University of Illinois, Department of Chemistry, Postdoctoral Fellow (Professor Kenneth Rinehart)

Degrees:
B.S. Kyoto University, March 1951
D.Sc. Kyoto University, February 1962

Professional Positions:
1951 ~ 1964: Instructor, Kyoto University
1964 ~ 1966: Lecturer, Kyoto University
1966 ~ 1981: Associate Professor, Kyoto University
1981 ~ March 1992: Professor, Kyoto University
1992 ~ 1998: Consultant, Fujitsu Kansai Systems Laboratory
March 1992 to date: Professor Emeritus, Kyoto University

Professional Society Memberships:
Japan Society for Bioscience, Biotechnology and Agrochemistry (Formerly Agricultural Chemical Society of Japan).
Chemical Society of Japan.
Pharmaceutical Society of Japan.
Pesticide Science Society of Japan.
American Chemica1 Society.

Editorial and Advisory Positions:
Quantitative Structure-Activity Relationship (Wiley-VCH): 1982 ~ 2003
QSAR and Combinatorial Sciences (Wiley-VCH): 2004 to date
Pesticide Biochemistry and Physiology (Academic Press): 1987 ~ 1997
Pest Management Science (Formerly Pesticide Science): 1990 to date
Pharmacochemistry Library (Elsevier): 1989 ~ 2002

Professional Activities:
Organizing Committee and Scientific Program Committee Member of the 5th International Congress of Pesticide Chemistry, Kyoto, 1982
Vice President, The Pesticide Science Society of Japan, 1983~1984
President, The Pesticide Science Society of Japan, 1985~1986
Chairman, The Kansai Section of the Japan Society for Bioscience, Biotechnology and Agrochemistry, 1989~1990

(Q)SAR: THE LIFELONG LEARNING FOR MY RESEARCH CAREER

Toshio Fujita

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As is well-known, the classical QSAR was first discovered by Professor Corwin Hansch and his group at Pomona College, Claremont, California, almost half a century ago. It was just after I joined him as a postdoctoral fellow in 1961. I was very fortunate to participate directly in this discovery. Both of us had been studying independently the structure-activity relationship of plant growth regulators of the substituted aromatic carboxylic acid type. At Pomona, variations in the growth promotion of a set of substituted phenoxyacetic acids to oat sprouts were examined in terms of the effects of substituents introduced into the unsubstituted reference. We had recognized that more than single physicochemical effect “simultaneously” participates in variations in the plant growth activity, and the first QSAR equation was formulated in the framework of so-called “linear free-energy relationships” using multiple regression analyses and such electronic parameters as the Hammett σ and a hydrophobic parameter as the π value. The latter was defined at that time from the 1-octanol/water partition coefficients. This first equation was subject to a couple of revisions because of renewed hypotheses for the electronic mechanism of substituents and a later inclusion of the bilinear model for size effect of substituents represented by STERIMOL steric parameters. Even though these correlations could be thought “original as well as fundamental”, they were only obtained under considerably restricted conditions. For instance, most compounds substituted at the ortho positions, most 3,5-disubstituted derivatives, 4-substituted analogs with substituents larger than Br as well as compounds with such hydrogen bondable/ionizable groups as OH and COOH were omitted from the analyses.

After returning to Kyoto, I expanded and deepened the QSAR research mostly in major insecticidal sets of compounds in the Department of Agricultural Chemistry. The compound sets include acetylcholinesterase inhibitors, BHC and DDT types of compounds, synthetic pyrethroide analogs, and substituted benzoylphenylureas and dibenzoylhydrazines. In these research projects, we usually synthesized compounds and measured their biological activity by ourselves. These QSAR studies also came off well when compound sets are devoid of restrictive conditions as in the case of phenoxyacetic acids indicated above. Thus, we emphasized our effort also on exploring procedures to overcome restrictions and/or proving their free-energy related background. We found a procedure to analyze the “ortho-effect” by hypothesizing that their electronic and steric effects could be composed of ordinary and proximity components so that ortho-substituted compounds can be included on the same basis as meta- and para-substituted compounds in the QSAR analyses. We also suggested free-energy related background of STERIMOL steric parameters defined mechanistically from width and length of substituents in the unit of Å.

In this lecture, I would like to show mainly examples of our physical-organic chemical studies performed to improve mechanistic understanding of the classical QSAR results in general. As a chemist starting his career from syntheses of small-molecular bioactive compounds, statistical as well as physical-organic chemical disciplines to explore QSAR were rather foreign and perseverant, but they have been continuingly fruitful and enjoyable learnings through my life of 85 years old.

Peter Ertl

Novartis Institute for Biomedical Research, Switzerland

Peter Ertl studied organic chemistry and received his PhD at the University of Bratislava before joining Ciba-Geigy in Basel. After a merger with Sandoz to form Novartis he became Head of the Cheminformatics group in Pharma Research, responsible for development of new methods for the calculation of molecular properties and cheminformatics tools. Peter is author of more than 100 publications and book chapters concerning all areas of cheminformatics and computational chemistry. In the cheminformatics community he is best known as author of the JME structure drawing applet and the fast fragment based method to calculate molecular polar surface area.
http://peter-ertl.com

NAVIGATION IN CHEMICAL SPACE TOWARDS BIOLOGICAL ACTIVITY

Peter Ertl

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One of the most common tasks that cheminformatics experts in pharmaceutical industry are facing practically daily is analysis and visualization of large collections of molecules. Typical areas, where this is needed are analysis and enhancement of company compound archive, analysis of high-throughput screening data, design of combinatorial libraries, chemogenomics analyses and many others. But also researchers in academia are facing similar challenges when analyzing large public molecular databases that become available recently or even structures generated *in silico*. This presentation will provide overview of various methods used to analyze and visualize chemical space with particular focus on needs of medicinal chemists.

When displaying results, for chemists it is of great importance that the molecules are represented by their actual structures, or at least by their scaffolds and not only by points as it is common in other scientific fields. This particular requirement makes chemistry visualizations challenging because of necessity to squeeze a lot of information on rather limited computer screen real estate.

In the presentation various chemistry visualization techniques will be discussed, starting from classical display of molecules as tables and grids, through visualization based on analysis of scaffold, up to advanced cheminformatics visualizations techniques recently developed at Novartis, such as a method for natural ordering or scaffolds or Molecule Cloud diagrams.

References

1) Intuitive Ordering of Scaffolds and Scaffold Similarity Searching Using Scaffold Keys. P. Ertl, J. Chem. Inf. Model. 54, 1617 (2014)
2) The Molecule Cloud - compact visualization of large collections of molecules, P. Ertl and B. Rohde, J. Cheminf. 4:12 (2012)
3) The Scaffold Tree - Visualization of the scaffold universe by hierarchical scaffold classification. A. Schuffenhauer, P. Ertl, S. Roggo, S. Wetzel, M. Koch, H. Waldmann, J. Chem. Inf. Modelling. 47, 47-58 (2007).
4) Quest for the Rings - In silico exploration of ring universe to identify novel bioactive heteroaromatic scaffolds. P. Ertl, S. Jelfs, J. Muehlbacher, A. Schuffenhauer, P. Selzer, J. Med. Chem. 49, 4568-4573 (2006).

John C. Reed

F. Hofmann-La-Roche, Switzerland

John C Reed is Global Head of Roche Pharma Research and Early Development (pRED), and Member of the Enlarged Roche Corporate Executive Committee. With his broad scientific and medical background, Dr Reed is responsible for driving pRED's strategy of translating a better understanding of disease mechanisms into promising new therapeutics.

Dr Reed joined Roche on April 2, 2013. Before coming to Roche, Dr Reed was CEO at Sanford-Burnham Medical Research Institute in La Jolla, California. Under his leadership, Sanford-Burnham built its reputation as one of the world's leading medical research institutes, with advances from Dr Reed's own laboratory at the institute generating programs for cancer, neuroprotection, autoimmunity and other diseases. He is personally recognized as one of the world's top biomedical researchers. Dr Reed has held faculty positions with several leading American universities.

He has authored several hundred medical research publications and is among the world's most highly cited scientists for his research contributions. He is an inventor of more than 100 patents, and the founder or co-founder of several biotechnology companies. Dr Reed has served on multiple scientific journal editorial and advisory boards, and as a director of several public biopharmaceutical and biotechnology companies. He earned his MD and PhD at the School of Medicine of the University of Pennsylvania. Respected professional organizations have recognized Dr Reed's work with numerous awards and honors. In 2011, Dr Reed was elected Fellow of the American Association for the Advancement of Science.

OPPORTUNITIES AND CHALLENGES IN THERAPEUTICS DISCOVERY AND DEVELOPMENT

John C. Reed

Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, CH-4070 Basel, Switzerland

Small molecule drug discovery has become an intensely data-rich discipline. Medicinal chemists have become accustomed to considering a multitude of parameters to optimize towards the profile of a clinical candidate. Also relevant are that crystal structure information for new targets is more readily accessible and that biological readouts have become increasingly sophisticated. These developments are challenge and opportunities.

At Roche we realize that the data accumulate during the course of our projects which is tremendously valuable for informing future payouts. Our goals are to extract knowledge from data and to make legacy data actionable for today's project teams. Three topics will be covered that illustrate these efforts: (1) method development in structure-based drug design utilizing empirical approaches, (2) initiatives to enhance the utility of our warehouse of biological data and linking it to external information, and (3) ways of preserving medicinal chemistry know-how so that it can be readily re-utilized.

Will Pitt

UCB Pharma, United Kingdom

Dr Will Pitt is a Senior Principal Scientist in Computer-Aided Drug Discovery group of UCB Pharma, based at their research site in Slough, UK. He was initially trained in structural biology and molecular modelling in the Crystallography Department of Birkbeck College, London. It was an exciting time in the Department; structure-based drug design was in its infancy. Group leaders within the department included Tom Blundell. Will did his PhD with Julia Goodfellow, predicting the binding sites of water molecules on the surface of proteins using empirical methods and molecular dynamics. Since leaving Birkbeck,

Will has spent almost 20 years within the pharmaceutical industry, actively applying SBDD as part of medicinal chemistry teams. His interests have diversified during this time and now include explorations of chemical space. He has contributed to numerous papers, chapters and patents. Perhaps the publication for which he his best known is entitled “Heteroaromatic rings of the future”. This paper describes the creation and analysis of a virtual chemical library. However, the talk that he will give at this conference is on an entirely different subject. It is based upon work done as a result of a renewed association with Tom Blundell, during a recent 4 year secondment to his lab at the University of Cambridge. UCB Pharma is seeking to produce novel treatments that will bring relief to the sufferers of severe medical disorders. This sometimes means taking on challenging protein-protein interaction and allosteric targets. Will’s recent work is motivated by these challenges and concerns the simultaneous use of ensembles of protein crystal structures and molecular dynamics trajectories in what he is calling ensemble-based drug discovery.

ENSEMBLE-BASED DRUG DESIGN, COMBINING PROTEIN STRUCTURES AND SIMULATIONS

Will Pitt

UCB Pharma, 216 Bath Rd - SL1 3WE Slough, United Kingdom

It is not uncommon for hundreds of protein crystal structures to be solved in support of a modern drug-discovery program. Likewise, the PDB is a rich source of structural data on active targets and homologous proteins. Even when only a small number of structures are available, molecular dynamics can be used to explore the conformational space around and between them. This talk will describe how analyses of these structural ensembles can be facilitated by the use of new methods. Instead of relying upon molecular superposition, patterns are discovered in structure augmented sequence alignments. In this way, local order and correlated changes can be identified, even in radically different structures of the same protein. This can be particularly useful when trying to understand or predict the mechanism of action of allosteric inhibitors. The talk describe these methods and how they can be used for drug discovery

Helena Danielson

Uppsala University, Sweden

Helena Danielson is Professor of Biochemistry at Uppsala University in Sweden since 2002 and Chief Scientific Officer of Beactica AB. She is a specialist in enzyme-based drug discovery and molecular recognition. Her education includes a Master of Science in Chemical Engineering at Lund University in 1982 and, as a Fulbright scholar, a Master of Science in Biochemistry, University of Rochester, Rochester, NY, USA in 1984, and a Ph. D. in Biochemistry at Stockholm University in 1987. As a postdoc at Karolinska Institute in Stockholm, Helena Danielson started a research project on HIV protease as a drug target for AIDS, and has since expanded her research to other enzymes and diseases, more recently also with an interest in membrane receptors and neurological drug targets. Helena Danielson has focused on developing enzymology for drug discovery, and in particular biomolecular interaction analysis for detailed studies of enzyme-inhibitor interactions and other important recognition processes in the life science area. Helena Danielson co-founded Beactica AB in 2006. The company is a specialist drug discovery company that generates novel drug leads from low molecular weight fragments by integrating biomolecular interaction analysis with in silico molecular docking techniques.

LEAD DISCOVERY AND OPTIMISATION BY USE OF INTERACTION KINETIC ANALYSIS

Helena Danielson

Uppsala University, Department of Chemistry, BMC, Box 576 - 751 23 Uppsala, Sweden

The versatile experimental design and information rich output of SPR biosensors has been become an established strategy for drug discovery. It is particularly well suited for fragment based drug discovery. Still, there are many challenges to overcome in order to implement the technology to its full potential. A sensitive and robust assay is critical for success. However, once an assay has been developed for a certain target, it can be used throughout the drug discovery process. The first steps involve the validation of sensor surfaces and identification of suitable experimental and data analysis strategies for efficient identification of hits. One of the major difficulties when exploiting biosensors with SPR detection for fragment-based drug discovery is to overcome the weak affinity of hits and distinguishing them from false positives. Identified hits can be validated by a number of techniques, including distinction between specific interactions to a defined binding site and weaker non-specific interactions to other sites or the general protein surface. Following the evolution of fragment hits into efficient leads is done by exploiting the versatile experimental design of SPR biosensors and by varying the target and experimental conditions. This can provide information about the identity of the binding site of interest, the stoichiometry and the basic characteristics of the interaction, such as the interaction mechanism, kinetics and affinity. In addition, by use of analogues series, protein variants and modifications of experimental conditions, more detailed characteristics of leads can also be obtained, for example selectivity, thermodynamics and chemodynamics.

References

1) Interaction Kinetic Data Generated by Surface Plasmon Resonance Biosensors and the Use of Kinetic Rate Constants in Lead Generation and Optimization. Danielson, U.H. Protein-Ligand Interactions, First Edition. Edited by Holger Gohlke. 2012 Wiley-VCH Verlag GmbH & Co. KGaA.

Catrin Hasselgren

AstraZeneca, Sweden

Catrin Hasselgren received her PhD in chemistry from the Chalmers Institute of Technology, Gothenburg in 2002. She joined AstraZeneca as a postdoctoral fellow in 2002 and worked on developing new tools and methods for applications such as site of metabolism predictions, P450 inhibition and hERG binding. She later became responsible for the scientific development of tools and models in the areas of genetic toxicity, reactive metabolites and reproductive toxicity and has contributed significantly to lead the design and introduction of several new systems that are used regularly within AstraZeneca. Since 2012, she heads the Computational ADME and Safety group within AstraZeneca.

COMPUTATIONAL TOXICOLOGY - AN ESSENTIAL PART OF DRUG SAFETY

Catrin Hasselgren

Drug Safety and Metabolism
AstraZeneca R&D Mölndal
Sweden

High attrition rates and the failure of late stage compounds due to toxicity issues are forcing pharmaceutical companies to evaluate drug safety at an earlier stage, as well as in a more structured manner. Computational modelling is a vital component in the individualized strategies designed to identify risks and for avoiding adverse events related to particular organs. Developing and applying computational models and informatics tools are a crucial part of current Drug Safety. Such tools are applied early and have the ability to highlight potential risks to project teams at a stage when very little is known experimentally about the compound series or the therapeutic target. These tools are becoming increasingly more important at later stages of the development, e.g., to support problem-solving activities.

There is a considerable wealth of information available from both public and proprietary experimental data. However, the data are commonly in a non-structured format and are not easily accessible to drug discovery project teams. Mining, curating and if appropriate, modelling, the available data can provide useful information and supports decision making. Important considerations in this context are the nature of the Safety endpoint and at what stage in the drug discovery process the models are being used.

This presentation will provide insight into the complexity of Safety data and give examples of how the data can be utilised depending on data quality and data structure. Emphasis will be mainly on supporting drug projects in the earlier phases up to clinical testing, with examples ranging from simple rule-based systems and QSAR models of screening data to modelling of more complex in vivo and clinical data.

John Overington

EMBL-EBI, United Kingdom

John studied Chemistry at the University of Bath, from where he graduated in 1987. He then studied for a PhD at Birkbeck College, University of London in the Department of Crystallography. Whilst there he was involved in developing automated approaches to protein modelling, contributing to the development of the software programmes COMPOSER and MODELLER, however his major research was on sequence-structure relationships, exploring the constraints applied by the local physical environment of a residue in it's mutation patterns (JOY and HOMSTRAD). After completing his PhD, John held a postdoctoral position at the Imperial Cancer Research Fund extending this research.

John then joined Pfizer, originally as a computational chemist, progressing to a role where he led a multidisciplinary group combining rational drug design with structural biology. During this time, John became fascinated by the reasons for target/drug attrition and target validation, and the falling productivity of the entire pharmaceutical industry.

John then moved to a small biotech company, where we developed a series of platforms to improve drug discovery, including the SAR database StARLite. In 2008 John was centrally involved in the transfer of this database to the EMBL-EBI, where the successor is known as ChEMBL, a large Open database of drug discovery data. More recently, the work has extended into patent informatics with the patent database SureChEMBL.

CHEMICAL INFORMATICS APPLIED TO HEALTH AND DRUG SAFETY

John Overington

EMBL-EBI, Wellcome Trust Genome Campus, Hinxton CB10 1SD Cambridgeshire United Kingdom

The link between the biological and chemical worlds is of central importance in many fields, not least that of healthcare and safety assessment. A major focus in the integrative understanding of disease biology are genes/proteins and the networks and pathways describing their interactions and functions; similarly, within chemistry there is much interest in efficiently identifying drug-like, cell-penetrant compounds that specifically interact with these targets. However there has, until recently, been relatively little research explicitly directed at understanding the linkages between these two domains. Key to our work in this area has been the construction of a large and general database linking pharmacological activities of compounds through to their targets (http://www.ebi.ac.uk/chembl), and understanding how particular privileged chemotypes recognize their cognate receptors. The scope and contents of the database will be presented, alongside some application of the data to understand target modulation in complex biosystems; specifically, we will show how the rich data within ChEMBL can be mined to give insight into drug efficacy and safety, and these mapped on to individual phenotypic and genetic differences.

Curt Breneman

Rensselaer Exploratory Center for Cheminformatics Research, United States

Curt Breneman grew up in Santa Monica, California, and earned a B.S. in Chemistry at UCLA in 1980 followed by a Ph.D. in Chemistry at UC Santa Barbara in 1987. After two years at Yale University with Professor Ken Wiberg, Dr. Breneman joined the faculty of the Department of Chemistry & Chemical Biology at Rensselaer Polytechnic Institute (RPI) where he is now a Full Professor and Department Head. Dr. Breneman founded the Rensselaer Exploratory Center for Cheminformatics (RECCR) in 2005 and remains its director. He is also on the Executive Committee of Rensselaer's "Big Data" IDEA Institute. The Breneman research group specializes in the development of new hybrid molecular property descriptors and specialized machine learning methods that can be applied to a diverse set of physical, polymer/nanocomposite material and biochemical problems. Of paramount interest are methods that can increase the information content of molecular descriptors by incorporating "just enough" physics, as well as machine learning techniques that can exploit this information to create validated, predictive property models. Current application areas include the thermomechanical and dielectric properties of polymers and polymer nanocomposites, as well as pharmaceutical ADME prediction, virtual high-throughput screening of drug candidates, protein chromatography modeling (HIC and ion-exchange), and HIV entry inhibitors.

FROM QSAR TO MQSPR AND BEYOND: PREDICTIVE MATERIALS INFORMATICS USING A BLEND OF HEURISTIC AND PHYSICS-BASED METHODS

Curt Breneman (1), Ke Wu (2), Linda Schadler (3)

1) Dean of Science (Acting)
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We report the development of a new set of web-based tools capable of combining data-driven knowledge capture with physics-based simulation methods to enable predictive modeling of the thermomechanical and dielectric properties of pure polymers and polymer nanocomposites. Several examples of this type of hybrid workflow will be described. The first will illustrate how MQSPR models can be developed and utilized to compute and compare relevant surface energy components of functionalized nanocomposites with those of candidate polymer matrices to predict nanofiller aggregation states using additional heuristics. Also described will be how the resulting predicted 3D ensembles of nanofiller particles may then be analyzed using FEA methods to predict structural properties as well as dielectric behavior, loss and intrinsic breakdown strengths.

Anna Linusson

UMEA University, Sweden

Anna Linusson, born 1970, has a master degree in biology at the University of Gothenburg. She obtained her doctorate in organic chemistry in 2000 at Umeå University with a thesis on library selection in combinatorial chemistry. Directly after, Anna Linusson joined AstraZeneca R&D Mölndal for a position as computational chemist in drug discovery projects. In 2004, she returned to Umeå University for a faculty position in computational chemistry at the Department of Chemistry. In the summer of 2013, she was appointed full Professor in Medicinal Chemistry at Umeå University. The focus of her research is directed towards fundamental aspects of interactions of small-molecular ligands with proteins, using both experimental and computational techniques. The research is performed within pharmaceutical relevant projects to contribute to the discovery of new molecules against for example rheumatoid arthritis, malaria and dengue fever.

Anna Linusson received the Corwin Hansch Award in 2011.

ON THE NATURE OF NON-CLASSICAL HYDROGEN BONDS AND AROMATIC INTERACTIONS

Lotta Berg (1), Brijesh Kumar Mishra (1), C. David Andersson (1), Fredrik Ekstrom (2), Anna Linusson (1)

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Two enantiomers displayed the same binding affinities to acetylcholinesterase (AChE) while differing in their thermodynamic profiles (*i.e.* enthalpy-entropy compensation).[1] The binding properties of the enantiomers were further investigated by the determination of their bioactive conformations to *Mus Musculus* AChE (*m*AChE) by X-ray crystallography followed by mapping of the non-covalent interactions using quantum mechanical methods. The non-covalent interactions identified in the complexes included a number of non-classical hydrogen bonds of the CH···O and CH···arene types, one of which (a hydrogen bond formed between an activated CH and the aromatic ring of Tyr337) was identified as the primary reason for the higher enthalpy component of one enantiomers compared to the other. To follow up on these results and to further characterize the non-covalent interactions in terms of their binding affinities and geometrical preferences, the non-covalent interactions in additional AChE-ligand complexes are mapped and will be presented. The interactions are studied in detail based on the geometries experimentally determined in the X-ray crystal structures using high level quantum mechanical methods. The aim was to gain a deeper understanding of local molecular interactions in biologically relevant systems and to connect the properties of the non-covalent interactions to the role that they play in the molecular recognition event.

References

1) Berg, L.; Niemiec, M. S.; Qian, W.; Andersson, C. D.; Wittung-Stafshede, P.; Ekström, F.; Linusson, A., Angew. Chem. Int. Ed. 2012, 51 (51), 12716-12720.

Nikolay S. Zefirov

Moscow State University, Russia

Professor Nikolay S. Zefirov graduated from Lomonosov Moscow State University (MSU) in 1958. For more than 50 years, he holds various positions at the Department of Chemistry of the MSU; since 1994, he was the head of Organic Chemistry Division and since 2014 he is the head of Medicinal Chemistry and Advanced Organic Synthesis division. He received PhD and Dr. Sci. degrees in 1961 and 1966, respectively. Professor Zefirov was elected a corresponding member and a full member of the USSR Academy of Sciences in 1981 and 1987, respectively. Since 1987, he is the head of the Laboratory of Mathematical Chemistry and Computer-Assisted Synthesis at the N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences (RAS). In 1989–2006, he was the director of the Institute of Physiologically Active Compounds of the RAS; in 2006, he was appointed as a scientific supervisor at this institute. Professor Zefirov was awarded the Prize of the Government of the Soviet Union (1989) and Russia (2001). He received the Lomonosov Award (1983) and Butlerov Award (1994). Professor Zefirov is a member of the International Academy of Mathematical Chemistry. In 1974–1991, he headed the Division of Organic Chemistry at the Mendeleev USSR Chemical Society; currently, he is the president of the Medicinal Chemistry Section of the Mendeleev Russian Chemical Society. His research interests cover theoretical and synthetic organic chemistry, medicinal chemistry, mathematical chemistry and computer-aided molecular design.

MOLECULAR DESIGN OF BIVALENT AND DUAL ACTION DRUGS

Nikolay S. Zefirov (1,2), Vladimir A. Palyulin (1,2), Olga N. Zefirova (1,2)

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2) Institute of Physiologically Active Compounds RAS, Chernogolovka, Moscow Region, 142432, Russia

The approaches to the design of “dual action” drugs and bivalent ligands considered in this paper involve molecular modeling techniques with subsequent synthesis and biological testing. For the development of new neuroprotective compounds the molecular models have been built of all domains in closed and open forms of metabotropic (mGluR1-8) and ionotropic (NMDA, AMPA) glutamate receptors. The combined application of QSAR techniques, artificial neural networks and molecular modeling enabled the evaluation of ligand structural features important for high affinity to the particular types and subtypes of receptors. The search for active compounds has been achieved using the idea of a specific blockade of calcium ion influx via activated NMDA receptor and a simultaneous slight potentiation of AMPA receptors. This hypothesis was successfully used in the design of new neuroprotectors with cognition enhancing properties. Hit compounds, in animal model of AD-type dementia simulated by cholinotoxin AF64A, revealed a significant improvement of memory in Morris water maze test while psychotomimetic side effects were absent.

Secondly, on the basis of a 3D structure of the positive modulator binding site of AMPA receptor, a series of bivalent compounds based on new scaffolds has been designed using molecular docking techniques and the manual refinement of structures. Extraordinary high potency of the designed compounds starting from picomolar concentrations has been revealed, which corresponds to the highest values among all currently known positive AMPA receptor modulators. The pronounced cognitive enhancing properties have been demonstrated in a series of animal tests, while any noticeable toxicity was not found for lead compounds during the preclinical studies.

Third, we synthesized a hybrid molecule containing colchicine moiety linked to an adamantane based taxotere mimetic, which manifested a high cytotoxicity *in vitro* against A549 human lung carcinoma cells and dual mechanism of action. Later more cytotoxic analogues of this compound were synthesized including N-(7-adamant-2-yloxy-7-oxoheptanoyl)-N-deacetylcolchicine [EC_{50}(A549)~6 nM], which was named *tubuloclustin* for its ability not only to cause disassembly of microtubules, but to promote the formation of stable tubulin clusters, morphologically distinct from microtubule bundles induced by taxol and tubulin paracrystals induced by vinblastine. This ”dual” activity was found to correlate with the increment of mitostatic activity.

These works were supported by Russian Foundation for Basic Research grants.

Tudor Oprea

University of New Mexico, United States

Tudor Oprea is internationally recognized as a leader in cheminformatics and the application of knowledge management and data mining in drug discovery and repurposing, with focus on small-molecules, translational research informatics, and health record data mining. He earned an M.D. (general medicine, 1990) and a Ph.D. (molecular physiology, 1992) in Timisoara, Romania, before serving as post-doctoral fellow at Washington University School of Medicine (St. Louis MO, 1992-1994) and at Los Alamos National Laboratory (Los Alamos NM, 1994-1996), respectively. During his six years with AstraZeneca R&D in Sweden, Dr. Oprea contributed to the development of lead-likeness, a key concept in early drug discovery. After joining UNM in 2002, Oprea contributed to the successful identification of selective, potent compounds for a number of biologically important targets, which include GPER (the G-protein estrogen receptor), the formyl peptide receptors FPR1 and FPR2, the small GTP-ases Rac1 and Cdc42, and the ABCG2 efflux transporter. Oprea's work led to pilot clinical studies for Raltegravir, an anti-AIDS medicine, and Ketorolac, a non-steroidal anti-inflammatory drug, both studied as anti-cancer agents at the UNM Cancer Center. Oprea's research interests include chemical space navigation, lead and probe identification, virtual screening, machine learning, systems chemical biology, signal transduction and pharmacokinetics, as well as clinical informatics research. In 2002, he founded Sunset Molecular Discovery LLC, a company that produces chemogenomics databases such as WOMBAT and WOMBAT-PK. Oprea has co-authored over 180 publications, edited one book, and is co-inventor on 5 granted US patents. A member of the ACS, AAPS and AMIA, Oprea received the 2002 Corwin Hansch Award from the QSAR and Modelling Society and the 2013 AAPS Journal Manuscript Award from AAPS. Between 2005 and 2012 he served as Chair of the Cheminformatics and QSAR Society. In 2014 he started the Hansch Fujita Foundation, which recognizes young scholars who are active in the field of computer-aided molecular design.

THE ROAD AHEAD: NEW CHALLENGES FOR COMPUTATIONAL FORECASTS

Tudor I Oprea

Translational Informatics Division, Department of Internal Medicine, University of New Mexico School of Medicine, Albuquerque NM, USA

How many disease entities are known? How many are addressed by medicines? How many drug targets are annotated to these medicines? According to the Disease Ontology resource [http://disease-ontology.org/], over 8000 diseases concepts have been indexed. The DRUGSDB database, maintained at the University of New Mexico (UNM), contains over 48,000 approved drug labels, which contain over 1400 active pharmaceutical ingredients (API), including biologics. These APIs, mapped for indications and off-label indications, cover over 2000 disease entities, and are in turn annotated to over 1200 human proteins.

The National Institutes of Health have recently launched a new Common Funds initiative [https://commonfund.nih.gov/idg/index], "Illuminating the Druggable Genome" (IDG), with the primary goal of shedding more light on the "dark" areas of the genome. The IDG Knowledge Management Center, led by UNM, has annotated the human proteome [http://www.humanproteomemap.org/], to ascertain which proteins are perturbed by APIs (for small molecules and biologics), which proteins can be manipulated by small and macro-molecules, and which proteins are as yet to be characterized [http://habanero.health.unm.edu/tcrd/]. Based on data extracted from literature, drug labels and other sources, we estimate that APIs or chemicals that are not approved drugs perturb less than 10% of the human proteome; and that approximately two thirds of the proteome are in need of scientific illumination, respectively.

The challenges for the road ahead are clear: We have yet to therapeutically address almost 75% of the diseases; and that at least two thirds (up to 90%) of the human proteome (not to mention non-human proteins, e.g. from infectious agents) need specific perturbagens to study their function and clinical utility. Here we highlight some of our new computational approaches to prioritize targets from the "dark genome", and how mixture informatics enables us to study API combinations, and better understand metabolic liabilities and drug interactions. These tools will help us evaluate new drug combinations, new targets and their disease associations, thus narrowing the scope of experiment and clinical validation.

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Oleg RAEVSKY

Institute of Physologically Active Compounds, Russia

Prof.Dr. Oleg. A. Raevsky, Head of QSAR laboratory (since 1984 up to now), Head of Department of computer-aided molecular design (since 1994 up to now), Vice Director (science) of Institute of physiologically active compounds of Russian Academy of sciences (since 1989 up to now). He is author of first in Russia QSAR textbook (1984), a monograph devoted to structure-activity relationships (2013), 12 patents on QSAR computer programs and about 300 publications. O.A.Raevsky is author of unified common H-bonding scale, original 2D and 3D descriptors, Discrete-regression QSAR models.

IN SILICO PREDICTION OF AQUEOUS SOLUBILITY, FROM RANDOM GLOBAL MODEL FORWARD INDIVIDUAL LOCAL REGRESSION FOR EACH CHEMICAL OF INTEREST

Oleg Raevsky (1), Veniamin Grigor'ev (1), Daniel Polianczyk (1), Olga Raevskaja (1), John Dearden (2)

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2) School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool L3 3AF, United Kingdom

Aqueous solubility is everyone's everyday experience. For pharmaceuticals solubility is a key factor in controlling bioavailability. Hence the prediction of solubility is a prime focus of QSAR. There are many QSAR models for aqueous solubility prediction [1]. Nevertheless there are still problems in the development of good predictive models for this property.

This study provides three QSAR aqueous solubility models for crystalline organic chemicals and drugs constructed on large data sets:

1. for un-ionized pure chemicals and drugs,

2. for chemicals and drugs at pH 7.4 (thermodynamic solubilization),

3. for chemicals and drugs at pH 7.4 (kinetic solubilization).

We used the following approaches for the construction of QSAR models:

1. Regression analysis based on the experimental data for lipophilicity and melting point,

2. Multi Linear Regression (MLR) with different physicochemical descriptors,

3. k-nearest neighbors (k-NN) based on structural similarity,

4. Support Vector Regression (SVR),

5. Arithmetical mean property (AMP) [2],

6. Local regression property (LoReP) [3].

During our work, we tested models for a few subsets of chemicals having neighbors with different levels of similarity. Calculations on all chemicals were performed without limitation of similarity level for neighbors (Tanimoto index, $Tc \geq 0.0$). For such subsets, standard errors were in the range of 0.85–0.90 in the best AMP and LoReP models. At the level $Tc \geq 0.5$, the remaining chemicals were calculated with sd = 0.57–0.65 (that is, close to the error of experimental solubility determination).

Indicated models are based on molecular polarizability (α) and partition coefficient (AlogP) as independent variables. The first descriptor relates to steric interactions. Partition coefficient may be regarded as a composite descriptor relating to steric and H-bonding interactions.

Thus, these two types of interactions can be regarded as fundamental to the solubility of organic compounds.

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Andreas Bender

University of Cambridge, United Kingdom

Dr Andreas Bender is a Lecturer for Molecular Informatics with the Unilever Centre for Molecular Science Informatics at the Department of Chemistry of the University of Cambridge, leading a group of about 20 postdocs, PhD and graduate students and academic visitors. In his work, Andreas is involved with the integration and analysis of chemical and biological data, aimed at understanding phenotypic compound action (such as cellular readouts, and also organism-level effects) on a mechanistic level, ranging from compound efficacy to toxicity. He received his PhD from the University of Cambridge as a Cambridge Gates Scholar in 2005 and worked in the Lead Discovery Informatics group at Novartis in Cambridge/MA as well as at Leiden University in the Netherlands before his current post. In 2012 he received the LRI Innovative Science Award of the European Chemical Industry Council (CEFIC) and in 2013 he was awarded an ERC Starting Grant to model mixture effects of chemical structures in biological systems using mechanistic approaches, an area currently very little understood.

LESSONS LEARNED FROM CHEMICAL AND BIOLOGICAL DATA - SCIENTIFICALLY, AND PERSONALLY

Andreas Bender

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When advancing in a given field, little by little, one is sometimes excited to discover something new - and equally often wondering about the foolishness of one's own past beliefs. This applies to scientific thinking, as well as to the way one goes about leading his daily life.

(Both points being, for a scientist, of course closely connected with each other). This presentation will on the one hand cover aspects of using chemical and biological data for compound design and selection. On the other hand it will cover what I have learned, at my tender age, from leading a research group, getting lost in Jaipur, and making mistakes on a daily basis (some of which repeatedly).

Roberta Bursi

Grünenthal, Germany

Dr. Roberta Bursi has obtained her Ph.D. in Computational Chemistry at the University of Southern California, Los Angeles. Dr. Bursi has more than 15 years' experience working in the Pharmaceutical industry where she has promoted, developed and implemented quantitative methods across drug research and development processes.

Dr. Bursi is currently heading the Pharmacometrics Department at Grünenthal, Germany.

INTEGRATING PHARMACOMETRICS INTO DRUG DEVELOPMENT

Roberta Bursi

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Since the late nineties, Pharmaceutical R&D organizations have been confronted with unsustainable drug development costs increases and decreasing number of new drug registrations. Several root causes have been identified to be at the origin of this trend and new R&D strategies have started to take shape in the attempt to reverse it.[1-4] A recent FDA report[5] has identified an urgent need for a new product development toolkit including computer-based predictive models to improve predictability and efficiency along the critical path of developing a new medicine from laboratory concept to commercial product.

Pharmacometrics or Quantitative Pharmacology is an emerging science designed to influence drug development and regulatory decisions by conducting quantitative analysis of pharmacokinetic and pharmacodynamic data. Pharmacometrics uses models based on pharmacology, physiology and disease to quantify interactions between drugs and patients. This involves pharmacokinetics, pharmacodynamics and disease progression with a focus on populations and variability. Drug models describe the relationship between exposure (or pharmacokinetics), response (or pharmacodynamics) for both desired (e.g. efficacy) and undesired (e.g. safety) effects.

Examples of model-based drug development will be provided.

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5) FDA Critical Path Initiatives white paper (2004)

Joerg Kurt Wegner

Janssen Pharmaceutica, Belgium

Joerg studied chemistry followed by a PhD in computer science at the University of Tuebingen, Germany. From 2005 he continued his career as industrial PostDoc at Tibotec (Infectious Disease branch of Janssen, Johnson&Johnson, Mechelen, Belgium). During this time he worked on resistance prediction for HIV sequences based on protein structure information and interaction energy calculations in CHARMM (Patent 2006). This information was utilized in medicinal chemistry projects to design alternate series of anti-resistant drugs for highly active antiretroviral therapy (HAART) resulting in a patent in 2010. He continued supporting various other infectious disease projects ranging from target identification, fragment-based drug design to late lead optimization and resistance modelling of clinical outcome data as computational chemist.

Since 2012 he extended his Janssen career (located in Beerse, Belgium) by moving into the areas of high-dimensional data using chemical probes, which can be either –omics readouts like transcriptomics (biological view) and/or –omics wide protein data (medchem view). He is coordinating and involved in multiple research and collaboration projects in this area, including high-performance computing (HPC), and is working in integrating this logic into the internal project flows of therapeutic area project teams.

Besides his scientific commitments he serves as Janssen (social media) ambassador for attracting young (scientific) talent via http://www.janssenjobs.be and is a passionate photographer as time allows.

For more information check for @joergkurtwegner on all platforms, e.g. LinkedIn, Twitter,..

LARGE-SCALE CHEMOGENOMICS IN PHARMA - DEFINITION, BENCHMARKING, AND APPLICATION

Joerg Kurt WEGNER (1), Marvin STEIJAERT (2), Vladimir CHUPAKHIN (1), Hugo CEULEMANS (1), Pieter PEETERS (1), Alexander VAPIREV (1), Sepp HOCHREITER (3), Andreas MAYR (3), Guenther KLAMBAUER (3)

1) Janssen Pharma, Beerse, Belgium
2) OpenAnalytics, Belgium
3) University of Linz, Austria

We will clarify and define the term chemo-genomics and how this differs and complements each other by putting the emphasis on the CHEMO or the -OMICS side. Specifically in this talk we will focus on the benchmarking of CHEMO-genomics by presenting the first large-scale benchmark of multiple methods for predicting a target-target discrimination for industry-scale compound-proteintarget-activity data. Of course, this will include data from other public free and commercial sources. One of those public sources being ChEMBL. CHEMOgenomics target prediction should not be confused with QSAR models for isolated single targets. The overall complexity of CHEMOgenomics is multifold and and the mining optimization is a dual optimization challenge.

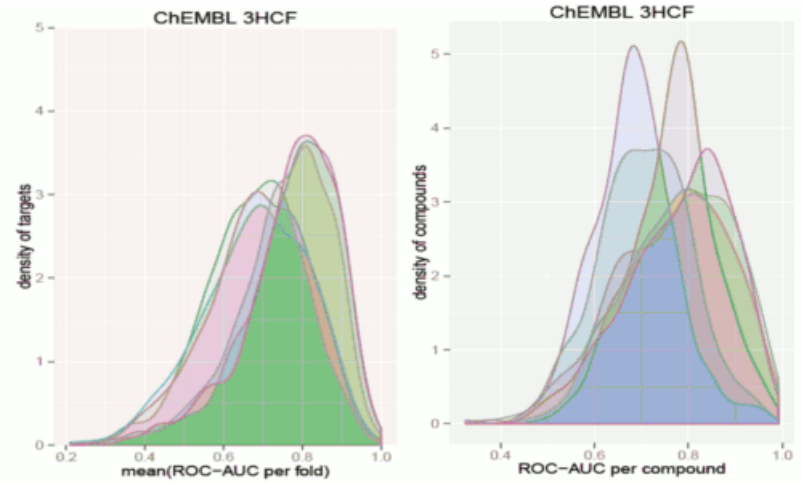

Figure (left): ROC analysis for all protein targets with the goal of a compound active-inactive discrimination. In contrast to QSAR on a single protein target are the additional challenges to discriminate among thousands of targets and to leverage correlations among target activities as proteochemometrics does for single protein target classes. Just that we do this on a genome-scale. Each histogram reflects a different method or parameter setting. Figure (right): ROC analysis for all compounds with the goal of a target-target discrimination. The shortest description for this task is target identification for supporting experimental and cost-efficient triaging for e.g. phenotypic screening initatives. Each histogram reflects a different method or parameter setting.

We will explain how we have tackled the various scientific challenges, and we will also publish a normalized gold standard based on ChEMBLv17 and industry-scale mockup data for algorithm evaluation at scale and for ensuring progressing this scientific domain and for challenging the scientific community. Finally, we will explain how such approaches are used in a process-driven pharmaceutical environment within project teams.

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Ferran Sanz

University Pompeu Fabra, Spain

Professor of Biostatistics and Biomedical Informatics at Pompeu Fabra University (UPF). Scientific staff of the Hospital del Mar Medical Research Institute (IMIM).
Director of the IMIM-UPF Research Programme on Biomedical Informatics (GRIB).
Author of more than 120 articles in ISI-indexed journals.
Mentor of 18 PhD thesis.
Coordinator of eight EU-funded initiatives and a STOA report for the European Parliament. Currently academic coordinator of the IMI (Innovative Medicines Initiative) eTOX project on the in silico prediction of drug toxicity.
Partner in several EU-funded projects, including the ongoing OpenPHACTS and EMIF IMI projects.
Academic Coordinator of the Spanish Technology Platform on Innovative Medicines (PTEMI). Coordinator of the Biomedical Informatics Node of the Spanish Institute of Bioinformatics (INB). Scientific Director of Bioinformatics Barcelona (BIB).
President of the European Federation for Medicinal Chemistry (EFMC) from January 2003 to December 2005.
Vice-rector for Scientific Policy of the UPF from January 2004 to March 2009, currently delegate of the rector for strategic projects in the biomedical field.
Member of the Scientific Committee of Innovative Medicines Initiative until 2013.

eTOX: INTEGRATIVE STRATEGIES FOR PREDICTING DRUG TOXICITIES

Ferran Sanz

Research Programme on Biomedical Informatics (GRIB). IMIM. Universitat Pompeu Fabra. Barcelona. Spain

The early prediction of potential toxicological problems of drugs under development constitutes a key issue for the pharmaceutical industry. The IMI eTOX project (www.etoxproject.eu) is contributing to the progress in this field by building an integrated database that contains data extracted from toxicological reports stored in the archives of 13 pharmaceutical companies that participate in the project. These shared data, plus relevant information sought from public domain resources, is being used for developing predictive models for relevant toxicological endpoints. Integrative strategies are also applied in the development of the models since multi-level, multi-scale and consensus approaches are being applied. Different modeling experts are contributing to the building of the models using diverse and complementary methodology. Standardization is a key issue for the whole process (e.g., ontologies allowing data integration, protocols for proper characterization of the models). The read-across of the database and the generation of predictions with any of the available models can be done by means of a unified and user-friendly interface (eTOXsys).

Gerhard Ecker

University of Vienna, Austria

Gerhard F. Ecker is an Austrian medicinal chemist and expert in the fields of Pharmacoinformatics at the University of Vienna. He is the Professor for Pharmacoinformatics and Head of the Pharmacoinformatics Research Group at the Department of Medicinal Chemistry, University of Vienna. He also coordinates the research focus “Computational Life Sciences” of the Faculty of Life Sciences.

Gerhard Ecker received his doctorate in natural sciences from the University of Vienna in 1991, became appointed Associate Professor for Medicinal Chemistry in 1998 and Full Professor for Pharmacoinformatics in 2009.

Gerhard is is Editor of Molecular Informatics and coordinates the EUROPIN PhD programme in Pharmacoinformatics. Currently he is also President of the European Federation for Medicinal Chemistry.

Research: Gerhard Ecker’s research focuses on computational drug design which not only led to the identification of highly active propafenone-type inhibitors of P-glycoprotein, but also paved the way for development of new descriptors and virtual screening approaches for identification of new scaffolds active at P-gp. With the increasing knowledge on the importance of P-gp for ADME, his interest moved towards the prediction of P-gp substrate properties. Around 2010 he extended the studies also on other antitargets, such as the hERG potassium channel, as well as on the serotonin transporter, the GABA receptor and the insulin receptor.

OPEN PHACTS - THE USE OF OPEN DATA FOR IN SILICO MODELS

Gerhard Ecker

University of Vienna, Dept. Pharmaceutical Chemistry, Althanstrasse 14, 1090 Wien, Austria

Within the last decade, Open Innovation has become a hot topic in the area of drug discovery. There are hundreds of databases related to life sciences in the public domain. Furthermore, with the launch of ChEMBL and the availability of PubChem, a large amount of bioactivity data became available to individual scientists. Within the Open PHACTs project, we developed a semantically enriched platform for integration of data sources, which allows for querying across different domains. This enables to target complex research questions and to generate new knowledge. However, as most public databases are compiled from literature sources, they are heterogeneous in their coverage. In addition, assay descriptions are not uniform and most often lack relevant information in the primary literature and consequently also in databases. This poses the question how useful large public data sources are for deriving predictive computational models.

Within this talk possibilities and limitations when exploiting Open Data will be outlined on basis of concrete use cases for ABC-transporter and the TRPV1 channel.

Maria Putseleva

Delegation of the European Union to Russia Federation

Maria Putseleva is a Policy Officer in the Science and Technology section of the Delegation of the European Union to the Russian Federation. She received her MA degree in International Relations and European Studies from the Central European University in Budapest, Hungary in 2004 and joined the EU Delegation to Russia in 2005. She has been working in her current position since 2010.

EU'S FRAMEWORK PROGRAMME FOR RESEARCH AND INNOVATION HORIZON 2020: COOPERATION OPPORTUNITIES

Maria Putseleva

Policy Officer, Science and Technology Section, Delegation of the European Union to the Russian Federation

EU-Russia cooperation in the areas of science, research, higher education and innovation has been developing very successfully for many years now. It is characterised by unprecedented breadth and depth, spanning practically all scientific areas, involving individual researchers and students, universities, scientific laboratories as well as business and industry, and taking place at the level of the EU itself, at the level of the EU Member States, as well as at the multilateral and international level.

At the EU level, one of the most established forms of research cooperation with Russia is the participation of Russian scientists in the EU's Framework Programmes for Research and Technological Development, where Russia has traditionally been one of the most active and successful international cooperation partner countries.

Starting from 2014, the EU's Framework Programme for Research and Innovation, Horizon 2020, is the main instrument of cooperation in the areas of research and innovation at the EU level. Horizon 2020 is the biggest EU's Research and Innovation programme ever, with nearly €80 billion of funding available for seven years (2014 to 2020). It aims to foster innovation through collaboration, bringing together researchers, innovators and industry from the European Union and beyond. Importantly, the programme is open to participants from Russia. Russian researchers and innovators are strongly encouraged to take part in Horizon 2020, either as partners in European collaborative research projects or as evaluators of project proposals.

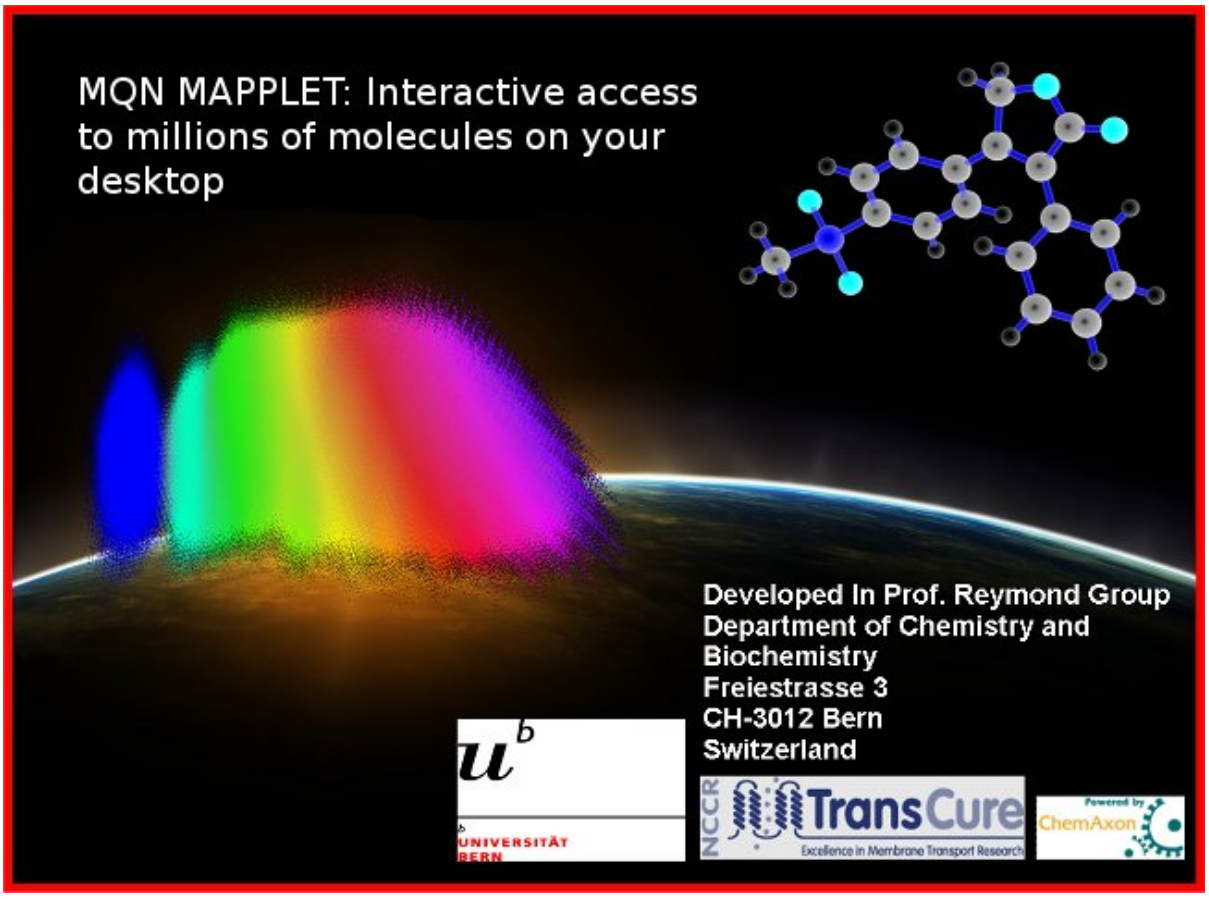
Oral Communications Abstracts

INTERACTIVE VISUALIZATION OF LARGE DATABASES IN 2D AND 3D USING THE CHEMICAL SPACE MAPPLET AND ITS APPLICATION TO DRUG DISCOVERY

Jean-Louis Reymond

Department of Chemistry and Biochemistry, NCCR TransCure, University of Bern, Freiestrasse 3, 2012 Bern, Switzerland, www.gdb.unibe.ch

To facilitate the interaction between chemists and very large databases up to billions of drug-like small molecules such as ZINC, PubChem, ChEMBL, and the Chemical Universe Databases GDB, we have created a Java applet that enables interactive visualization of color-coded maps of their chemical space. These maps are projections from high-dimensional property spaces defined by fingerprints such as MQN (Molecular Quantum Numbers, 42 descriptors) or SMIfp (SMILES fingerprint, 34 descriptor). We have now extended the original 2D-mapplets (1, 2) to an interative 3D-viewer, as well as realized the application for additional pharmacophore-based fingerprints. The use of the interactive mapplets for database visualization, the analysis of polypharmacology, and for drug discovery applications will be discussed (3, 4).



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CHEMICAL DATA VISUALIZATION AND MODELING: BIG DATA CHALLENGE

Alexandre Varnek (1), Héléna A. Gaspar (1), Gilles Marcou (1), Dragos Horvath (1), Igor Baskin (2)

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2) Department of Physics, Moscow State University,Lenin Hills 1/3, Moscow, 119992, Russia

Rationalizing novel compound discovery implies understanding of the structural relationships between chemically feasible compounds, which intuitively amounts to their mapping in some relevant Chemical Space (CS) based on appropriate molecular descriptors. As relevant CS are high-dimensional spaces, mapping basically amounts to meaningful dimensionality reduction, preserving the neighborhood properties of the initial CS. For chemoinformatics, developing approaches and software tools able to visualize and to analyze large chemical databases is a main challenge, albeit the ~70 million compounds recorded in public databases still represent a very small portion of chemical universe, estimated at 10^{33} chemically feasible drug-like molecules [1]. Among numerous methods of data visualization, Generative Topographic Mapping (GTM) occupies a particular place because it allows both to visualize compound collections, and to model molecular properties, providing probability distribution functions (DPDF), both in the high-dimensional CS and in 2D latent space. Recently, we have shown that DPDF can be used to build GTM-based classification and regression models and to define their applicability domain [2, 3]. Here, this is illustrated on several datasets including Biopharmaceutics Drug Disposition Classification System, aqueous solubility and some others [3].

Unlike most of the known visualization approaches, GTMs may now be built for large datasets, thanks to an in-house implemented iterative algorithm. This technique has been used in the home-made ISIDA/GTM program in order to visualize a database containing some 2.2 million molecules issued from 37 suppliers. Some parameters describing coverage of chemical space, subset overlap, activity landscape analysis, have been derived. Thus, we demonstrate that GTM is an interesting tool tackling the “big data” problem.

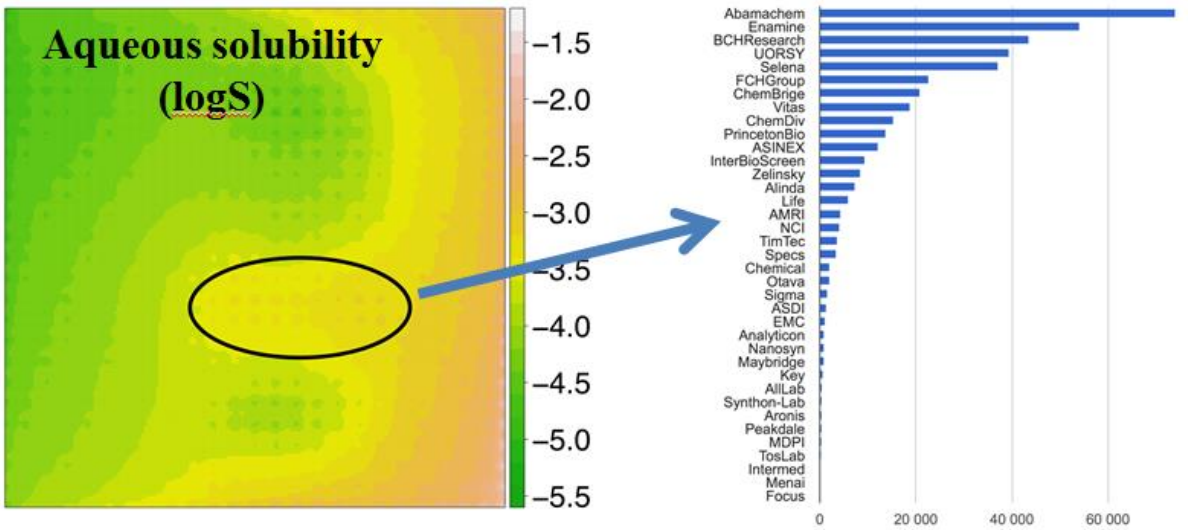

Figure 1. *Aqueous solubility (logS) distribution in the chemical space of 2.2 M compounds obtained using GTM (left) and the number of compounds provided by each supplier in the selected area of the chemical space (right)*

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LARGE-SCALE SAR-MINING AND VISUALIZATION IN PHARMACEUTICAL RESEARCH

Liying Zhang (1), Jared Milbank (1), Chris Poss (1), Jeremy Starr (1), Preeti Iyer (2), Dilyana Dimova (2), Disha Gupta-Ostermann (2), Antonio de la Vega de Leon (2), Jurgen Bajorath (2), Veer Shanmugasundaram (1)

1) Computational Analysis & Design, Center For Chemistry Innovation and Excellence, Pfizer, CT, USA
2) Department of Life Science Informatics, University of Bonn, Bonn, Germany

The exploration of structure-activity relationships (SARs) plays a critically important role in lead discovery and lead optimization. SAR is typically explored for individual compound series on a case-by-case basis, both in experimental and computational analysis. This talk will discuss some cutting-edge data-visualization and computational methods for systematic and large-scale exploration of SARs and comparison of global and local SAR features contained in compound data sets. The study of SAR is one of the central themes in medicinal chemistry and the concept of a graphical SAR method that globally organizes large compound data sets on the basis of local structural relationships is novel and powerful. The substrate for this presentation includes – Network Graphs, SAR Matrices, Ligand-Target Differentiation Maps, BiPartite Matched-Molecular Series Graphs. An introduction to the visualization/analysis, project team application and Spotfire DXP connections will be presented.

PROTEIN ACTIVE SITE COMPARISON WITH SiteHopper: PHYLOGENY TO POLYPHARMACOLOGY

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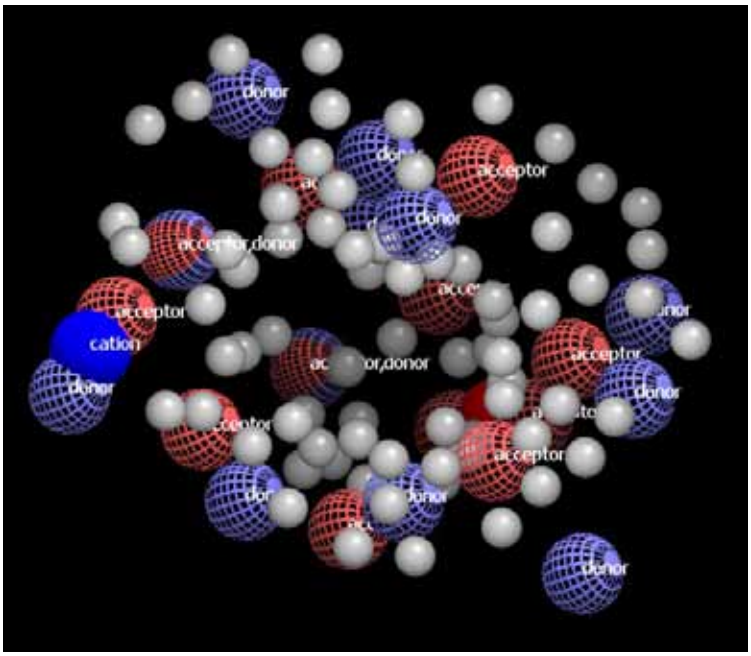
USA

There is a long history of using sequence alignment data to understand evolutionary relationships.[1] More recently attempts to use sequence alignment and comparison to predict cross-reactivity and polypharmacology have been made with varying degrees of success.[2] We present a new method, SiteHopper, which rapidly aligns and compares a three-diminsional representation of protein active or binding sites. This method is expected to show superior performance to sequence comparison in compound cross-reactivity/polypharmacology versus sequence because it directly compares the shape and underlying chemistry of different protein binding sites. Case studies will be presented to show that SiteHopper is able to find similarity between binding sites for targets with very different sequences.



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LIGAND PROMISCUITY AND CONFORMATIONAL SPECIFICITY IN THE ARYL HYDROCARBON RECEPTOR (AhR): THE CASE OF L-TRYPTOPHAN METABOLITES.

Antonio Macchiarulo (1), Daniela Dolciami (1), Roberto Nuti (2), Marco Gargaro (2), Paolo Puccetti (2), Francesca Fallarino (2)

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The aryl hydrocarbon receptor (AhR) is a cytosolic receptor regulating a wide range of biological and toxicological effects. We have recently shown that L-Tryptophan metabolites are able to bind and activate AhR, providing a link between Tryptophan catabolism, disease tolerance pathways and endotoxin tolerance [1]. Specifically, the occurrence of endotoxin tolerance has been reported in several disease settings, including sepsis, trauma, surgery, and pancreatitis, underlining its clinical significance. The notion that pharmacologic modulation of genes associated to the onset of endotoxin tolerance would be beneficial in clinical settings dominated by acute hyperinflammatory responses to infection, trusts AhR into the limelight as an interesting druggable target.

Combining homology modeling, docking studies and molecular dynamic simulations with mutagenesis experiments and real-time RT-PCR, in this communication we report that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and two different L-Tryptophan metabolites, namely L-Kynurenine and FICZ (6-formylindolo[3,2-b]carbazole), are able to bind to AhR, exploiting different key interactions with distinct set of fingerprint residues. As a result, they stabilize different conformations of AhR that, in turn, selectively regulate downstream signaling and transcriptional events of specific target genes. Collectively, these results open new avenues for the design and development of AhR modulators that, by targeting specific conformations of the receptor associated- gene modulation, may offer novel therapeutic opportunities in infectious diseases.

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MOLECULAR FIELD TOPOLOGY ANALYSIS (MFTA) AS A TOOL FOR MULTI-TARGET QSAR

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A key goal of drug design is usually the development of ligands selectively interacting with a particular biotarget. However, in many cases the ligands should be designed so that they could bind to several desirable biotargets from “a good list” while avoiding interactions with antitargets (“bad list”) that may be related or very different from the good targets. If the number of targets involved is not too high, the Molecular Field Topology Analysis (MFTA) can be used as a QSAR tool to develop models discriminating “good” and “bad” compounds as well as to optimize their activity and selectivity profiles using individual endpoint models and/or specially constructed multi-target selectivity parameters.

In MFTA the local features are compared for different molecules in the framework of a supergraph approach which is based on the topological alignment of all training set structures having similar scaffolds. MFTA models reveal the local molecular properties/features (partial atomic charges, steric parameters, H-bond donor and acceptor ability, local lipophilicity, etc.) which are necessary for the interaction of ligands with each biotarget. Alignment of these features can be instrumental in the design of molecules binding to several desired biotargets while not binding to a set of forbidden ones.

This approach is demonstrated for the ligands of ionotropic and metabotropic glutamate receptors, adenosine receptors, a number of $GABA_A$ receptor subtypes, serine esterases and serine/threonine kinases.

CONFORMATIONAL ENERGIES OF SMALL-MOLECULE LIGANDS IN PROTEIN-LIGAND COMPLEXES: A QUANTUM-CHEMICAL ANALYSIS OF PDB STRUCTURES

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We present a study on the conformational energies of protein-ligand complexes in the Protein Data Bank (PDB). Starting from about 357,000 ligand instances deposited in the Ligand Expo database of the experimental 3D coordinates of all small-molecule instances in the PDB, we created a "high-quality" subset of ligand instances by various filtering steps including application of crystallographic quality criteria and structural unambiguousness. Submission of 640 Gaussian 03 jobs yielded a set of about 400 successfully concluded runs. We used a stepwise optimization of internal degrees of freedom at the DFT level of theory with the B3LYP/6-31G(d) basis set and a single-point energy calculation at B3LYP/6-311++G(3df,2p) after each round of (partial) optimization to separate energy changes due to bond length stretches vs. bond angle changes vs. torsion changes. Even for the most conservative choice of all the possible conformational energies – the energy difference between the conformation in which all internal degrees of freedom except torsions have been optimized and the fully optimized conformer – significant energy values were found. The range of 0 to ~25 kcal/mol was populated quite evenly and independently of the crystallographic resolution. A smaller number of "outliers" of yet higher energies were seen only at resolutions above 1.3 Å. The energies showed some correlation with molecular size and flexibility but not with crystallographic quality metrics such as the Cruickshank diffraction-component precision index (DPI) and R_{free}-R, or with the ligand instance-specific metrics such as occupancy-weighted B-factor (OWAB), real-space R factor (RSR), and real-space correlation coefficient (RSCC). Repeating these runs with the aqueous solvent model SCI-PCM yielded a qualitatively very similar picture. We discuss possible interpretations and explanations of these energy ranges found as well as ramifications for the modeling of protein-ligand interactions.

IMPORTANCE OF CONFORMATIONS IN LIGAND-BASED DRUG DISCOVERY APPROACHES

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Ligand conformations are required for most 3D ligand-based methods, such as pharmacophore modeling, shape-based screening, and 3D-QSAR model building. Many studies of conformation generation methods have focused on the unbiased reproduction of crystal structures (i.e. bioactive conformations); however, it is not clear how this directly relates to ligand alignments and quality of the results.

In this work, we study different conformation generation modes of ConfGen and the impact on virtual screening (Shape and e-Pharmacophore) and 3D-QSAR predictions (atom-based and field-based). In addition, we present a new biased conformational search and alignment method that uses the maximum common scaffold between a query and each screening molecule to ensure identical coordinates of the common core, thereby minimizing the noise introduced by constant parts of the molecules. A full conformational search of the remaining degrees of freedom of the screening molecule follows. In general, we find that virtual screening results are relatively insensitive to the conformational search protocol; hence, a conformational search method that generates less conformations could be considered "better" because it is more efficient for screening. However, for 3D QSAR modeling we find that for unbiased conformational sampling protocols, more thorough conformational sampling tends to produce better QSAR predictions. In addition, significant improvements in QSAR predictions are obtained with the augmented conformational search protocol developed in this work, which ensures that conformational diversity is only explored for the unique parts of each molecule.

Finally, we introduce a new ultrafast conformational search method which has the ability to process hundreds of molecules per second. We show that the ability of the new method to reliably generate bioactive conformations is on par with ConfGen at a fraction of the cost (approximately 100x faster than the fastest mode of ConfGen). We will discuss the implications of ultrafast sampling for ligand ligand-based screening and compound design, such as removing the need to pre-generate conformation databases and being able to screen virtual libraries substantially larger than was previously tractable.

PREDICTING DYNAMICALLY DOMINATED ALLOSTERY FROM CONSTRAINT NETWORK ANALYSIS

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A quantitative description of allostery is fundamental to an understanding of processes in living systems and of practical relevance when developing allosteric modulators. Initial models of allosteric mechanisms were based on observations of conformational changes from static structural information. More recent models stress the influence of dynamics and large-scale conformational disorder instead. This provides the challenge from a computational point of view to develop an efficient methodological framework for analyzing, understanding, and predicting allostery in dynamic systems.

Here we present Constraint Network Analysis (CNA) as such a framework.(1) CNA applies concepts grounded in rigidity theory to analyze molecular flexibility from constraint network representations of (bio-)molecular complexes.(2) The approach works on conformational ensembles or ensembles of network topologies, that way considering thermal motions and, hence, dynamics of molecules in an efficient way.(3,4) Novel indices at the global (macroscopic) or local (microscopic) level allow for a quantification of molecular flexibility.(5)

We applied CNA in terms of a perturbation approach to gain structure-based insights into allosteric signaling and coupling in dynamic proteins. Validating the approach against NMR relaxation data for the system Eglin c shows that is correctly identifies contiguous pathways of allosteric coupling and accurately predicts the magnitude of coupling energies. When applied to the therapeutic target PTP1B, predicted pathways of allosteric coupling cover residues of functional importance, and when applied to the adhesion protein LFA-1 involved in immunobiology, the approach correctly predicts the sign of the cooperative coupling. In all, this demonstrates that the approach quantitatively describes allostery in dynamic systems. Finally, we extended our approach to allow for the identification of sites in proteins that are allosterically coupled even in cases when no allosteric modulator is known yet. This makes CNA an interesting tool in the context of target identification and validation.

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WHICH DISTANCE FOR SIMILARITY/DIVERSITY ANALYSIS?

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Distance and similarity measures play a key role in most of the common of chemometrics and QSAR/QSPR techniques, such as, for instance, cluster analysis, classification, exploratory data analysis.

Several measures of distance for real-valued data are presented and their behaviour compared on different data sets. The studied distance measures are: Euclidean, Manhattan, Lagrange, Lance-Williams, Canberra, Clark, Soergel, Bhattacharyya, Wave-Edge, Jaccard-Tanimoto, Angular and correlation distances. Moreover, the Mahalanobis distance is also considered together with the recently proposed local Mahalanobis distances.

Principal Component Analysis, Multidimensional scaling and Minimum Spanning Tree are the main tools used to compare the distances in different data sets. The behaviour of the different distances in the nearest neighbour distributions is also evaluated as a proxie for classification purposes.

NOVEL METHOD FOR MULTI TARGET SELECTIVE PHARMACOPHORE DESIGN USING COMPLEMENTARY INTERACTION FIELD AT THE ACTIVE SITES OF ACID PROTEASES, IN SEARCH OF ANTI MALARIAL.

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From past two decades, key objectives of rational drug discovery have been the designing of selective ligands for specific binding sites on individual molecular targets. Target selectivity has very important role in drug development process especially in the pre clinical phase. Tuning of binding selectivity is main objective of drug discovery. Recent challenges in drug research emphasizes the designing of drug which binds with more than one targets of interest (Multi-target or broad selectivity) and does not bind with the undesirable targets (narrow selectivity for avoiding toxicity). For example, off targets interaction such as with ion channels and Cytochrome possess adverse side effects. In case of proteins belonging to kinase family, where each member binds to ATP for transferring phosphate groups to substrate, the aim of designing inhibitors is to hit only one or a subset of kinases from one biochemical pathway of interest while avoiding other kinase whose inhibition may result in major side effects. By modulating the selectivity profile of inhibitors, multiple kinase of interest can be targeted or a panel of proteins can be targeted. Importance of development of such methods will be useful to combat the disease which adapt to fast resistance against traditional compounds like, infectious diseases and cancer. Interaction Network biology has shown that as biological systems can often find alternative compensatory signalling routes to bypass the inhibition of individual nodes, therefore modulating multiple targets simultaneously is required to effective inhibition. Most of the Chemoinformatics methods such as QSAR, Pharmacophore, Docking etc. are structure/ligand based and extensively used to define selectivity in active sites of proteins. But the major limitations of these methods are that one should have the prior knowledge of a known set of ligands. On the other hand, many methods such as GRID, FLAP are used in defining hot spots inside the active site which can be used for selective ligand designing from known protein structure by identifying the selectivity between families of proteins. Present work is attempted to use three dimension interaction profile of active site of class of proteins, identify selective positions for binding of functional groups (from inhibitors) called probes and develop multi target pharmacophore which retains specificity and selectivity. The goal of this study is by computational methods to develop multi-target pharmacophore using only protein structures (no inhibitor/ligands are used) to guide the discovery of novel inhibitors of Plasmepsins (acid protease class of protein known as anti malarial targets), displaying selectivity over its human homologs, Cathepsin D and Pepsin and assess their ability to become potent anti-malarial compound. Development of such novel tools are attempted using combination of different approaches such as interaction field, clique graph and Inductive logic programming to identify and compare, specific & selective complementary features at favourable interaction points in the active site residues in malarial acid proteases. Identification of such features has resulted in designing of five and six featured specific & selective pharmacophores which were used for screening compounds in ChEMBL (https://www.ebi.ac.uk/chembl/) for their anti Plasmepsin II activity against database of compounds with known antimalarials and successful in finding good specific and selective hits.

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IDENTIFICATION OF MECHANISM OF ACTION OF DNA-TOPOISOMERASE II INHIBITORS BY MOLECULAR MODELING STUDIES

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Therapeutically active drugs have been mostly discovered and put into market by the use of computer aided drug design studies in the recent years[1]. There has been considerable interest in DNA topoisomerases over the last decade, as they are shown to be one of the major cellular targets in anti-cancer drug development. The synthesis and DNA Topoisomerase II inhibitory activities of many new heterocyclic compounds possessing benzazoles and oxazolopyridines have been performed by our research team before[2-4]. Previously, we also synthesized some corresponding 3-amino-benzothiazolium forms of benzothiazole derivatives and tested their DNA Topoisomerase-II inhibitory activity to develop novel antitumor agents. Among the compounds, one of them has been found extremely active than the others and the reference drug etoposide.

For the mechanism of action found experimentally was proven by molecular modeling studies and the lead optimisation and generation were realised[5].

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ALERTING ABOUT SINGLE ALERTS: BRIDGING SAR AND QSAR APPROACHES FOR FLAGGING OR AVOIDING COMPOUNDS WITH UNDESIRED TOXICITY PROFILES.

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Historically, SAR and QSAR approaches have been used as independent computational toxicology tools: the former to identify chemical alerts with the emphasis on mechanistic interpretation whereas the latter for quantitative toxicity assessment agnostic of the underlying toxicity mechanisms. We advance a bridging data-analytical strategy that detects chemical alerts by interpreting QSAR models in terms of statistically significant chemical features. However, we show that single alerts cannot be used universally to predict compound toxicity (or suggest toxicity-reducing chemical modification) in isolation from taking into account concurrent effects of other chemical features present in a compound. We illustrate these concepts with molecular modeling studies of endocrine disruption, skin sensitization, and hepatotoxicity. We show how this hybrid SAR-QSAR approach can be used to prioritize or design compounds with the reduced toxicity. We advocate for the synergistic use of chemical alerts and QSAR models for designing novel compounds and predicting their toxicity, respectively.

CHEMICAL SYSTEMS BIOLOGY IDENTIFICATION OF DRUG TARGETS RELATED WITH CARDIOVASCULAR ADVERSE EFFECTS

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Cardiovascular adverse effects (AEs) are one of the most serious complications of drug therapy which often leads to death. Therefore, identification of these effects at the early stages of drug discovery is essential. For this purpose, the *in vitro* testing and *in silico* prediction of interactions between drug-like substances and various off-target proteins associated with serious AEs are performed. However, current knowledge about relationships between cardiovascular AEs and drug interactions with protein targets is extremely incomplete. We developed a novel *in silico* approach for identification of AEs – related protein targets for the most serious effects: myocardial infarction, arrhythmia and heart failure. This approach is based on the computational prediction of drug-target interaction profiles for 1738 human targets carried out for 828 drugs, including positive and negative examples for each cardiovascular AEs. Information about AEs for these drugs was extracted from SIDER [1], RxList [2] and Meyler's Encyclopedia of Adverse Reactions and Interactions [3]. Prediction of drug-target interaction profiles was based on PASS technology [4-7] applied to the ChEMBLdb 16 [8] and DrugBank [9] data. Through a statistical analysis, we revealed the 541 most significant associations between protein targets and cardiovascular AEs: myocardial infarction (155 targets), arrhythmia (206 targets) and heart failure (365 targets). Because not all of the identified associations may be causal, an analysis of biological functions of these proteins was performed. Biological processes associated with the revealed targets were identified by gene ontology and pathway enrichment analysis. It was shown that the revealed processes related to etiology of respective diseases. The revealed proteins were manually annotated in relation to these biological processes using functional, expression and disease-related data extracted from the literature. The analysis of relationships between the revealed proteins and proteins with known disease-related data was performed using functional linkage gene network and signal transduction networks. Based on this information the revealed proteins for each AE were classified into three categories (certain, probable, and plausible) of confidence of relations with etiology of cardiovascular AEs.

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ACTIVE QSAR MODELLING FOR EVIRONMENTAL TOXICITY PREDICTION OF CHEMICAL SUBSTANCES

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Generally, QSAR models for a data set that consisted of structurally diverse compounds don't give us good prediction for the prediction set. In order to solve such a problem and explore an alternative approach that gives us higher performance in the prediction, we proposed a technique for active QSAR Modeling that is based on active sampling of a temporary training set. In this method, when a query is specified, structurally similar compounds are searched and collected to make a local model around the query. Then a QSAR model for the prediction is explored with a part of the whole data that are available, and the obtained temporary model is used for the data prediction of the query. The model is discarded after the data prediction for the current query. We tested the performance of our approach to the sophistication of QSAR modeling with an artificial set of the synthesized data and a real data set of aquatic toxicities of chemicals. The results suggested that the present approach would often give us better prediction performance than that obtained by the ordinal QSAR modeling with whole data.

On the other hand, the prediction result depends on the number of compounds for the temporary training set used for making the model. And, it is difficult to know the optimal number of the neighbors to be used, in advance. In the present work, we employed a threshold of the similarity at exploring the neighbors but not the number of neighbors to be searched. Computer experiment showed us that the method with the threshold of similarity gives a better performance. Besides, it was shown that a QSAR model obtained from the whole data could give us better prediction when the appropriate neighbors are not available enough. Alternatively the performance of the method also depends on the local data structure around a query of interest. But, it is impossible to see a data structure of the local space around the query in advance. We employed kNN, RMSST (Rooted Minimum Spanning Sub-Tree) and Centroid method to explore the neighbors. Once, we generated the QSAR models with the different training sets that are obtained by the different neighbor searching methods, and we evaluated the statistical performance of the models. We used the best approximation model among them. Computational experiment with a data set of toxic chemicals suggested that the current approach can provide us much better predictions for the case.

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THE IMPACT OF LARGE-SCALE GENETIC DATA ON DRUG TARGETS

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The recently announced 1000$-genome will inevitably have significant impact on the way Drug Discovery and Development is performed. Having human sequences along with model organism sequences available on a broad scale will enable insights that have not been possible thus far. Namely, we will be able to better design drugs for specific population groups or dial out population-specific off-targets, which will of course open up new routes for cheminformatics applications as well.

Within this study, we have analyzed the genomic data made available from the 1000 genomes project [1]. More specifically, we have been studying drug response rates on a molecular level. From each of the 1092 available human genomes we identified the sequences of all known drug targets covered in DrugBank [2]. We then extracted the sequences and annotated respective variations (mutations, deletions, insertions, duplications, inversions, translocations) for each drug target for each individual genome. Then we compared the sequences on a target-level and quantified the variations in order to correlate them with drug response rates. Respective results will be shown in this contribution.

Furthermore we identified a set of targets where the variations lead to immediate impact on binding pocket composition in certain populations or population groups. For these we built homology models based on existing 3D structures from the PDB database where a structure with a bound ligands was available [3]. It turns out that in a few cases drug responses can be explained on a molecular level. Specific examples will be shown.

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APPLICATIONS OF PROTEOCHEMOMETRICS ? FROM SPECIES EXTRAPOLATION TO CELL LINE SENSITIVITY MODELLING

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Proteochemometrics (PCM) is a computational method to simultaneously model the bioactivity of multiple ligands against multiple protein targets, and therefore permits to explore the selectivity and promiscuity of ligands on different protein classes [1,2]. Indeed, the simultaneous inclusion of both chemical and target information enables the extra- and interpolation to predict the bioactivity of compounds on targets, which can be not present in the training set [3]. In this contribution, we will firstly show a methodological advance in the field [4], namely how Bayesian inference (Gaussian Processes) can be successfully applied in the context of PCM for (i) the prediction of compounds bioactivity along with the error estimation of the prediction; (ii) the determination of the applicability domain of a PCM model; and (iii) the inclusion of experimental uncertainty of bioactivity measurements. Additionally, we will describe how the application of PCM can be useful in medicinal chemistry to concomitantly optimize compounds selectivity and potency, in the context of two application scenarios, which are: (a) modelling isoform-selective cyclooxygenase inhibition; and (b) large-scale cancer cell line drug sensitivity prediction.

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"WALKING TOXIC PATHWAYS" - CHANGES IN GENE REGULATION CIRCUITS PREDICT HUMAN TOXICITY OF CHEMICAL COMPOUNDS AFTER REPEATED DOSE INHALATION EXPOSURE.

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Massive changes of expression of hundreds of genes as well as changes in genomic and epigenomic landscapes are observed in human tissues, such as lung and epithelium after inhalation exposure to toxic chemical compounds. Such changes represent just an "echo" of relatively few causative molecular processes (pathways) in the cells taking place during the formation of the cellular response to the toxic compounds. Non-reversible structural changes in gene regulatory pathways, so-called pathway rewiring, under influence of external toxic agents may cause transformation of the cell homeostasis switching it from the normal state to a chronic disease state or lead to the cell death. Such structural changes often happen due to spreading of epigenetic modifications of chromatin and reaching regulatory regions of key survival or death genes during realization of cellular response to the external toxic agents. We call such structural pathway changes as "walking toxic pathways". Analysis of this phenomenon helps us to understand the mechanisms of molecular switches (e.g. between programs of cell death and programs of cell survival) and to identify causative biomarkers of toxic processes in the cells and organs. This gives us a chance to predict *in silico* human repeated dose inhalation toxicity for novel chemical compounds after their expression studies in human cells helping to reduce number of necessary animal toxicity studies.

QSPR MODELING OF CHEMICAL AND PHYSICAL STABILITY OF PHARMACEUTICALS

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One of the major concerns in modern drug discovery and development is chemical and physical stability of small molecule pharmaceuticals. Chemical stability is crucial for compounds at all stages of pharmaceutical R&D, from early drug discovery to formulation of liquid or solid dosage forms. Physical stability is typically related to stability of the solid form and can be described by such properties as melting point, heat and free energy of fusion and energies of sublimation.

QSPR models of oxidative chemical stability were built based on a large data set of electrochemical measurements at two pHs. Examples of the models application to pharmaceutical compounds will be discussed.

Several models were built to tackle the problems of physical stability and solubility. These models include: a QSPR model of hydration free energy, and a thermodynamic cycle aqueous solubility model (based on a combination of QSPR models of sublimation and hydration free energies). These models allow for deconvolution of lattice vs. molecular hydration energy contribution of poorly soluble drugs. The models are important for guiding molecular optimization in drug discovery and selection of optimal formulation strategy in development.

RECENT TRENDS IN QSAR MODELING OF CHEMICAL MIXTURES

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Usually the humans, animals, or environment are the subjects of combined action of not a single but several chemicals. However, Quantitative Structure-Activity (Property) Relationship (QSAR or QSPR) modeling is well developed for single molecules and only beginning to emerge for chemical mixtures. Mostly it is caused by the lack of reliable experimental data on biological and/or physical-chemical effects of mixtures.In this presentation, we will discuss most recent theoretical developments and applications in this new area of QSAR.

The QSAR modeling of mixtures requires the use of specific descriptors to characterize the different chemicals involved, taking into account their stoichiometry in the mixture. All the studies can be divided into several groups depending on the descriptor types used: *(i)* descriptors based on the mixture partition coefficients or biological descriptors; *(ii)* additive molecular descriptors (weighted sum of descriptors of individual components); *(iii)* integral non-additive descriptors of mixtures (mixture components are taken into account in a different manner from the additive scheme); and *(iv)* fragment non-additive descriptors (structural parts of different mixture components simultaneously taken into account by the same descriptor.

Depending on the dataset and potential application(s) of the models, four different strategies of external validation could be used: *(i)* "points out" – prediction of the investigated property for any composition of mixture from the modeling set, *(ii)* "mixtures out" – filling of missing cells in the initial mixture data matrix, *i.e.,* prediction of the investigated property for mixtures with unknown activity created by combining pure compounds from the modeling set, *(iii)* "compounds out" – prediction of the investigated property for mixtures formed by one pure compound present and another compound absent in the modeling set, and (iv) "everything out" - prediction of the investigated property for mixtures formed by two novel compounds absent in the modeling set. The latter is the most rigorous method of external validation in QSAR modeling of mixtures.

We will present several case studies including QSAR modeling of antipoliovirus activity of binary combinations of antivirals, prediction of drug-drug interactions, and QSPR modeling of $T_{boiling}$ of mixtures of organic solvents. Given the importance and the growing need for such models in drug discovery and chemical hazard assessment, we expect the development of innovative modeling workflows and the improvement of existing QSAR/QSPR approaches for mixtures in the near future. Specifically, the accumulation of additional data and its thorough curation as well as rigorous internal and external validation can significantly improve the quality of QSAR models of mixtures and enable their application for virtual screening of large databases of actual or uncharacterized mixtures.

MATERIAL-INFORMATICS: CHEMOINFORMATICS AND COMBINATORIAL MATERIAL SCIENCE FOR THE DESIGN OF NOVEL PHOTOVOLTAIC CELLS

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The ability of photovoltaic (PV) technologies to meet the ever growing global demand for green energy could be realized if these technologies led to the development of solar cells which are cost effective and environmentally safe. Solar cells based entirely on metal oxides (MOs) have the potential to meet these criteria provided they could demonstrate an order of magnitude improvement in their power conversion efficiencies. The development of all-oxide PV cells could benefit from combining combinatorial material sciences for compounds synthesis with chemoinformatics tools for analyzing and rationalizing the empirical results and for designing new compounds.

Here we describe what we believe to be the first reported application of chemoinformatics techniques in the field of PV. In order to establish the tools in this new field, we focused our attention on several representative solar cell libraries. These were generated by combining different MOs (e.g., TiO_2, CuO, Fe_2O_3) in different proportions into combinatorial libraries each consisting of 169 solar cells[1]. Each cell was characterized by experimentally measured descriptors related to its composition and properties and by independent variables related to its PV performances. The resulting libraries, either alone or in combinations, were subjected to a newly developed chemoinformatics workflow consisting of data visualization, outliers removal, model generation and validation, and experimental design.

Insight into the distribution of cells in their descriptors space as well as into potentially interesting phenomena within the cells population (e.g., phase transition) was obtained through principle component analysis (PCA). Outliers were identified and removed using a newly developed algorithm based on the *k*-nearest neighbors (*k*NN) method[2] and the remaining cells were divided into training and test sets using a new representativeness function[3]. Individual models were derived for all PV properties using various techniques including *k*NN and genetic programming and validated by predicting these properties for test set compounds. Typically, good models were obtained with q^2 values for training set compounds and r^2 values for test set compounds > 0.8 (Fig.1).

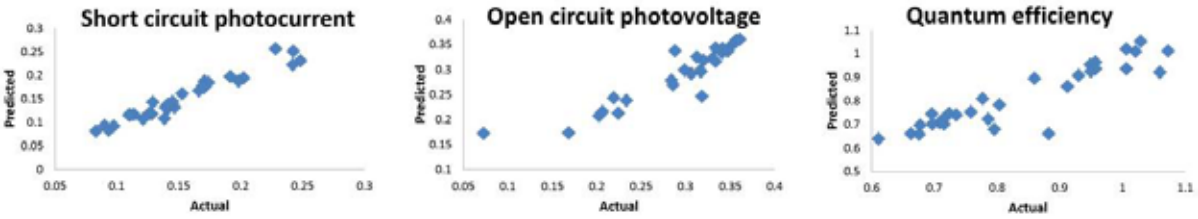

Figure 1: Performances of *k*NN-based models derived for key PV properties on external test sets selected from metal oxides combinatorial libraries.

Analysis of the resulting models provided insight into the relative importance of the different descriptors for each PV property highlighting "global descriptors" (often descriptors describing cell composition in terms of the different MOs) found to be important for several properties and across multiple libraries. Finally, the resulting models were used for the design of new compounds. These preliminary studies demonstrate the usefulness of chemoinformatics tools in the field of photovoltaics.

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META-QSAR

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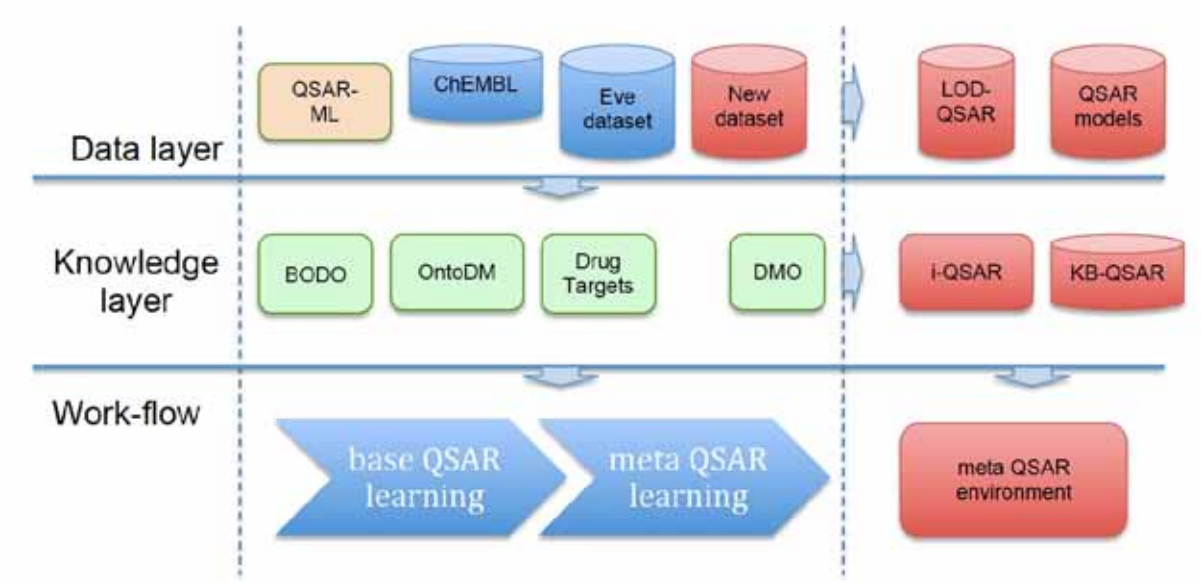
There is no single best way of learning and applying QSARs, nor could such a method exist. Instead, it is clear from theory and practice, that some target-type/ compound-type/ molecular-representation/ learning-method/ approaches work better together than others. However, despite the vast size of the QSAR literature previous comparative studies have only compared a limited number of QSAR problem combinations. Therefore, currently the QSAR scientist has little to guide her/him on which QSAR approach to choose for a specific problem.

The meta-QSAR project recently funded by the Engineering and Physical Sciences Research Council (EPSRC) UK aims to make a step-change in QSAR research. The project utilizes newly available public domain chemoinformatic databases, and in-house datasets, to systematically run extensive comparative QSAR experiments. We will then generalise these results to learn which target-type/ compound-type/ compound-representation /learning-method combinations work best together. This is meta-learning, using machine learning to learn about QSAR learning.

The project has two main parts: base QSAR learning, and meta QSAR learning (see Fig.1). The QSAR data and knowledge. QSAR datasets (e.g. ChEMBL [1], our in-house Eve dataset) will be stored in QSAR-ML [2] format and annotated with semantic descriptors defined in ontologies (e.g. in-house i-QSAR). These enriched datasets, along with the corresponding drug targets will be published as Linked Open Data (LOD) [3], and used as the input for the QSAR learning. Each QSAR learning run will be recorded and classified utilizing i-QSAR. These annotated datasets and learners will be the input for the meta QSAR learning. The major anticipated outputs of the project are: a comprehensive knowledge base (KB-QSAR) about what QSAR approaches work best in particular situations, a repository of QSAR models, and an environment for meta-QSAR investigations. We will make the knowledge we learn publicly available to guide future QSAR learning.



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PERFORMANCE EVALUATION OF COMMON VIRTUAL SCREENING TOOLS ON SELECTED REPRESENTATIVES OF DIFFERENT TARGET CLASSES

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Multiple virtual screening tools are readily available to accelerate drug discovery and support further optimization and development steps. In recent times, increasing attention was drawn to investigating the performance of these tools[1-8], however, to the best of our knowledge a comprehensive and prospective comparative study still needs to be accomplished. Different stages in drug development need to address multiple issues besides lead-identification, e.g. the investigation of potential drug-off-target interactions causing adverse events or influencing the pharmacokinetic profile. The involved targets and target classes usually exhibit different biological functions, and consequently also distinct structures and characteristics. This led us to the assumption that differing software tools may be better suited to meet the requirements of the respective research question.

In the course of our work, we selected representative examples of different target classes and applied widely used *in silico* tools like pharmacophore- and shape-based virtual screening, docking, and 2D-similarity-based profiling approaches to identify novel ligands and predict potential interactions. Top-ranked compounds retrieved from shape-based, pharmacophore-based, and docking-based virtual screening were selected for biological testing and further investigated with open source profiling tools. The results of the experimental evaluation enable us to examine and compare the performance of the *in silico* methods and investigate the advantages and limits of every tool for every target class. We will exemplify the substantial differences we observed in the performance and applicability of the various tool, suggesting that a careful and rational selection of the method of choice can considerably influence the success of the research project.

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STRUCTURAL AND FUNCTIONAL INTERPRETATION OF QSAR MODELS

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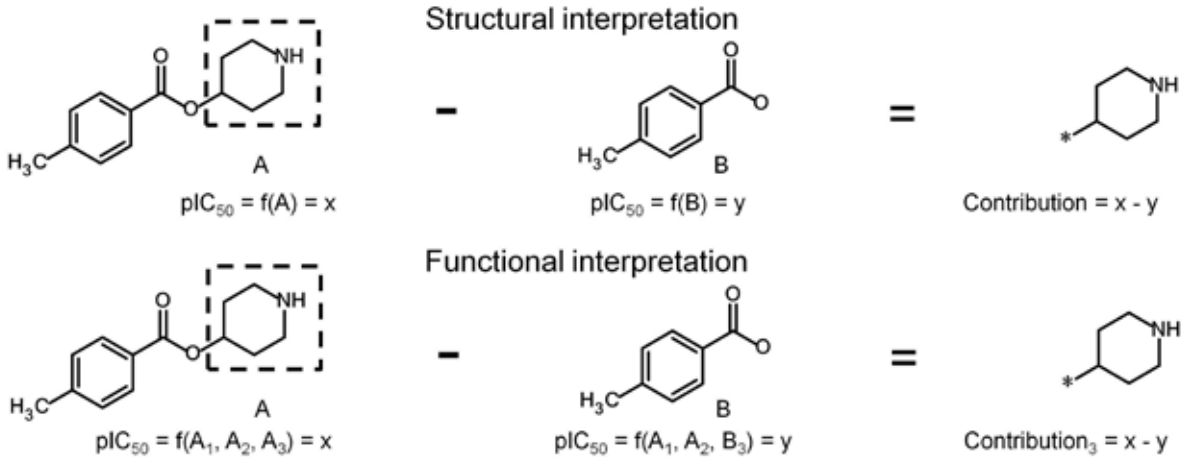
Recent advances in QSAR modeling were concentrated mainly on predictive ability of models. To achieve this goal a lot of machine learning methods were applied (support vector machine, random forest, neural nets, etc). These modern techniques don't have clear interpretation scheme and can be interpreted only in some specific cases or with significant restrictions. But knowledge about structure-property relationship in the easily readable form is very important for researchers. This can give some hints for fragment-based design or can help to deeper understand the investigated process.

Recently we developed approach for structural interpretation of any type of QSAR models (regardless modeling method and descriptors) which was inspired by matched molecular pairs approach [1]. Fragment contribution is calculated as a difference between predicted activity for the whole molecule and predicted activity for that molecule with removed fragment. As a result it becomes possible to estimate contribution of single fragments into the activity and rank fragments according to their contributions. Such information could be valuable for researches, especially if the considered dataset is structurally diverse and it is quite difficult to find consistent patterns which enhance or reduce activity of compounds. But the answer on the question "why the fragment possesses such contribution to the activity" is even more important.

In this work we made step forward and tried to estimate which physico-chemical characteristics of fragments influence on fragments' contributions to the activity. Such functional interpretation of QSPR models can lead a researcher to the idea of possible mechanism of action or binding mode of investigated compounds, etc. The key feature of the proposed approach is the usage of descriptors which reflect specific atomic properties. For representation of molecular structure of compounds we used tetraatomic fragments (simplexes) labeled by partial atomic charge, lipophilicity, refraction, H-bond donor/acceptor propensity. This gives us a possibility to estimate contribution of each fragments related to polarizability, H-bonds formation, electrostatic and hydrophobic interactions.

Applicability of the proposed approach of functional interpretation of QSAR models was demostrated on several examples including blood-brain permeation and affinity for fibrinogen receptors. Calculated fragments contributions and their relative ranks are in a good agreement with experimental observations and findings of molecular docking studies.



1, 2, 3 – groups of descriptors represented different physico-chemical characteristics (charge, H-bonding, etc) of compound A and B.

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EU-OPENSCREEN – A PAN-EUROPEAN RESOURCE AND INFRASTRUCTURE TO SUPPORT CHEMICAL BIOLOGY RESEARCH

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EU-OPENSCREEN is a pan-European research infrastructure initiative on the ESFRI roadmap (European Strategy Forum on Research Infrastructures). It aims at enabling academic chemical biology research to develop novel research 'tools' (i.e. chemical inhibitors or activators of biological targets) for all areas of the Life Sciences (incl. molecular, cell, plant, structural and microbiology; synthetic and medicinal chemistry; pharmacology and early drug discovery etc.).

EU-OPENSCREEN supports all stages of a tool development project, including assay development, high-throughput screening and chemical optimization of 'hit' compounds. EU-OPENSCREEN offers to scientists open access to its shared resources, including latest screening technologies, follow-up chemistry services for hit optimization, a unique compound collection composed of commercial and proprietary compounds, and a database containing validated output from the screening centers in a public as well as pre-release environment. Chemists are invited to include their compounds into this jointly-used compound collection which is screened against a wide range of biological assays. This allows chemists to annotate their compounds with rich information about structure-activity data.

EU-OPENSCREEN builds on existing networks and facilities in now 16 partner countries. It interacts with similar large consortia of other continents to advance mutual exchange of compound collections, linkage of databases, agreement on standards, and exchange of best practice. EU-OPENSCREEN is expected to start full operations in late 2015. It can already look back on a growing number of transnational activities: development of new design principles for its central compound collection; exchange of local compound libraries, joint screening projects, and creation of national interest groups.

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WHEN IS SOFTWARE ACCEPTED BY MEDICINAL CHEMISTS? SeeSAR: A LEAD OPTIMIZATION EXAMPLE

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Developments throughout our discipline have shown that traditional cheminformatics approaches enveloped in software have a tough time to be accepted by medicinal chemistry staff – and also by management. However, the classical split into a comp.chem. “expert” world and the “bench world” though is now under high pressure: consolidations/reorganizations and monetary pressure render the option of relieving Comp.Chems and MedChems taking over parts(!) of computational tasks highly attractive. Well... – At least in theory.

In practice, though, this is hampered mostly by three factors:

1. Too time-intensive workflows (from steps involving IT departments, through data curation, protein preparation, tautomer selection up to computational parameter setup – just to name a few.)

2. Too cumbersome usage / learning curves (it is not rare to have more than 100 places to click in standard cheminformatics suites right after startup.)

3. Too general visualization (for example, MedChem questions such as where a polar group is buried or where a bond is “torsionally hot” are not visible right away.)

Here, we will present SeeSAR (www.biosolveit.de/SeeSAR), new software entirely written from scratch to answer key MedChem questions with the abovementioned restrictions in mind. The tool features a millisecond-fast proposal for protein setup from PDB input alone (originating from the ProToss[1] code), the most consistent small molecule initialization and tautomer selection machinery NAOMI[2] (and its further developments including property calculation plus molecular 2D visualization) and a very sophisticated, new 3D graphics engine supporting true transparency, shader functionality and much more. Affinity estimates include entropic effects and computed within seconds on the HYDE framework[3], and a visual torsional strain analysis is carried out with the TorLib approach[4], and finally a 3D editing facility is embedded to test effects of typical SAR modifications.

The first version is ready to offer interactive help with very pragmatic MedChem questions such as:

* Which of these 5 compounds should I synthesize first?

* Why does this compound only show millimolar activity?

* Could a methyl exhibit a “magic” effect here?

Example cases will be shown, and the software will be available for “in situ” testing.

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COSMO SIGMA-SURFACES AND LOCAL SIGMA-PROFILES AS EXTREMELY ROBUST DESCRIPTORS FOR ALIGNMENT, 3D-SIMILARITY AND 3D-QSARR

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The surface polarization charge density σ, which a virtual conductor would place on the surface of an embedded molecule, can nowadays be easily calculated for almost any molecule based on quantum chemical DFT/COSMO calculations. Within the COSMO-RS theory[1] it has been demonstrated that the free energy of molecules in liquid phases, and as a consequence properties as vapor pressures, solubilities, partition coefficients, etc. can be very well calculated by statistical thermodynamics based on σ-profiles of solutes and solvents. This method meanwhile is widely used in chemical engineering, but also in pharmaceutical drug development for solvent screening and other purposes[2]. The success of COSMO-RS proofs that the polarization charge density s essentially holds all information required for the quantification of molecular interactions in the liquid phase, especially about electrostatic interactions and hydrogen bonding[3,4].

If σ is such a good descriptor for the interactions in solution, it should also be powerful for the quantification of receptor-ligand interactions, because these are of the same nature. This idea led to the development of local, grid-based σ-profiles (LSPs), which can be used for accurate "field-based" alignment and 3D-similarity of ligands (COSMOsim3D[5]). In a further step, the LSPs have been demonstrated to be optimally suited descriptors for molecular field analysis[6]. This COSMOsar3D method turns out to outperform traditional 3D-QSAR methods as COMFA or COMSIA with respect to accuracy of the trained models. Even more important may be the robustness robustness of the COSMOsar3D models, which have are almost insensitive to the choice of the grid position and spacing, and do not depend on any cutoff parameters.

In this presentation we will give an analysis of the origin of the superiority of the polarization charge density σ compared to the traditionally used electrostatic potential (ESP/MEP).

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STRUCTURAL SENSITIVITY ANALYSIS USING MATCHED MOLECULAR PAIRS

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Matched molecular pairs analysis (MMPA) is an increasingly popular technique for visualizing the effect of structural transformations on molecular properties. The first step in the process is to identify pairs of compounds that differ only by small structural changes. Pairs that share a common change are then grouped together and the distribution of changes in property values (e.g., biological activity or logP) across the pairs is examined. One of MMPA's strengths is that it takes all available molecular contexts for the change into account. Its primary weakness is that it is limited to pairs in which both molecules have been prepared and characterized.

We have explored an alternative approach in which differences in predicted properties are examined. This greatly broadens the scope of application, since it is not limited to existing compounds and does not require physical measurements. Moreover, when the models in question are based on atomic and molecular properties rather than on substructural fragments, it provides a powerful way to assess the sensitivity of the modeled property to substitution at other positions on a shared scaffold.

QDB: FROM STATIC TO DYNAMIC NATURE OF PUBLISHED QSAR-S

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The development of useful and reliable QSAR models is a creative process and requires lots of expertise from life sciences to statistics making it complex, but effective group of methods for understanding chemico-biological mechanisms and creating opportunities for the predictive purposes. One of downside of the complexity of QSAR methods is the proper communication of the modeling results (*in silico* models), which is difficult and causes the lack of reproducibility and transparency in the published models.

QSAR community is producing around one thousand scientific publications annually (according to Web of Science). The dominating communication approach for the publication of predictive models is printed media, which has its advantages and disadvantages. The main advantage is peer review process for the independent evaluation of the scientific work and established distribution channels to reach the intended audience. The disadvantage is consequence caused by the static nature of printed media that makes the accessibility and independent verification of claims rather difficult. The problems start with the sheer availability of the original data. The traceability and reproducibility of the whole *in silico* experiment from a scientific publication is more of an exception than a rule. All this hinders independent exploration, practical usage and putting published knowledge into work. Clearly, there is a need to improve digital organization and archival of results and data.

The presentation looks into the present state-of-the-art for the digital organization and archiving of predictive model information. Systems that allow accessibility, traceability and transparency of QSAR-s are constructively reviewed. Finally the proposal how *QsarDB data format* [1] helps to improve the best publishing practices of QSAR models is discussed. QsarDB data format helps to ensure that the most relevant content is available and QSAR knowledge is reproducible indiscriminately. *QsarDB repository* [2], a web based environment, where QDB archives can be deposited and used interactively will be also described. Up to now utility and benefits of QsarDB have been thoroughly tested by solving everyday QSAR and predictive modeling problems, with examples in the field of predictive toxicology, and can be applied for a wide variety of other endpoints.

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CROSS-MINING IN 3D-2D-1D, THE PDB, CHEMICAL LIBRARIES AND STRUCTURE ACTIVITIES TO EXTRACT SHARED MODES OF BINDING FOR PDB LIGAND SUBSTRUCTURES

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From the initial fast heuristic to compare/superpose 3D interaction surfaces within the Protein Data Bank [Jambon 2003], we have explored for the last 10 years many new chemo-proteomic applications for (A) Functional Annotation [Jambon 2005] [Doppelt 2007] [Doppelt-Azeroual 2010], (B) Binding Site Characterization to detect within a protein family very similar subpockets from more specific subpocket [Doppelt-Azeroual2009], (C) Drug repurposing & Scaffold Hopping [Moriaud2011a], (D) Fragment Based Drug Design by deconvoluting PDB ligand in Pubchem like smaller entities and then hybridising those protein-fragments having similar 3D interaction surfaces with the protein target [Moriaud2009] [Oguievetskaia2009], (E) Bioisosteric Replacement by searching in 2D fragments that are having a strong overlap after a 3D binding site comparison/superposition [Moriaud2011b], and even for unpublished proof of concept such as off-target identification and epitope scaffold search.

This time, for many Pubchem fragments present in multiple PDB structures, we compare in 3D each time their corresponding subpocket to the full PDB. The goal is to measure cases where these PDB substructures are observed in very similar 3D protein interactions and conserved in PFAM/EC protein functional classes. For proteins having this 3D subpocket similarity but not the 2D pubchem selected fragment, we look for this chemical moiety in Pubchem bioassays to check existing known affinities at this protein target.

We hope to provide a new application to better select fragments based on their existing mode of binding by crossmining in 3D-2D-1D, across the PDB, structure activities and chemical library data. This work explores one step further the overall chemo-proteomic challenge to better understand and predict interaction between, on one hand, ligands and all related fragments and, on the other hand, binding sites and all related subpockets

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SEMI-QUANTITATIVE SAR USING BAYESIAN MODELLING ON ACTIVITY CLIFFS

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3D-QSAR based on molecular interaction potentials can provide a wealth of information about the exact molecular characteristics required for activity. However, current techniques have a number of issues such as alignment noise, sampling errors and descriptor choice which can make it difficult to reliably produce effective models. We have presented in the past techniques for solving the sampling problem and shown that using accurate electrostatics combined with simple shape descriptors often gives meaningful models. However, there are still times when it is not possible to obtain a statistically valid linear regression model.

One useful qualitative data analysis method that is being increasingly used is activity cliffs analysis. In this technique, pairs of compounds are located that are similar (in some sense), but have different activities. Traditionally activity cliff analysis has used a 2D definition of similarity, but extension to 3D similarity metrics gives additional information that is very useful to locate the source of and reason for the activity differences.

An extension of 3D activity cliff analysis is to mine the entire data set for corresponding cliffs and use this to build a model for activity. Analysis of the data set to locate activity cliffs locates the pairs of molecules with the highest information content. However, this needs to be tempered with an analysis of how likely it is that the molecules are aligned correctly, as only properly-aligned molecules contain any information. We apply Bayesian corrections to the activity cliff data to obtain a map of the electrostatic and shape characteristics that seem to locally correlate with improving activity. The resulting model is semi-quantitative in that it attempts to describe the entire data set without building a linear regression model. This technique provides a valuable fallback to the computational chemist for information extraction from ligands in 3D.

SURFLEX QMOD: PROTEIN POCKET MODELING FOR AFFINITY PREDICTION

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Computational approaches for binding affinity prediction are most frequently demonstrated through cross-validation within a series of molecules or through performance shown on a blind test set. Previous reports of the Surflex-QMOD approach demonstrated its ability to produce accurate and scaffold-independent predictions of binding affinity by constructing an interpretable physical model of a binding site based solely on the structures and activities of ligands.[1] We now demonstrate how such a system performs in an iterative, temporal lead optimization exercise.[2] A series of gyrase inhibitors with known synthetic order formed the set of molecules that could be selected for "synthesis".[3] Beginning with a small number of molecules, based only on structures and activities, a model was constructed. Compound selection was done computationally, each time making selections based on confident predictions of high potency and selections based on quantitative measures of three-dimensional structural novelty. Compound selection was followed by model refinement using the new data. Iterative computational candidate selection produced rapid improvements in selected compound activity, and explicit incorporation of novel compounds uncovered more structurally diverse potent inhibitors than strategies lacking active novelty selection.

We also present a new hybrid structure-guided strategy that incorporates protein structures to inform models of structure–activity relationships.[4] Many QSAR methods have utility in making predictions within a highly related chemical series, but cannot generally be fruitfully applied to novel compounds due to limited domains of applicability. A new structure-guided Surflex-QMOD method demonstrates the ability to use protein structures as well as ligand structure-activity data to construct more robust physical models. These models can accurately predict binding affinities over a broad class of compounds while more accurately representing physical protein pockets and ligand binding modes. The structure-guided method was applied to CDK2[4], with detailed comparisons to the standard QSAR approaches and docking-based predictions. Additional comparisons included structure activity data for urokinase, Chk1, and PTP1b[5]. Results will be presented establishing a new integrated modeling approach that leverages molecular similarity, docking, and multiple-instance learning to produce broadly applicable accurate predictions in cases with limited protein structures but with high ligand diversity

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MIGHT TEMPLATE CoMFA INTEGRATE STRUCTURE-BASED AND LIGAND-BASED DESIGN?

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Template CoMFA offers an unprecedentedly robust and automatic means for generating a unified 3D-QSAR model from multiple X-ray (or pharmacophoric) templates and diverse structural series. Because such strong claims require strong proof, an unusually extensive validation study (perhaps the largest ever for a new CADD methodology) has been performed for template CoMFA, 74 different targets including templates extracted from 509 PDB files. Useful models (r^2 greater than .9 or q^2 greater than .2) were effortlessly obtained for 70 of these 74 targets.

Such an X-ray-constrained 3D-QSAR methodology might help to bridge the developing chasm between structure-based and ligand-based analyses. A CoMFA model could expand the interpretability of an individual X-ray structure by superimposing a summary of the ligand SAR – or an X-ray structure could suggest structural extrapolations most likely to exploit a promising 3D-QSAR trend. Other new possibilities might include one-off predictions that have meaningful confidence limits; or even guidance in evaluating docking poses when X-ray structures are unavailable. Results from exploring some of these possibilities will be presented.

Posters
Abstracts

QSAR MODELING OF KDM1A INHIBITORS USING MACHINE LEARNING APPROACHES

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Chromatin modifications have emerged as new fundamental regulatory mechanism for the control of gene transcription and are related with numerous biological processes. It is increasingly recognized that epigenetic modification constitute important regulatory mechanisms for the pathogenesis of malignant transformation. KDM1A (also known as LSD1, AOF2, BHC110 or KIAA0601), the first characterized histone demethylase in 2004, belongs to the flavin adenine dinucleotide (FAD)-dependent amine oxidase family and has been shown to be part of several corepressor complexes including CoREST, CtBO, and a subset of HDAC complexes. As a consequence of KDM1A inhibitors prospective clinical importance[1], in this study is reported the development of predictive QSAR models[2] using different advanced machine learning classifiers, including support vector machine (SVM), random forest (RF), boosting regression (BR), K-nearest-neighbor (KNN) and Naïve Bayes. All models in the present study were implemented in Python using Scikit-Learn[3] and RDKit (http://www.rdkit.org/). Preliminary data analysis showed that the most robust and predictive models were obtained by means of Naïve Bayesan Regression in combination with the Simulated Annealing variable selection.

Details and results will be presented.

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DEHYDROALTENUSIN CARBOCYCLIC ANALOGS AS STABLE AND SELECTIVE INHIBITORS OF DNA POLYMERASE ALPHA

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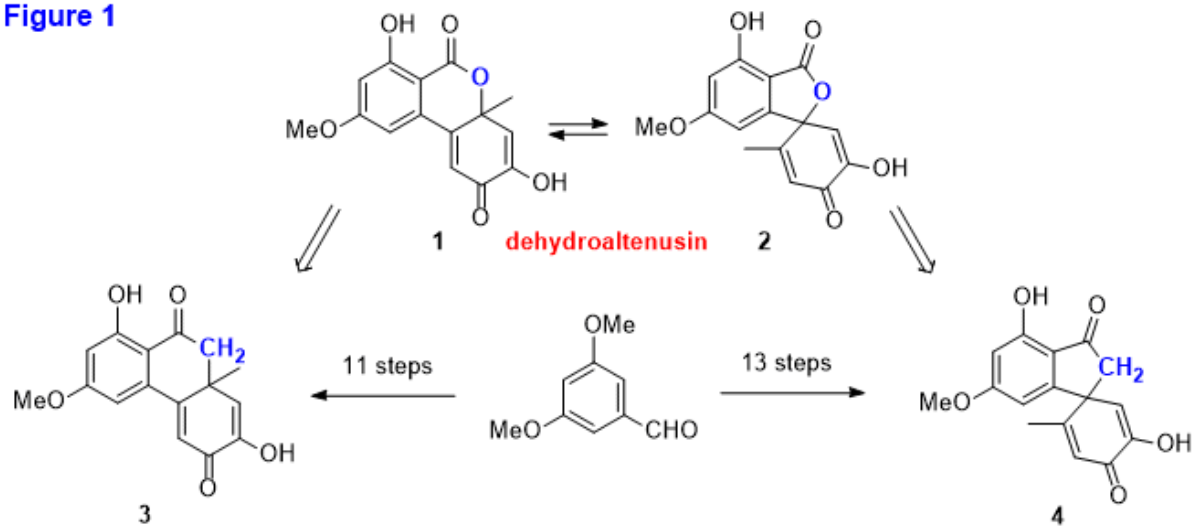
Selective inhibition of DNA polymerases is a viable strategy for treatment cancer.[1] Dehydroaltenusin is virtually the only known sub-micromolar selective inhibitor of DNA polymerase alpha (pol a) that exhibited activity *in vivo*.[2] However, the mechanism of action and potential usefulness of dehydroaltenusin are rather questionable, as the compound is unstable and, in polar solvents, forms an equilibrium mixture of two species: tricyclic lactone **1** and its spirocyclic isomer **2** (Figure 1).[3]

Figure 1



We have prepared racemic carbocyclic analogs of both forms of dehydroaltenusin – compounds **3** and **4**, whose structures we confirmed by X-ray crystallography. The target structures, as well as some of the key intermediates, contain novel and potentially useful pharmacophores. Only compound **3** was found to be selectively active against mammalian pol a and, since both carbocyclic analogs are chemically stable, it could serve as an appropriately robust chemical biology probe. Total syntheses and biological activity of the target compounds **3** and **4** [4] will be presented in the poster communication.

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MODELLING LIGAND SELECTIVITY OF SERINE PROTEASES USING PROTEOCHEMOMETRIC APPROACHES

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Serine proteases are implicated in important physiological functions like digestion and immune response. Like kinases, these targets also have a high intra-family similarity, leading to unwanted side effects. The availability of sequence and structure data has made it possible to design pharmacological agents that can discriminate successfully between their related binding sites. In this study, we have quantified the relationship between 12, 625 distinct protease inhibitors and their bioactivity against 67 targets of the Serine Protease family (20, 213 data points) using proteochemometric modelling (PCM). The comparison of 21 different target features in the PCM model motivated the usage of specific binding pocket descriptors, which helped in the identification of active site residues and selective compound chemotypes affecting the binding affinity and selectivity. Therefore, PCM successfully integrates the information from various targets in order to both inter- and extrapolate on the target and/or chemical space.

The most predictive PCM model, trained on compound structural fingerprints and Z-scales, exhibited Q^2_{CV} and RMSE values of 0.77 and 0.70 log units respectively. In total, 21 PCM models were generated with and without alignment dependent descriptors. These PCM models performed better than (i) a model trained on exclusively compound descriptors (Family QSAR), used as a baseline, which displayed Q^2_{CV} and RMSE values of 0.43 and 1.09 log units; and a model trained on exclusively protein descriptors, with Q^2_{CV} and RMSE values of 0.63 and 1.05 log units. Models trained on whole sequence descriptors (mean R^2=0.78±0.01, mean RMSE=0.70±0.02) were found to outperform models trained on binding pocket amino acid descriptors (mean R^2=0.67±0.05, mean RMSE=0.83±0.07). However, the two binding site sequence descriptors (Z-scales) had comparable performance (R^2=0.78; RMSE=0.69) to full sequence descriptors and were used in the final PCM model. Taken together, these data suggest that the incorporation of binding site information in the PCM model produces better predictions and explains compound-protein interactions. The addition of bioactivities from ortholog and paralog proteins improved model performance, as a PCM model trained on data points annotated on exclusively human proteases exhibited lower performance (R^2=0.69; RMSE= 0.65).

The interpretation of the PCM model singled out various chemical substructures of the compounds responsible for bioactivity and selectivity towards particular proteases (THRB, TRY and FA10). For instance, primary sulphonamides were identified as feature responsible for increased selective activity (by 0.79 log units) on Coagulation Factor 10 (FA10). Conversely the feature tertiary sulphonamide was found to be responsible for a selective decrease in binding activity towards FA10 by 0.8 log units, as it caused an increase in the activity against THRB and TRY (0.4 and 0.85 log units, respectively). Furthermore, presence of a prolinamide and secondary amide features were found responsible for the selective decrease in compound's affinity towards THRB (by 0.6 log units) and activity on THRB (1.31), TRY (0.07) and FA10 (0.09 log units) respectively. Among the binding pocket residues, the amino acids (Arginine, Leucine and Tyrosine) at position 35, 39, 60, 93, 140 and 207 were observed as majorly contributing residues for selective affinity on these three targets.

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RELATIONSHIPS BETWEEN STRUCTURES OF TEBUFENOZIDE DERIVATIVES AND THEIR INHIBITORY EFFECT ON QUINIDINE TRANSPORT BY P-GLYCOPROTEIN

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P-glycoprotein (P-gp) is a member of the ATP-binding cassette transporter family. It actively transports a wide variety of compounds out of cells and functions as an energy-dependent efflux pump to protect humans from xenobiotics (1). Since P-gp recognizes various compounds as substrates, it also plays an important role in multidrug resistance in the treatment of cancers (1). However, the mechanism of P-gp substrate recognition is complicated and still poorly understood. In our previous report (2), we screened diverse chemicals, especially agrochemicals by measuring the ATPase activity of human P-gp and found that dibenzoylhydrazine (DBH) insecticides such as tebufenozide (Figure) showed the ATPase activity. In this study, the inhibitory activity of tebufenozide derivatives against quinidine transport by human P-gp was measured to obtain the information about DBH-P-gp interaction. The structure-inhibitory activity relationship was then investigated using classical QSAR and CoMFA.

Firstly the transport of tebufenozide through MDR1-LLCPK1 cells which show high levels of P-gp activity was evaluated. However, the excretion of tebufenozide by P-gp was not found because of the high passive transcellular permeability of the compound. Inhibitory activity of tebufenozide and its derivatives against quinidine transport by P-gp was then evaluated by measuring the permeability of quinidine through MDR1-LLCPK1 cells. It was difficult to evaluate IC_{50} values for all tested compounds because of their low solubility. Therefore, inhibitory activity (%) at 30 μM was measured and logit-transformed inhibitory activity {logit A= log [activity(%)/(100−activity(%))]} was used for all QSAR analyses. The inhibitory activity of two series of tebufenozide derivatives, 13 compounds having 3,5-Me_2 group and 37 compounds having 2-Cl group on the A-ring, respectively, were separately analyzed. All computations except classical QSAR were done with the molecular modeling software package SYBYL ver. 7.3 (Tripos Associates, Inc.). CoMFA analyses were conducted with the “Advanced CoMFA” module of SYBYL. Classical QSAR analyses were performed with QREG, version 2.05.

In classical QSAR analyses of both series, hydrophobic factor, log P was most important for the activity. The electron-donating effect of the 4-substituents on the B-ring was significant for A-ring: 3,5-Me_2 derivatives whereas the electron-withdrawing 3-substituents and the long 2- and 4-substituents on the B-ring increased the activity of A-ring: 2-Cl derivatives. The CoMFA also showed similar results to those of classical QSAR. The different substituent effects in each series may suggest the difference of the binding mode to P-gp.

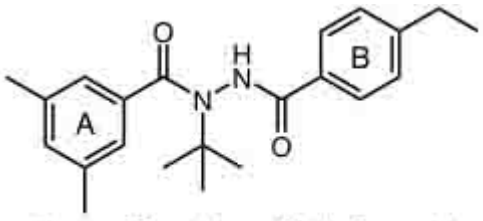

Figure Structure of tebufenozide

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RATIONAL DESIGN OF GENOMIC G-QUADRUPLEX CONFORMATION STABILIZERS BY MEANS OF LIGAND AND STRUCTURE BASED APPROACHES

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G-quadruplex (G4) structures are non-canonical nucleic acid conformations occurring in guanine-rich sequences connected *via* Hoogsteen's type hydrogen bonds (1) among four guanines and stabilized by monovalent cations (Figure 1).

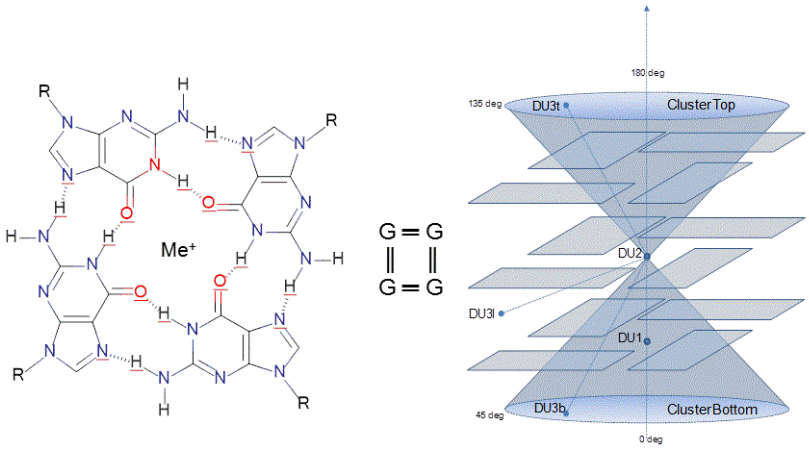

Figure. 1: Hoogsteen's type H bonds in G4 core forming typical G-quartets (sx) and the representation of a molecular descriptor useful for a rapid interpretation of the G4 binding recognition (dx).

Relevant key locations at genome level, such as telomeric ends or oncogenic promoters, are involved in G4 folding. The rationale of stabilizing the G4 conformation represents a novel approach for the drug design of innovative antineoplastic agents. The Protein Data Bank (PDB) includes several X-ray and NMR determined models of G4 structures in some case complexed with stabilizing ligands. These PDB entries are ideal starting points for rational drug discovery campaigns.

Some years ago we have started *in silico* studies with the characterization of PDB models of human telomeric sequence *d*[$AG_3(T_2AG_3)_3$] (h-TELO) by conformational studies, docking simulations (2) and, more recently, virtual screening experiments (3) carried out by means of combined ligand/structure based approaches. The issue of the flexibility and conformational polymorphism of the G4 targets (4), also as function of sequence modification (5), has been explicitly considered in order to rationally design stabilizing ligands.

In this communication *in silico* experiences carried out in our laboratory are presented, especially highlighting the successful identification of new G4 stabilizers.

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STRUCTURE-ACTIVITY ANTIVIRAL PROPERTIES OF POLYPHENOLS FROM PLANTS

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The emergence of drug resistant variants of the influenza virus has led to a need to identify novel effective antiviral agents and study of their structure-activity. As an alternative to synthetic drugs, the consolidation of empirical knowledge with ethnopharmacological evidence of medicinal plants offers a novel platform for the development of antiviral drugs. The aim of this study was to study structure-activity antiviral properties of polyphenols from plants. 30 compounds with polyphenol structere were tested against the H5N3 and H7N1 subtypes of the influenza virus. It was shown that galloyl derivates of flavonoids inhibited reproduction virus and the enzymatic activity of viral neuraminidase. The results presented in this study suggest that plants could be a potential source for new antiviral drugs. The plant extracts investigated could serve as promising candidates for the development of third generation anti-influenza drugs, thereby challenging the neuraminidase drug resistant viruses in an attempt to safeguard human health and the global economy.

SUBSTRATE - INOSITOL TRANSPORTERS INTERACTIONS: DOCKING AND MD SIMULATIONS

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Inositol is a cyclic polyol naturally occurring as seven optically inactive stereoisomers and one enantiomeric pair. Commonly found in nature are myo-, scyllo-, chiro- and epi-inositol. myo-Inositol is a component of all eukaryotic cells and is the most widespread isomer. Within the human body, brain is the most saturated organ of inositol, mainly myo- and scyllo-inositol. Their concentration in the brain is about 100-fold greater than circulating levels. Both isomers are endogenously found. In brain, inositol can be provided via in situ transformation of glucose and via entering through the blood-brain barrier and blood-CSF barrier. One of molecular mechanisms for maintenance of inositol brain levels is active transport via stereospecific carrier molecules – sodium myo-inositol transporters (SMITs).

Inositol is extensively studied as therapeutic agent in last decades. Preliminary studies showed effective treatment with myo-inositol in cases of psychiatric disorders like depression, panic, obsessive compulsive disorder. Recently it has been found that scyllo-inositol successfully inhibits the growth of Aβ amyloid plaques and cognitive deficits in TgCRND8 mice which show many of the hallmark features of Alzheimer's disease. Currently scyllo-inositol is in human clinical trials for the treatment of AD.

In this study a set of inositol derivatives was docked into SMIT-1 and SMIT-2 proteins in order to define the main structural features responsible for the ligand-transporter interactions. The transporter structures were modeled by homology using as a template the crystal structure of a protein from the same family – the sodium/galactose transporter (SGLT, pdb code: 3DH4). The docking protocol was optimized in terms of scoring functions and flexible binding site. The best poses were refined further by molecular dynamics. The final modeled complexes were analyzed and the main ligand-transporter interactions were revealed.

IN SILICO SEARCH OF ACETYLCHOLINESTERASE BLOCKERS AMONG MODIFIED THEBAINE DERIVATIVES

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The group of thebaine derivatives containing C-6,7 or C- 7,8 fused cyclic moieties in the C ring as well as a variety of substituents in C-1, C-3 C-7 or C-8 position, were studied as inhibitors of human acetylcholinesterase (AChE) using docking experiments. As a result of virtual screening 12 compounds were selected based on minimum binding energy (Table 1). The interactions of ligands and amino acid residues in the binding site were studied.

Table 1. Results of molecular docking.

L	BA	L	BA	L	BA	L	BA	L	BA	L	BA	L	BA	L	BA
DP	-12.1	10f	-10.2	12c	-9.6	6e	-9	8i	-8.3	10d	-7.7	11d	-6.8	9c	-6.1
7d	-12	6a	-10.1	10a	-9.6	11a	-8.8	11d	-8.3	12a	-7.7	8d	-6.8	8j	-6
1a	-11	7a	-10	11p	-9.5	6j	-8.8	8f	-8.1	8k	-7.6	11o	-6.7	11b	-6
7c	-11	GL	-10	9b	-9.4	12b	-8.6	1c	-8.1	10e	-7.4	11c	-6.7	11e	-5.5
2c	-10.9	6l	-9.9	8g	-9.3	8a	-8.6	6f	-8	8h	-7.3	6g	-6.7	8c	-5.3
6b	-10.6	3b	-9.8	6h	-9.3	11i	-8.5	11e	-8	6p	-7.3	11m	-6.6	6i	-5.2
Ib	-10.6	6m	-9.7	7b	-9.3	6s	-8.5	8n	-7.9	1d	-7.2	2b	-6.5	11i	-4.2
11q	-10.5	6n	-9.7	10b	-9.2	3a	-8.4	10c	-7.8	2a	-7.1	6q	-6.5	11k	-3.8
4	-10.3	5	-9.7	6k	-9.1	6c	-8.4	11e	-7.8	6r	-7	8l	-6.3	8m	1.2
8e	-10.2	9a	-9.7	11h	-9.1	11f	-8.4	6d	-7.8	6o	-6.9	8b	-6.2	8o	4.2

L - Ligand; BA - BindingAffinity, kcal/mol; DP - donepezil; GL - galantamine.

Screening of 78 dihydro- and tetrahydrothebaine derivatives using molecular docking has identified 12 potential blockers of AChE. The affinity of these compounds to the binding site of AChE exceeds that of galantamine and is comparable with the affinity of donepezil - the known blocker of AChE. As a result of our analysis of the "structure - activity" relationship, some features of studied derivatives have been found to be essential for effective interaction with the binding site of AChE. The conformational flexibility of ring C of fusedmorphinanes is essential for binding to AchE. Affinity is high in case of 5,6-cyclopropylfused dihydrothebaines, 7,8-pyrrolidine-, 7,8-dioxopyrrolidino, 7,8-succinyl- fused 6,14-endo-ethenotetrahydrothebaines. It has been revealed that 6,14-endo-ethenotetrahydrothebaines have greater affinity to AChE compared with compounds of 6,14-endo-ethenodihydrothebaine-hydroquinone series. Substituents in the aromatic ring A have significant impact on the affinity of the compounds. Affinity increases for compounds having a hydroxy-, acetylamino-, sulfonylamino- and dimethylamino-substituent into the C(3) position instead of the methoxy-substituent. Furthermore, 6,14-endo-ethenodihydrothebaine-hydroquinone derivatives containing an heteroalkynyl substituent in the A-ring effectively interact with binding site of AchE.

The interaction of annelated dihydro- and tetrahydro-thebaine derivatives with amino acid residues in the binding site of AchE was also studied. Most frequently these compounds react with tryptophan residue 86, phenylalanine residue 338 and tyrosine residue 124. Also essential for the binding are tyrosine residues 337 and 341, serine residue 286 and tryptophan residue 125.

Thus, the modified derivatives of the alkaloid thebaine are a promising group of compounds to be searched for new effective blockers of AChE. Such search can be performed using molecular modeling in silico with further pharmacological studies in vitro and in vivo.

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NEW INSIGHTS ONTO THE PARP-1 MOLECULAR STRUCTURE. MOLECULAR DYNAMICS AND PHARMACOPHORE MODELING STUDIES AIMING THE DISCOVERY OF NOVEL ANTICANCER AGENTS

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PARP-1 is a nuclear enzyme which represents the most abundant and best characterized member of PARP family. It plays a critical role as a DNA damage sensor. PARP-1 recognizes and binds to DNA strand-breaks through a N-terminal region, following which its C-terminal catalytic domain becomes activated, causing formation and addition of polyadenosine-ribose to acceptor proteins, thereby modeling their functions [1, 2].

The development of medicinal chemistry approaches to synthesize a high number of potent and selective PARP-1 inhibitors has been pursued with therapeutic relevance in a range of several diseases including cancer.

PARP inhibitors have shown especial relevance in tumors deficient in BRCA-1 or BRCA-2 function. Although some PARP-1 inhibitors have entered in clinical trials, recent data indicate that these compounds usually lack binding specificity among PARP family members. In this way, deeper studies of the protein structure to disclose new insights into PARP-1 recognition features and to develop novel and more selective PARP-1 inhibitors are required [3, 4, 5].

In this work we performed explicit-solvent Molecular Dynamics (MD) simulations with inhibitors complex with PARP-1 catalytic domain to analyze complex functional dynamics and to disclose new insights onto the active site of the enzyme. The complexes after MD were used to generate selective structure-based pharmacophores, based on receptor-ligand interactions.

The pharmacophore models were used for virtual screening of large compounds databases. After docking analysis, the best candidates were selected for evaluation by enzyme inhibition assays.

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FXR-OMICS: IDENTIFICATION OF STRUCTURAL REQUIREMENTS FOR FXR BINDING

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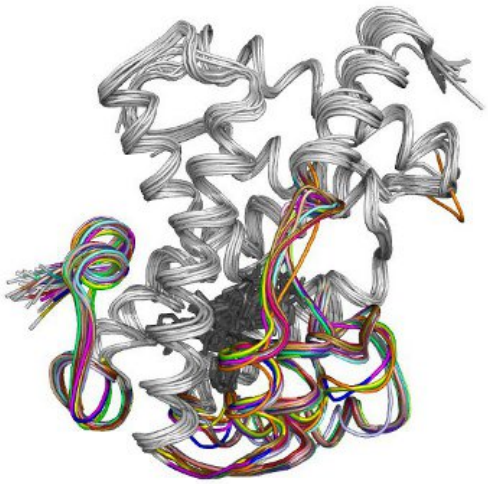
Farnesoid X Receptor (FXR)is a member of the nuclear receptor superfamily. It is highly expressed in liver, intestine and kidney and plays an important role in positively regulating genes involved in bile acid homeostasis, fat and glucose metabolism. [1] Recently was also demonstrated that FXR is involved in the downregulation of genes involved in inflammation, therefore it is considered an ascending target for metabolic and inflammatory diseases. [2]

During the last decade, intense research on FXR ligands has yielded different types of compounds: several steroidal and non-steroidal agonists and partial agonists, several antagonists and some gene modulators, able to selectively activate only specific pathway. From a therapeutic point of view, targeting FXR with a full agonist will likely to cause a series of adverse side effects, due to the broad spectrum of regulated genes. [3] Thus, understanding the molecular basis distinguishing between full agonism, partial agonism and gene modulation is crucial for the development of new drugs targeting FXR.

During the last years, several crystal structures of FXR have been reported and deposited in the Protein Data Bank, in complex with agonists and partial agonists. All the structure present the same general architecture but some differences exist between them. With our study we wanted to analyze in detail these FXR crystal structures, by using PCA and Structural Interaction Fingerprints, to gain deeper insight into specific structural and binding features having a key role in determining the activity profile of the different ligands. Moreover we also applied the collected information to better understand the activity profiles of already reported FXR ligands. The obtained results can later be used in the development of new binders with a specific activity profile.



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RIGHT- AND LEFT-HANDED THREE-HELICAL PROTEINS: EXPERIMENTAL AND SIMULATION ANALYSIS OF DIFFERENCES IN FOLDING AND STRUCTURE

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Despite of the large number of publications on three-helix protein folding there is no study devoted to the influence of handedness on the rate of three-helix protein folding. From the experimental studies we make a conclusion that the left-handed three-helix proteins fold faster than the right-handed ones. What may explain this difference? An important question arising in this work is whether the modeling of protein folding can catch the difference between the protein folding rates of proteins with similar structures but with different folding mechanisms. To answer this question, the folding of eight three-helix proteins (four right-handed and four left-handed), which are similar in size, was modeled using the Monte Carlo and dynamic programming methods. The studies allowed us to determine the orders of folding of the secondary-structure elements in these domains and amino acid residues which are important for the folding. The obtained data are in good correlation with each other and with the experimental data. Structural analysis of these proteins demonstrated that the left-handed domains have a lesser number of contacts per residue and a smaller radius of cross section than the right-handed domains. This may be one of the explanations of the observed fact. The same tendency is observed for the large dataset consisting of 332 three-helix proteins (238 right- and 94 left-handed). From our analysis, we found that the left-handed three-helix proteins have some less-dense packing that should result in faster folding for some proteins as compared to the case of right-handed proteins. We are the first to investigate the relationship between protein handedness and the rate of protein folding. Our findings demonstrate that small three-helix, left-handed proteins are less densely packed and should result in faster folding than that of right-handed, three-helix proteins. At the same time, right-handed, three-helix proteins have higher mechanical stability than the left-handed proteins. Moreover, from our analysis we have revealed that bacterial three-helix proteins have some advantages in packing over eukaryotic right-handed, three-helix proteins, which should result in faster folding.

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CORRELATING EVOLUTIONARY AND CHEMICAL DIVERSITY USING CHEMGPS-NP

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Natural Products (NPs) are "privileged structures" that have inspired the design of many approved drugs. They represent a heterogeneous class of compounds with a high diversity in terms of chemical structures and biological activities. In the light of the importance of these compounds in drug discovery program, *in silico* tools aimed at exploring the chemical space defined by Natural Products have been developed.

ChemGPS-NP is a global chemical positioning system for the exploration of biologically relevant chemical space and represents an extension of the previous ChemGPS model by addition of Natural Products.[1, 2] This global space map is based on 35 physico-chemical properties; the resulting multidimensional data is simplified through a Principal Component Analysis (PCA) in 8 dimensions (or Principal Components) describing the variance of the physico-chemical properties. Molecules with known chemical structures can be projected in the ChemGPS eight-dimensional map and resulting properties can be analyzed and compared with other molecules.

An important concept in medicinal chemistry is the relationship between similarity of structural features, physico-chemical properties and biological activity. In other words, similar molecules are likely to present similar biological properties.[3] In this perspective, the location of a molecule in the ChemGPS-NP can be used to predict its biological profiles by analyzing the biological activities of the surrounding molecules in the ChemGPS-NP space.

In this work, we analyze the complementarities between the description of molecular similarity using ChemGPS-NP and fingerprint-based methods (such as ECFP4). The influence of different similarity measures such as Euclidean distance, Tanimoto index between groups of molecules presenting similar or difference biological activity profiles will be investigated.

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CONTRAST GRAPH PATTERNS AND THE DETECTION OF TOXICOPHORES

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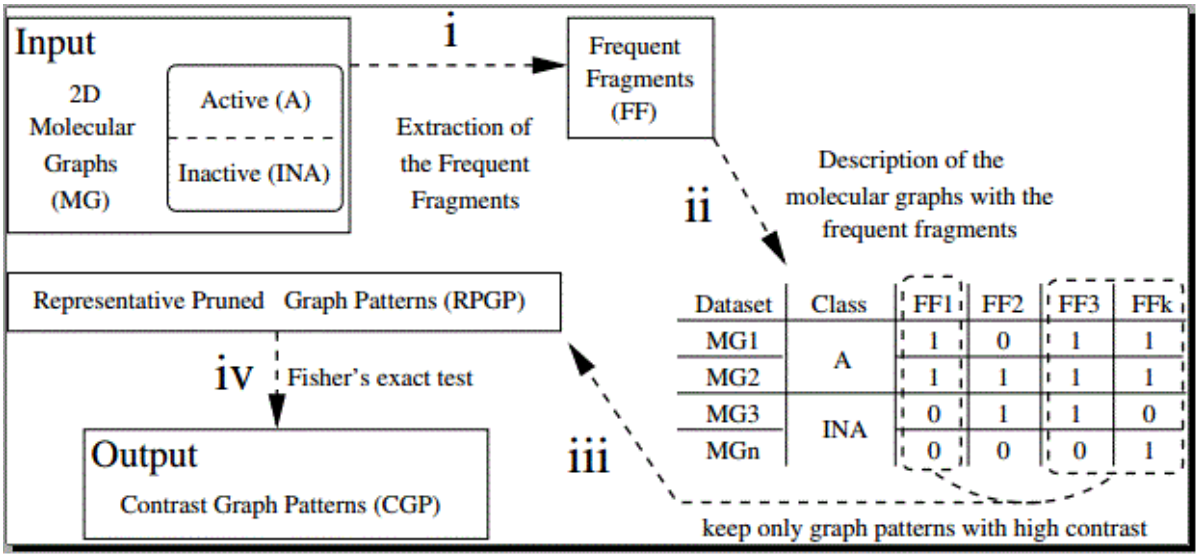
A method, based on the notion of Emerging Pattern (EP) [1], called the Representative Pruned Graph Pattern (RPGP) was developed in our laboratories [2]. Given a chemical dataset partitioned into two classes (e.g. actives molecules and non-actives ones), a RPGP is a conjunction of molecular fragments such that: (i) its frequencies between the classes are sufficiently different, (ii) its frequency in the target class is high enough to be significant to support a further use and (iii) it is defined as a closed pattern in the database. This notion positively answers the need of an automatic and understandable method for extracting the conjunctions of fragments related to a given behavior [3,4]. In practice, RPGPs are often numerous and does not allow to be analyzed easily. A recent evolution of our method has considered the Fisher's exact test for defining the most significant RPGPs. The resulting patterns are called the Contrast Graph Patterns (CGPs). This communication will present the approach and two applications in the field of (eco)toxicology.



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PROVISIONAL IN-SILICO CLASSIFICATION OF BIOPHARMACEUTICAL SYSTEMS IN EARLY DRUG DISCOVERY AND DEVELOPMENT

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Classification of drug candidates based on the Biopharmaceutics Classification System (BCS) and the Biopharmaceutics Drug Disposition Classification System (BDDCS) has become an important issue in pharmaceutical research. The combined modeling approach for BCS/BDDCS is an unexplored area with high relevance for application in early drug discovery and development. In this sense, the main goal of the study was to develop robust *in-silico* models to classify the solubility, permeability and metabolism properties that define both systems, allowing the definition of a new computational biopharmaceutical filter.

Three extensive and heterogeneous databases (solubility, permeability and extent of metabolism) and three machine-learning techniques (support vector machine, kappa nearest neighbor and multilayer perceptrons) were used to develop QSPR classification models. Nine classification models were selected and three voting systems were constructed. The final consensus models had global accuracies greater than 82% for each property. The *in-silico* BCS was validated with a dataset of 139 compounds classified by WHO and the *in-silico* BDDCS was assessed with external dataset of 131 compounds. In the first case, the models correctly classifies 88.4% of class I drugs, 78.3% of class II, 76.6% of class III and 80.8% of class IV. Likewise, the *in-silico* BDDCS system correctly classified 78.7% of class I drugs, 80.0% of class II, 87.9% of class III, and 71.4% of class IV. On the basis of both *in-silico* BCS/BDDCS systems was defined a biopharmaceutical filter that includes eight possible outputs of drugs, drug-like molecules or NMEs. Potentialities of *in silico* BCS/BDDCS biopharmaceutical filter was evaluated using different drug, drug-like and NME datasets. The results fairly demonstrated the validity of *in-silico* biopharmaceutical systems for provisional classification of oral drugs in early drug discovery and development.

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A NOVEL COMPREHENSIVE APPROACH FOR PREDICTION OF LIGAND BINDING AFFINITIES TO CYTOCHROME P450s

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1. Introduction

Because of the possible effects of Cytochrome P450 (CYP) enzymes on the fate and toxicity of drugs and drug-like compounds, predicting CYP inhibition and binding affinities is of direct relevance to pharmaceutical scientists, medicinal chemists and toxicologists. However, especially for very malleable and flexible proteins such as CYPs, it is a major challenge to calculate ligand-binding affinities or free energies from computer simulation. Here we present an innovative tool that is developed in the context of the IMI-JU *eTOX* project and which aims to determine the binding affinity of small molecules towards CYP450s and in which automated molecular dynamics simulations are applied to accurately and efficiently incorporate effects due to the large flexibility and malleability of CYP450s.

2. Methods

Efficient and accurate free energy models will be presented for flexible drug-metabolizing CYP isoforms. The models are based on molecular dynamics simulations and an iterative linear interaction energy (LIE) method [1,2,3].
Statistical and chemometrics techniques have been employed to assess the applicability domain of such models and the reliability of the predicted affinity.

3. Results

Using our plasticity and free energy models, protein plasticity of the flexible Cytochrome P450 isoform 1A2 could be effectively and accurately included, to obtain ligand-binding free energies (affinities) within experimental accuracy and without a priori knowledge of preferred binding modes of the ligands. This allowed the implementation of these models in a fully automated workflow, in which the structure of the ligand to screen is the only input.
Reliability of predicted binding free energies was evaluated combining the results from several statistical analyses. The proposed protocol was able to provide a qualitative indication on the magnitude of the errors in prediction obtained.

4. Discussion and Conclusions

The combination of simplicity of use and accuracy makes the proposed protocol an attractive and complete tool for *in silico* toxicological screenings of new lead compounds against flexible proteins such as Cytochrome P450s.

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LARGE SCALE FREE ENERGY CALCULATIONS ON CONGENERIC LIGAND SERIES - APPLYING FEP IN PRACTICAL DRUG DESIGN

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One key to success of computational structure based ligand design is the accurate prediction of binding free energies for novel compounds. Molecular Dynamics based free energy calculations (FEC) have been proposed as one of the most suitable methods to reach this goal, which would significantly impact the modern drug design process. However, despite many successful studies, FEC have for more than 20 years failed to fulfill this promise. Possible reasons for this include force field deficiencies, insufficient sampling and difficulties in assessing the quality of simulation results. One of the main obstacles in addressing these issues has been the lack of large scale validation studies on diverse series of ligands, due to the lack of computational resources and the time consuming process of simulation setup and analysis.

Here, we will present results from FEC conducted on several protein-ligand systems of pharmaceutical interest. Covering more than 10 targets and more than 200 compounds, the results offer more than an order of magnitude more data than typical FEC studies and allow statistically valid conclusion about their efficacy. We show that relative binding free energies can be calculated with good accuracy in most cases, typically with R^2 values in the range of 0.5-0.8 and mean unsigned errors (MUE) of less than 1 kcal/mol on average when comparing to experimental data. We show that FEC consistently outperform other binding energy estimation methods such as Docking and MMGBSA. Statistical error estimates from individual calculations are much smaller than observed deviations from experimental results, but improved error estimates can be obtained from constructing redundant graphs of ligand transformations.

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ASSAY RELATED TARGET SIMILARITY (ARTS) AS A METRIC TO COMPARE KINASE BIOACTIVITY PROFILES

Aakash Chavan Ravindranath (1), Rucha K Chiddarwar (1), Oscar Mendez-Lucio (1), Andrew Howlett (1), Robert C Glen (1), QSTAR Consortium (3), Jörg K Wegner (2), Andreas Bender (1)

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The investigation of bioactivity profiles of compounds against sets of protein targets is at the core of current chemogenomics methods.[1] However, how to utilize bioactivity profiles to best assess similarity and dissimilarity of proteins in bioactivity space is much less clear. Hence, in this study, firstly protein target similarities were generated using sequence information, chemical features of ligands, and assay related target similarity (ARTS)[2] of their corresponding ligands, to generate a hierarchical target clustering for a set of 80 kinases and bioactiviy (K_d) measured on 72 compounds[3]. It was found that ARTS-based clustering, as opposed to sequence-based clustering, grouped together targets that have similar gatekeepers, which are known to have a major influence in ligand binding. Moreover, similarity based on ARTS correlates (~0.45) with the structural similarity of different gatekeepers. As a case study, the kinase MEK5 of the STE family is clustered together with TK family members by ARTS. To better understand the reason behind this, we looked at the binding affinity of the well known inhibitor Dasatinib, which is more potent against MEK5 (of the TK family) than against any other STE member, and found as a reason that the binding pocket of the MEK5 has the same amino acid gatekeeper as the TK family members. This allows the compound to bind deeper into the pocket, whereas the other members of the STE family have the larger methionine (M), which blocks the binding site.

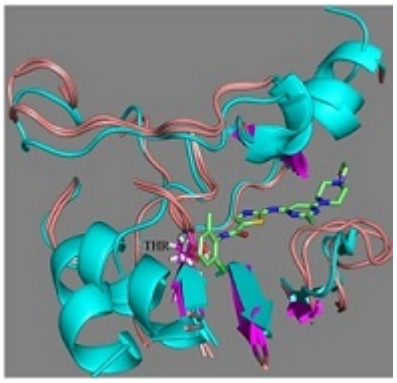

Figure 1. Thr(T) gatekeeper overlap between kinases ABL1,ABL2 and MEK5. Superimposed protein structure of ABL2, ABL1 and MEK5 show the Thr(T) gatekeeper residue at the same position in the binding pocket (pK_d of 10.33, 9.76, 8.48 respectively). The pocket is similar in all the three proteins and as they also share the small gatekeeper Thr(T), the compound Dasatinib binds deeper into the binding pocket, thus making the MEK5 closer in bioactive space to the members of the TK subfamily.

Comparison of the three methods (namely fragment-, sequence-based and ARTS) showed that ARTS outperforms the other two by classifying ~64% of the neighbors in agreement with the number of active compounds shared, whereas the other two methods only classified ~7% and ~11% of the neighbors. ARTS-based clustering also shows that compounds are closer in bioactivity space with a similarity average of 0.41 and standard deviation of 0.244, even though they are diverse in structure space with a similarity average of 0.0793 and standard deviation of 0.11 (similarity based on ECFP4 fingerprints), showing that ARTS is also able to correctly identify bioactivity similarity in the absence of structural similarity. The ARTS method is transferable to other protein families as well. Hence, overall we conclude that ARTS provides a better understanding of protein similarity in bioactivity space, adding knowledge which can be useful in elucidating side effects of ligands and might lead to the repurposing of known drugs for related targets.

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SAR-PLATFORM: AN INTEGRATED PLATFORM FOR BUILDING INTERPRETABLE PREDICTIVE MODELS TOWARD LEAD OPTIMIZATION

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Quantitative structure activity relationship (QSAR) models are widely used for *in silico* prediction of various endpoints during medicinal chemistry optimisation. Non-linear models are the most predictive ones but their key limitation is a lack of interpretability to guide chemists in the design of new compounds with improved properties. A web-based integrated platform, 'SAR-Platform', for enabling substituent-based QSAR model building, prediction and interpretation was developed. Robust linear and machine learning (non-linear) models [1,2]have been built for a series of congeneric compounds based on structural information of R-groups (substituents) around the common scaffold. These models combine the predictive power of modern machine learning techniques with the straightforward interpretability of the familiar Free-Wilson and MMPA (molecular match pair analysis) approaches. Contributions to bioactivity can be conveniently visualized at the fragment level to provide guidance to the medicinal chemist. The SAR-Platform has been applied to several in-house and external data sets and very encouraging results were obtained. We strongly believe that this platform will have wide applicability in lead generation and lead optimization projects to speed up the drug discovery process.

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IN SILICO DOCKING ELUCIDATION OF POSSIBLE TERTIARY COMPLEX COMPRISING THROMBIN, ANTITHROMBIN AND FUCOSYLATED VS. NON-FUCOSYLATED CHONDROITIN SULFATE DERIVATIVES

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Sulfated glycosaminoglycans from mammalian s such as heparin and its derivatives are extensively applied in medical practice as anticoagulant drugs. However their side effects such as hemorrhage and heparin-induced thrombocytopenia, force search for anticoagulants of another nature. Recently, fucosylated chondroitinsulfates (FCS) from echinoderms related to the new class of glycosaminoglycans were found to possess potent anticoagulant and antithrombotic effects. Their efficiency was higher than that for heparinoids. Notably, non-fucosylated chondroitin sulfate did not exhibit any inhibiting activity.

This is explained by the possibility of formation of a tertiary complex comprising thrombin, antithrombin and an FCS molecule. The stability of this complex is determined by the strength of interaction between the inhibitor and the active sites of thrombin and antithrombin and the inhibitor's ability to form simultaneous interactions with the both proteins. It can thus be supposed that linear chondroitin sulfate (Figure 1A) is not able to form such tertiary complexes, while upon introduction of a fucose residue (Figure 1B and 1C) it becomes an effective coagulation inhibitor.

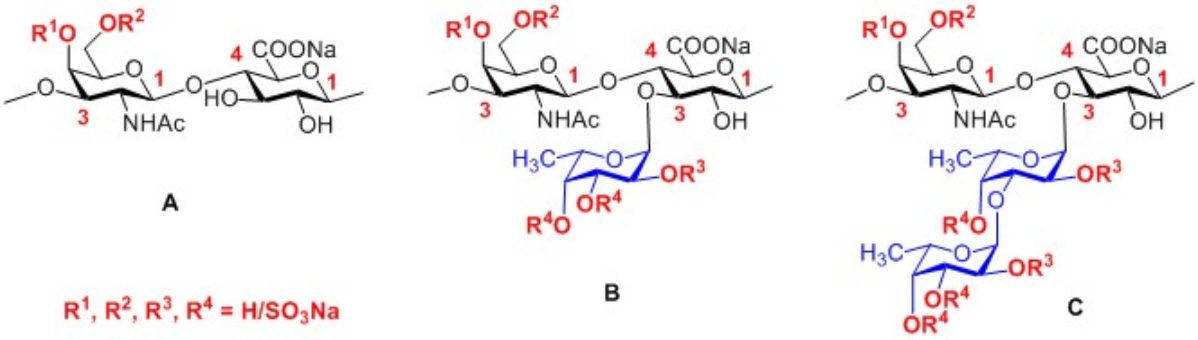

Figure 1. Fragments of a non-fucosylated chondroitin sulfate (A) and of two chondroitin sulfates containing a fucose residue (B) and (C).

During the ongoing studies of FCS, that take place in our laboratory, we have performed a series of docking studies of both fucosylated and non-fucosylated chondroitin sulfate fragments to the active sites of thrombin and antithrombin. Autodock v 4.0 and 4.2 software was used for this purpose. It was found that generally fucosylated derivatives exhibit higher binding energies than fragments of the chondroitin sulfate without fucose. Additionally, molecular dynamics studies allowed us to estimate the minimal length of the oligosaccharide chain necessary for the formation of the tertiary complex.

Acknowledgment. This work was supported by the Russian Scientific Foundation, grant number 14-13-01325.

NOVEL BIOLOGICALLY ACTIVE SHORT PEPTIDES BASED ON HETEROCYCLE SUBSTITUTED NON-PROTEIN AMINO ACIDS: PASS PREDICTION AND SYNTHESIS

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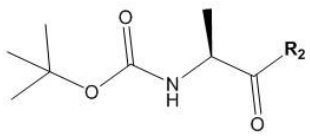
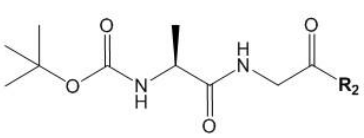
For the last decades the ever-growing interest for chemistry of short peptides was stipulated by their successful application in various fields of medicine. Especially the use of peptide-nature drugs containing non-protein amino acids is of high interest, because for the enzymes it is difficult to recognize the substrate due to unusual groups in the amino acid structure, which slows down proteolysis and prolongs the effect of drugs [1].

The prediction of biological activity spectra via PASS online was done for several virtual formyl and BOC protected di and tripeptides containing methionine, glycine and/or alanine, and heterocyclic substituted non protein amino acides; (S)-β-[4-allyl-3-(piridine-3'-yl)-5-thioxo-1,2,4-triazol-1-yl]-α-alanine (R_1) and (S)-β-[4-allyl-3-(piridine-4'-yl)-5-thioxo-1,2,4-triazol-1-yl]-α-alanine (R_2) [2].

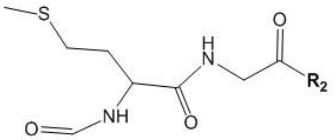
According to the PASS predictions, most peptides have significant biological activity spectra, and likely to be integrin antagonists, inhibitors for molecule cell adhesion, agonists of fibroblast growth factor, inhibitors of ATP proteasomes and drugs for mucositis treatment. The greatest probability of activity being anticipated with tripeptides N-f-(S)-methionylglycyl-R_2, BOC-(S)-alanylglycyl-R_2 and dipeptide BOC-(S)-alanyl-R_2 with Pa values ranging from 0.550 to 0.700.



BOC-(S)-alanyl-R_2

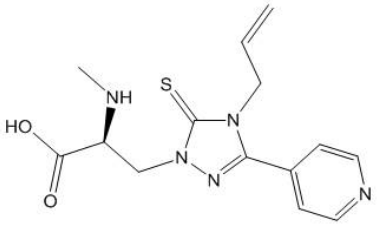


BOC-(S)-alanylglycyl-R_2



N-f-(S)-methionylglycyl-R_2

R_2=



(S)-β-[4-allyl-3-(piridine-4'-yl)-5-thioxo-1,2,4-triazol-1-yl]-α-alanyl

Mentioned peptides were synthesized by the method of activated esters [3]. The influence of synthesized peptides on the activity of hydrolase enzymes (trypsin, proteasome ATPase) is now being studied.

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NEW REGULATORY ELEMENTS IN SERCA2 CA2+ PUMP AS TARGET FOR PHARMACA DEVELOPMENT IN HEART FAILURE TREATMENT

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Heart failure (HF) is a cardiovascular disease characterized by a progressive and chronic deterioration of heart muscle contraction. Previous research has indicated that HF is accompanied by an abnormal Ca^{2+} cycle in cardiomyocytes, characterized by a disturbed activity of the cardiomyocyte specific Sarco-(endo)plasmatic reticulum Ca^{2+} ATPase 2a (SERCA2a).
Detailed lab animal testing in HF models has shown that an increase in the Ca^{2+} affinity of SERCA2a stimulates its pump activity and raises the chances of survival.

To this end, we adopt a novel strategy of increasing the Ca^{2+} affinity of SERCA2a in HF based on unique molecular characteristics of the alternative splice variant SERCA2b that only differs from SERCA2a in its C-terminal region. Owing to the presence of a 49 aminoacid C-terminal tail (2b tail) in SERCA2b, compared to a 4 aminoacid tail in SERCA2a, SERCA2b demonstrates a higher Ca^{2+} affinity opposed to SERCA2a.

By using molecular dynamics simulations and molecular docking studies together with mutagenesis experiments, we try to unravel the molecular basis for the mode of action of this 2b tail. Our goal is to design small molecules that can mimick the activity of the 2b tail on SERCA2a in treatment of HF.

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PEPTIDE BINDING PREDICTION TO HLA-DQ PROTEINS - A PROTEOCHEMOMETRIC APPROACH

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Major histocompatibility complex (MHC) proteins class II, are glycoproteins binding within the cell to short peptides with foreign origin, called epitopes, and present them at the cell surface for inspection by T-cells. Apart from presenting foreign antigens, they are able to present also common self-antigens and trigger autommune diseases as coeliac disease and diabetes mellitus type 1.

The HLA-DQ proteins are human MHC class II proteins. They are extremely polymorphic – more than 400 DQA1 and DQB1 proteins are listed in the IMGT/HLA database. The polymorphism is located mainly in the peptide binding site. In the present study, we apply a proteochemometric approach to derive a model for prediction of peptide binding to HLA-DQ proteins. Proteochemometrics is a specific QSAR approach designed to deal with ligands binding to multiple proteins. The training set in the present study consisted of 2995 known binders to the five most frequent HLA-DQ alleles: DQA1*03:01/DQB1*03:02, DQA1*05:01/DQB1*03:01, DQA1*01:02/DQB1*06:02, HLA-DQA1*04:01/DQB1*04:02, and DQA1*01:01/DQB1*05:01. The sequences of peptides and proteins were described by three z-descriptors relating to hydrophobicity, steric effects and polarizability of amino acids. Cross terms accounting for the protein-peptide interactions also were included.

The derived QSAR model was validated by an external test set of 660 HLA-DQ known binders and non-binders. The correlation coefficient between predicted and observed binding affinities r^2_{pred} was 0.807. The derived model was implemented into a web server for binding predictions freely available at http://www.pharmfac.net/EpiTOP.

QSAR METHOD FOR METABOLISM SITE PREDICTION BASED ON XENOBIOTIC STRUCTURAL FORMULAS AND PASS ALGORITHM

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Many xenobiotics, including drugs, are metabolized by multiple enzyme systems in the human organism; the main set of enzymes is the cytochrome P450 superfamily. Computational predictions of interactions with cytochromes P450 can increase the efficiency and decrease the cost and time of drug discovery and development.

We have created novel QSAR method [1], which predicts sites of metabolism (SOM) of xenobiotics using only information about 2D structural formulas of molecules. This method based on new descriptors (modification of MNA descriptors [2]) and the program PASS algorithms [3, 4]. It was applied for prediction of regioselectivity of 3A4, 2C9, 2C19, 2D6 and 1A2. We have prepared different training sets for five P450 isoforms consisted of both positive examples (structure with one marked atom, which are real SOMs of the appropriate P450 isoforms) and negative examples (structure with one marked atom, which are not real SOMs of the appropriate P450 isoforms).

Leave-one-out cross-validation (LOO CV) procedure was performed for validation of prediction quality and the Invariant Accuracy of Prediction (IAP) values were calculated. The average IAP for five isoform is about 89%.

The external validation was made with evaluation sets containing data on biotransformations for 57 cardiovascular drugs. An average IAP of regioselectivity for evaluation sets was 0.83. It was shown [1], that the proposed method exceeds accuracy of SOM prediction by RS-Predictor [5] for 1A2, 2D6, 2C9, 2C19, and 3A4 and is comparable to or better than SMARTCyp [6] for 2C9 and 2D6.

We have extended our method on the prediction of glucuronidation sites, catalyzed by UDP-glucuronosyltransferase (UGT) and made it available at the web site (http://way2drug.com/somp/).

Acknowledgments: The study was supported by RSCF grant 14-15-00449

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WAY2DRUG – COMPUTATIONAL PLATFORM FOR BIOACTIVITY PREDICTION AND COLLABORATIVE DRUG DISCOVERY

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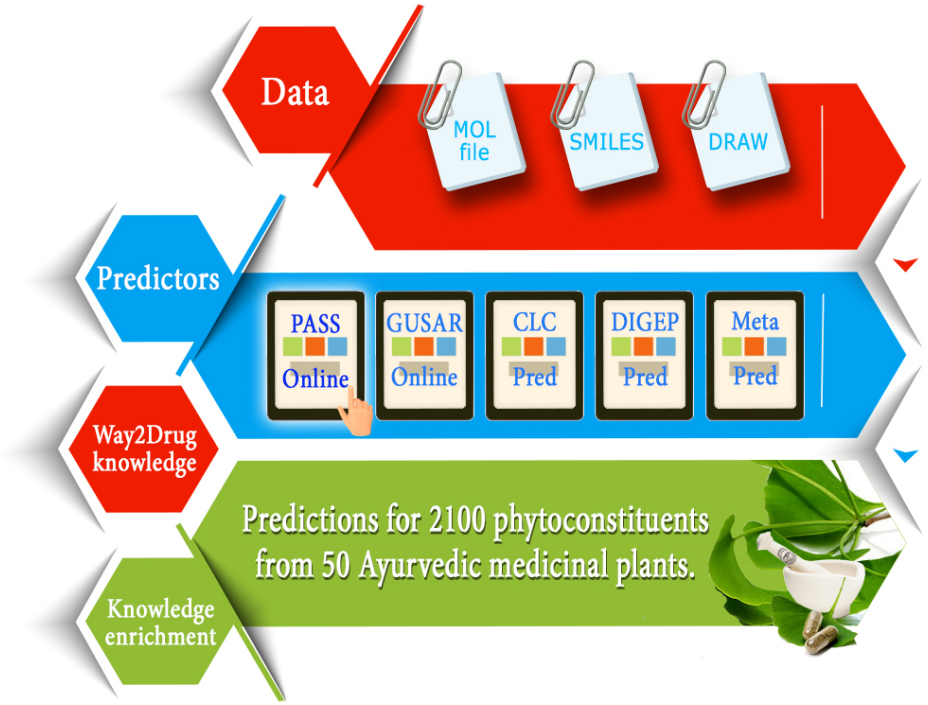
Chemo- and bioinformatics today deal with a "data deluge" derived from the availability of high-throughput screening results obtained with postgenomic technologies. Plethora of (Q)SAR and molecular modeling methods designed to assist researcher in effective retrieval of the available data sometimes leads to a difficult challenge: which method(s) to choose?

The quality of (Q)SAR models depends on (1) representativity of the training set; and (1) accuracy and predictivity of the methods used for analysis of (quantitative) structure-activity relationships. Since the reasonable quality of our computational tools PASS and GUSAR has been already demonstrated in many internal and independent studies [1-3], we decided to make attempt on improvement of the training set. Utilization of data on biological activity of drug-like compounds from several public sources (PubChem, ChEMBL, DrugBank, etc.) does not guarantee that the compounds submitted for bioactivity prediction by particular user will fall to the (Q)SAR model applicability domain. Thus, we decided to create a portal Way2Drug [4], which provide several web-resources for bioactivity prediction jointly with the interface for input of novel information by the user. This additional information may be used to improve the quality of the (Q)SAR models by re-training the predictive tools.

Currently five predictive tools are presented at Way2Drug portal: PASSOnline predicts over 4000 kinds of biological activity; GUSAROnline predicts acute rat toxicity and interaction with antitargets; CLC-Pred predicts cytotoxicity for tumor and normal cell-lines; DIGEP-Pred predicts drug-induced changes of gene expression profiles; Meta-Pred predicts sites of metabolism by five major drug-metabolizing isoforms of P450. Results of bioactivity predictions for 2100 phytoconstituents from 50 Ayurvedic medicinal plants are presented as well [4].



Acknowledgements. This work was partially supported by RFBR grant No. 12-07-00597.

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COMBATING BACTERIAL ANTIBIOTIC RESISTANCE: NOVEL LACTAMASE INHIBITORS

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β-lactams represent the most widely used group of antibiotics with broad spectrum of antibacterial activity. However, most bacteria can develop antibiotic resistance, typically caused by beta-lactamase enzymes. Existing inhibitors of beta-lactamases can prevent antibiotic degradation arising from beta-lactam ring hydrolysis, but due to the additional development of resistance to these compounds, they are not sufficiently effective. Thus, the identification of new inhibitors and new mechanisms of lactamase inhibition is a priority.

To address this challenge, we computationally screened 8 million organic molecules using the ViCi software (http://www.embl-hamburg.de/vici), which we specially developed for this purpose. The software permits the rapid screening against a known inhibitor template and selects the closest matching compounds in terms of shape and electrostatic composition. Four known low-affinity lactamase inhibitors were given to the software as a starting point.

Despite the ubiquity of the various strains of beta-lactamase, access to the full set of characterized clinical samples is a big problem. Biobank of recombinant strains of *E.coli* - producing a variety of class A beta-lactamases, and efficient expression system for production of the recombinant class A beta-lactamases in *E.coli* cells have been elaborated in order to permit their study *in vitro* and *in vivo*.

Recombinant TEM-1 enzyme was produced and used to assay the top compounds suggested by ViCi screening. Two new potential inhibitors bound to the allosteric site of TEM-1 were identified, both having an order of magnitude higher *in vitro* affinity for the enzyme than their template. To further develop the identified lead compounds we look for ways of increasing their solubility and reducing their expected toxicity. Chemical design and modification of the lead compounds as well as their *in vitro* tests are now in progress.

X-ray crystal structure determination of the native enzyme and its complexes with ligands is the next step in testing of proposed inhibitors. The crystal structure of recombinant TEM-1 lactamase has been solved to a resolution of 2.0 Å. The ViCi software will then be used to identify compounds for the next iteration of screening. Docking protocols, validated by crystallography, will also be used to refine the results, aiding our rapid convergence to more avidly binding compounds. The current status of the X-ray crystallographic, computational and laboratory studies will be presented.

NEW MORE POLAR SYMMETRICAL BIPYRIDINIC COMPOUNDS: STUDY OF SETTING UP A NEW SCAFFOLD FOR THE INHIBITION OF CHOLINE KINASE α1 (ChoKα1)

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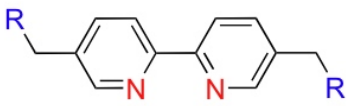
Choline kinase (ChoK) is the first enzyme of the Kennedy pathway for the biosynthesis of phosphatidylcoline, the mayor phospholipid component of mammalian cells and a precursor of second messengers that can modulate growth or survival pathways. In human tumours, the enzyme Choline Kinase (ChoK) is overexpressed and, consequently, ChoK inhibitors have proven to be effective antitumoral drugs *in vitro* and *in vivo*.

Research of the anti-tumor properties of biscationic compounds has received significant attention over the last few years. A novel family of 1,1'-([2,2'-bipyridine]-5,5'-diylbis(methylene))bis-substituted bromide (**9a-k**), containing two nitrogen atoms in the spacer of the linker that connect the biscationic compounds, considered as hypothetical hydrogen bond acceptors, were synthesized and evaluated as choline kinase inhibitors and their antiproliferative activity against six cancer cell line. Just as we predicted, the most promising compounds in this series are 1,1'-([2,2'-bipyridine]-5,5'-diylbis(methylene))bis(4-(methyl(phenyl)amino)-quinolinium bromide derivatives **9g-I**, that significantly inhibit cancer cell growth at even submicromolar concentrations, especially against leukemia cells, and also inhibit the ChoKα1 with good or moderate values, as predicted initials docking studies. In addition the most active compound **9h** remarkably induce apoptosis in two cells lines following the mitochondrial pathway.



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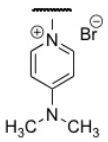
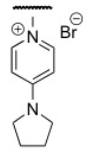
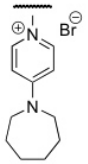
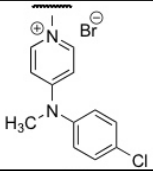
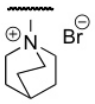
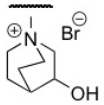
R						

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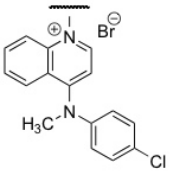
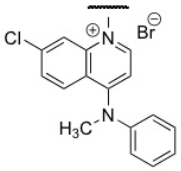
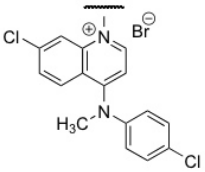
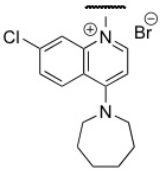
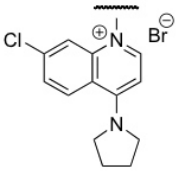
R					

PHARMACOPHORE-BASED VIRTUAL SCREENING TO DISCOVER NEW ACTIVE COMPOUNDS FOR HUMAN CHOLINE KINASE α1

Lucía Serran-Aguilera (1), Roberto Nuti (2), Laura Comas (4), Luisa-Carlota López-Cara (1), Julian Pardo (4), Antonio Macchiarullo (2), Antonio Entrena (1), Ramón Hurtado-Guerrero (3)

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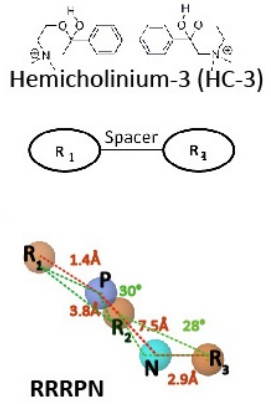
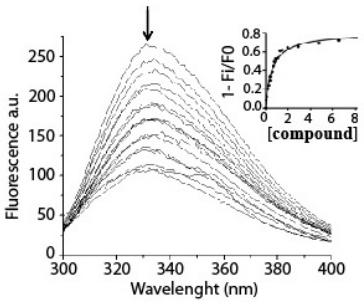
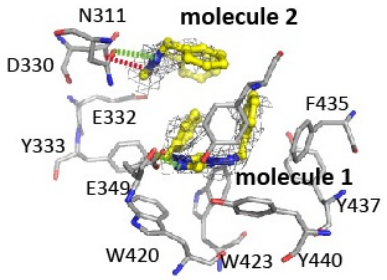
Choline kinase (CK) catalyses the transfer of the ATP g-phosphate to choline to generate phosphocholine and ADP in the presence of magnesium leading to the synthesis of phosphatidylcholine. Of the three isoforms of CK described in humans, only the α isoforms are strongly associated to cancer and have been validated as drug targets to treat this disease[1]. Over the years, a large number of HsCKα biscationic inhibitors based on Hemicholinium-3 (HC-3) have been developed[2], though the relevant common features important for the biological function have not been defined. Here, selecting a large number of previous HC-3-based inhibitors[3], we discover through computational studies a pharmacophore model that is formed by five moieties that are included in the 1-benzyl-4-(N,N-phenylmethyl)pyridinium fragment. Then, using a pharmacophore-based virtual screening, we identified 6 molecules that showed binding affinities to HsCKα1 in the low μM range. Finally, protein crystallization and growth inhibition assays of tumor cells with these compounds were performed suggesting that one of these molecules is bound to the choline and ATP-binding site while the compound with better affinity for the enzyme shows EC50 values in the low μM range. In conclusion, we show a pharmacophore model that not only has allowed us to dissect the structural important features of the previous HC-3 derivatives but also to discover small monocationic-compounds with good ligand efficiencies.







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DOCKING STUDIES JUSTIFYING THE CHOLINE KINASE INHIBITION OF A SERIES OF 6-BENZYLTHIO-9H-PURIN-9-YL-PYRIDINIUM DERIVATIVES

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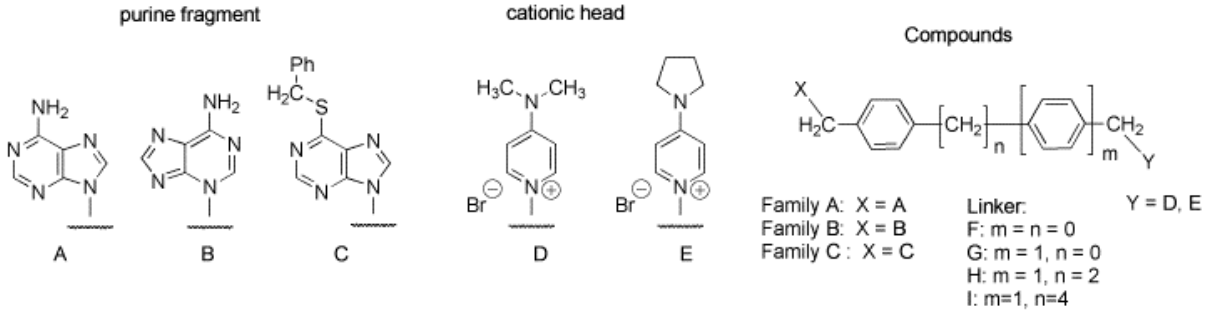
Choline kinase (ChoK) is the first enzyme of the Kennedy pathway for the biosynthesis of phosphatidylcoline, the mayor phospholipid component of mammalian cells and a precursor of second messengers that can modulate growth or survival pathways. In human tumours, the enzyme Choline Kinase (ChoK) is overexpressed and, consequently, ChoK inhibitors have proven to be effective antitumoral drugs *in vitro* and *in vivo*.

Recently, the rational design, synthesis and biological evaluation of a series of non-symmetrical ChoK inhibitors bearing a purine moiety (**A, B or C**), a 4-substituted pyridinium ring (**D** or **E**), and a linker (**F**, **G**, **H** or **I**) that connects both fragments has been published. [1-3] In the first paper,[1] two families of these compounds were obtained (Families **A** and **B**). In the first family (Family **A)** the linker is connected to the adenine *N*-9 nitrogen atom, while in the second family (Family **B**) the linker is connected to the adenine *N*-3 nitrogen atom. In the second paper,[2] a new series of non symmetrical ChoK inhibitors was published (Family **C**). In this new family, the 6-NH_2 amino group was substituted by a 6-benzylthio fragment in order to increase the lipophilicity of these new molecules to obtain better antiproliferative activity, obtaining really good activity against HeLA cell line. In the third paper, the ChoK inhibition activity of compounds of Family C has been published.[3]

Docking studies were performed in order to design these compounds and to justify the ChoK inhibition activity. Two of these molecules have been crystalized in complex with ChoK-a1. [4,5]



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TOWARDS PHARMACOPHORE AND DOCKING-BASED VIRTUAL SCREENING OF HUMAN P2Y12 RECEPTOR ANTAGONISTS WITH THE HOMOLOGY-MODELED PROTEIN STRUCTURE

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The identification of important chemical features of human $P2Y_{12}$ inhibitors will be helpful to develop anti-coagulation agents. The homology model of human $P2Y_{12}$ receptor was built from three templates. Ligand-based pharmacophore models were generated using the known active human $P2Y_{12}$ inhibitors and these models have been employed in docking-based virtual screening to identify the leads from various databases. The hit molecules are sorted out by applying several filters such as fit values of the pharmacophore models, Lipinski's rule of five and protein-inhibitor interaction fingerprints. Therefore, these results should be useful to develop new $P2Y_{12}$ inhibitors.

PREDICTING DEGRADATION OF ACTIVE PHARMACEUTICAL COMPOUNDS IN FORMULATIONS USING QUANTUM CHEMISTRY

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Understanding and controlling degradation of the active pharmaceutical ingredient is important for successful pharmaceutical development. Knowledge of degradation pathways is important when selecting excipients to give the most stable formulation, predict shelf life, to give advice on compounds toxicity or to avoid late stage surprises.

The major degradation pathways are hydrolysis and oxidation and the two most common oxidation mechanisms are peroxide oxidation and autoxidation. As oxidative degradation is less tractable to assay, this work will focus on degradation by autoxidation.

A quantum chemical approach using B3LYP was successfully applied to predict autoxidation. We have modelled a large number of reactions and the results are shown to be predictive and the approach is now routinely applied in our in-house projects. This approach has been shown to decrease the number of experiments needed to solve degradation issues in both early and late stage development.

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"Prediction of drug candidates' sensitivity towards autoxidation; computational estimation of C-H dissociation energies of carbon centred radicals" Andersson, T; Evertsson, E; Broo, A; accepted for publication in Journal of Pharmaceutical Sciences

IS THE NAIVE BAYES (Q)SAR APPROACH ACTUALLY "NAIVE"?

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We have previously proposed the local correspondence concept [1], which is based on the fact that most biological activities of organic compounds are the result of molecular recognition, which in turn depends on the correspondence between particular atoms of the ligand and the target. Using this concept we have developed a consistent system of atom-centered neighborhoods of atoms descriptors (MNA, QNA, and LMNA), and have implemented them in several SAR/QSAR/QSPR modeling approaches [2-5]. For instance, MNA descriptors have been employed for predicting biological activity spectra of organic molecules in the PASS software for more than 20 years. PASS has been used by many scientists for discovery of new pharmaceutical agents in different therapeutical fields [2]. The PASS algorithm was derived from the naive Bayesian approach, which is usually considered as "too simple", but it provides high accuracy of recognition in many cases [5]. We have found that this can be explained based on the fact that ligand-target complex binding energy is an integral effect of each of the atoms of a molecule interaction with the appropriate target sites. Contribution of each atom is depended on the atom itself and influence of its environment. A simple assumption about distribution of the ligand-target complexes affinity in the chemical space gives directly the naive Bayes approach for affinity estimation.

We have found physically based distribution of the affinity of ligand-target complex and proposed a new PASS algorithm. It uses the traditional PASS training set with categorical representation of the biological activities. Nevertheless, the ligand-target affinity estimations are calculated for each of the activity types in the new PASS Affinities software. These estimations are proportional to the affinity values like $\log(1/K_d)$, where K_d is a dissociation constant for the appropriate ligand-target complex. Prediction accuracy of PASS Affinities is close to that of traditional PASS, but its prediction results can be interpreted in more reasonable physical-chemical meaning.

Acknowledgements. The work is partially supported by RFBR grant No. 12-07-00597.

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CHEMOMETRIC AND IN SILICO STUDY OF BLOOD-BRAIN BARRIER PERMEATION FOR ALPHA ADRENERGIC AND IMIDAZOLINE RECEPTORS LIGANDS

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Blood–brain barrier permeation including rate of brain penetration (logPS), brain/plasma equilibration rate (logPS-brain), and extent of blood-brain barrier permeation (logBB) calculated in silico [1] for 29 drugs interacting with imidazoline and α-adrenergic receptors was investigated in this study.

Quantitative structure-property relationship (QSPR) analysis, principal component analysis (PCA) and hierarchical clustering analysis (HCA) were performed in order to examine correlations between blood-brain permeation parameters (logPS, logPS-brain, and logBB), as dependant variables and experimentally obtained chromatographic retention parameters ($\log K_w$ at pH 4.4, slope (S) at pH 4.4, $\log K_w$ at pH 7.4, slope (S) at pH 7.4, $\log K_w$ at pH 9.1, and slope (S) at pH 9.1), capillary electrophoresis migration data (μ_{eff} at pH 4.4, μ_{eff} at pH 7.4, and μ_{eff} at pH 9.1), and calculated molecular descriptors [2,3], as independent variables.

In the created QSPR models, hydrophilicity (Hy) and H-indices (H7m) were selected by use of partial least square (PLS) methodology [4] as important parameters negatively correlated with both logPS and logPS-brain, while topological polar surface area (TPSA(NO)) was chosen as molecular descriptor negatively correlated with both logPS and logBB. In the PCA/HCA clusters, formed on the basis of chromatographic, electrophoretic and molecular properties of drugs, significant positive correlations were obtained between the slope (S) at pH 7.4 and logBB in A/B cluster and between the $\log K_w$ at pH 9.1 and logPS in C/D cluster.

Upon the results of the performed chemometric and in silico analysis the reported theoretical investigation could be used as simple and reliable tool for evaluation of brain penetration process and initial ADMET study of novel α-adrenergic and imidazoline receptors ligands.

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EU-OPENSCREEN –NEW TOOLS FOR LIFE SCIENCE RESEACH IN EUROPE

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EU-OPENSCREEN is a pan-European research infrastructure initiative on the ESFRI roadmap (European Strategy Forum on Research Infrastructures). It aims at enabling academic chemical biology research to develop novel research 'tools' (i.e. chemical inhibitors or activators of biological targets) for all areas of the Life Sciences (incl. molecular, cell, plant, structural and microbiology; synthetic and medicinal chemistry; pharmacology and early drug discovery etc.).

EU-OPENSCREEN offers to scientists access to unique shared resources and expertise. These include latest screening technologies, follow-up chemistry services for hit optimization, a unique compound collection composed of commercial and proprietary compounds, and a database containing validated output from the screening centers in a public as well as pre-release environment. Chemists are invited to include their compounds into this jointly-used compound collection which is screened against a wide range of biological assays. This allows chemists to annotate their compounds with rich information about structure-activity data.

Recently we describe a collaborative effort to define and apply a protocol for the rational selection of a general-purpose screening library, to be used by the screening platforms affiliated with the EU-OPENSCREEN initiative [Horvath, D. et al. ChemMedChem. 2014 Jul 15. doi: 10.1002/cmdc.201402126]. It is designed as a standard source of compounds for primary screening against novel biological targets, at the request of research partners. Given the general nature of the potential applications of this compound collection, the focus of the selection strategy lies on ensuring chemical stability, absence of reactive compounds, screening-compliant physicochemical properties, loose compliance to drug-likeness criteria (as drug design is a relevant, but not exclusive application), and maximal diversity/coverage of chemical space, aimed at providing hits for a wide spectrum of druggable targets.

This poster presentation is on behalf of the whole EU-OPENSCREEN consortium.

[(cym)Ru(OH2)(2-pybzIm)](TfO)2 FORMS DIMERS IN SOLUTION. MONOMER FORMS INTERCALATED-COVALENT COMPLEXES WITH DNA

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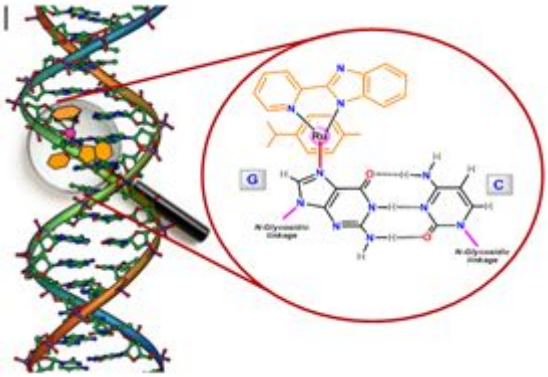
[(cym)Ru(OH_2)(2-pybzIm)]($TfO)_2$, **[4c](TfO)$_2$,** is a ruthenium complex prone to dimerization both in solution and in the solid state.[1] X-Ray measurements have shown that the dimer species are formed by π-π stacking interaction of the benzimidazole ligand and H-bonding between the water molecules coordinated to metal and the ligand N site. The T-jump kinetic curves due to the 2D ↔ D_2 equilibrium recorded in the microsecond time scale have allowed us to determine the formation (k_f) and dissociation (k_d) kinetic constants and the dimerization constant, $K_d = k_f / k_d = (8.9 \pm 1.4)\times10^3$ M^{-1} at I = 0.1 M ($NaClO_4$).[2]



To our knowledge, Ru(II) dimers in solution had not been reported hitherto, implying that in some instances the monomer can display even higher biological activity. The T-jump experiments, UV-Vis and viscometry measurements as a function of time, and circular dichroism, viscometry and melting temperature measurements at different concentrations along with 2D ^1H-^1H ROESY spectra have shown that the monomer reacts with DNA to yield the bifunctional intercalated (through the benzimidazol ligand)-covalent (Ru/N7G), **[4c](TfO)$_2$/DNA, c**omplex. The cytotoxic activity of **[4c](TfO)$_2$** was evaluated in A549 cell line from human lung carcinoma by the MTT cell viability assay.

Acknowledgement. The financial support by the Spanish Obra Social "la Caixa" OSLC-2012-007 and Junta de Castilla y León (Fondo Social Europeo, project BU-299A12-1), Spain, is gratefully acknowledged.

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HIDING IN TREES: SELECTING INTERESTING STRUCTURAL PATTERNS IN PUBLICLY AVAILABLE HIV1 RT LIGAND DATA

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HIV1 reverse transcriptase (RT) inhibitors and drug-resistant mutations over the recent past have led to an increasing amount of data regarding chemico-biologicalactivity space. This data allows chemoinformatics to understand the structural patterns of known active and inactive chemicals and their chemotypes. To understand the extent of the interesting fraction of synthesizable chemistry for HIV1 RT and what chemotypes prevail, the publicly available ligands, their different kind of chemotypes, which have experimental activity data, have been investigated and analyzed.

All data on HIV1 RT used was extracted from ChEMBL v. 18. The database queries resulted in 19640 bioactive ligands. After extensive curating, the final dataset consisted of 750 compounds with reported Kd and Ki values, which were measured against wild type and 13 different HIV1 RT mutants: K103N, L1001I, Y181C, V106A, Y188L, Y181I, M184V, G190A, V179D, K65R, P236L, P119S, T165A. The curated data was analyzed using a hierarchical classification of common core structures (as implemented in Scaffold Hunter) that resulted in patterns of known and virtual scaffolds, mapped with experimental activities and physico-chemical structural properties.

The results showed integrated visualization and analysis of the chemical and biological activity data. Altogether, six different ‘parent’ groups were discovered: carbocycles, N-, O-, N,O-, N,S-, and S-heterocycles, and the majority of the scaffolds contain at least two rings. The most widespread ‘parent’ types or inner core structures are N-heterocycles and N,O-heterocycles. To date, 13 approved drugs for HIV1 RT are used: abacavir, delavirdine, didanosine, efavirenz, emtricitabine, etravirine, lamivudine, nevirapine, rilipivirine, stavudine, tenofovir disoproxil, zalcitabine, and zidovudine. A scaffold tree was also constructed for approved drugs, where 12 drugs out of 13 contain core N-heterocycles and 1 molecule contains an N,O-heterocycle as a ‘parent’ structure. The approved drugs scaffold tree largely coincides with the above mentioned data scaffold tree. Analyzing these virtual scaffolds allows to discover the ‘holes’ not sufficiently covered by the compounds in the database and may be promising starting points for further investigation.

CHEMINFORMATICS: A DIRTY JOB, BUT... ANY REMEDY IN SIGHT?

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Cheminformatics is a dirty business, there is “dirt” on all levels of the process:

(A) There is dirt on the input level; databank or SD files may contain “duplicates” (What is a “duplicate” anyway? Two tautomers of the same molecule?), or “almost-duplicates” (perhaps two protonated forms of one molecule?), even “false duplicates” (for example two different names for the same molecule?) and many more flavors.

(B) Most certainly, also output is “polluted” - solutions which cheminformatics tools generate contain unwanted data: Dockers, for example, typically generate hundreds of solutions. Which of those is the diamond? Most others will typically be only “waste”.

(C) Finally, the third level of noise is on the visual result / analysis level: Anything confusing or distracting the eye from the relevant when analysing data.

The obvious solutions are to maximize the signal-to-noise ratio, but automatisms cannot be applied everywhere - or need a degree of adjustability. In this poster, I will present an overview of collaborative approaches to several of the very typical contamination and dissecting problems. Most of the software presented has been developed by our preferred academic partner, the Rarey Group at ZBH Hamburg University, in collaboration with typically a Big Pharma company, and ourselves.

For (A), the input level, a clear, unambiguous molecular representation in the computer is necessary. File format dependencies must be avoided as good as possible. This is achieved within the NAOMI framework [1] which has been developed during the last few years. Based on the NAOMI framework, a graphical frontend, including easy removal of duplicates of all sorts has been embedded in form of the tool MONA [2].

As an example for (B), the output level, it shall be shown how a statistics-based torsional analysis and subsequent visualization can help to distinguish mediocre from good after docking. This has been realized in the TorsionAnalyzer software [3] in collaboration with ZBH and Roche.

For (C), the visual analysis phase, a widespread example is PoseView [4] which simplifies matters drastically by omitting one dimension. PoseView draws 2D sketches from 3D protein-ligand complex input. Another example is using modern graphics card capabilities to visualize HYDE [5] affinities, as in the latest BioSolveIT tool for Lead Optimization, SeeSAR [6].

Almost all these tools are freely available for academic research at www.biosolveit.de/techtrans.

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QSAR MODELLING OF THE REVERSE TRANSCRIPTASE INHIBITORS USING LARGE HETEROGENEOUS DATA SETS FROM THE INTEGRITY DATABASE

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The information contained in the large databases (DB) of chemical compounds, which represent an important source of data sets for QSAR modeling, is characterized by the variability of activity values measured in different experiments and/or by different laboratories [1]. Currently two most popular databases on structures and biological activity are Thomson Reuters Integrity DB [2] and CHEMBL [3].

The purpose of our study is to investigate how the inconsistency of heterogenic data in the training sets influences on the quality of QSAR models that may be obtained, and propose the approach to improve the accuracy and predictivity of the models based on the data sets from INTEGRITY and CHEMBL databases (DB).

We used data sets of reverse transcriptase (RT) inhibitors extracted from the Integrity and CHEMBL DB to study the quality of QSAR models built using the data sets associated to different methods and materials of biological testing. QSAR models were built using computer program GUSAR (General Unrestricted Structure-Activity Relationships) [4, 5], which superiority was shown in comparison with several other popular methods [4]. The accuracy and predictivity of the obtained QSAR models was estimated using leave 30% out cross-validation (LMO), 5 fold cross-validation and y-randomization (y-rand) procedures.

QSAR models built on the basis of the total heterogeneous datasets included all compounds that were tested on RT inhibiting activity have very poor accuracy and predictivity. We developed a general automated workflow, which allows splitting data extracted from the databases onto sub-sets grouped according to the materials and methods of testing. The proposed workflow allows combining data from INTEGRITY and CHEMBL databases as well. Using presented workflow we determined basic parameters that allow forming more homogeneous datasets using INTEGRITY and CHEMBL databases. Data from INTEGRITY can be automatically divided onto sub-sets according to the material, method of biological testing and data source (journal paper, abstract of conference or patent documents). Data from CHEMBL can be automatically divided onto sub-sets according to the source of data only. For obtained subsets we have built QSAR models and tried to associate the accuracy and predictivity of the models with the specific parameters of the sub-sets preparation. Data sets from INTEGRITY can be divided onto two major groups – (1) data set corresponded to the PCR-based methods and data set corresponded to the cell-based methods of biological testing. The accuracy of QSAR model is higher in general when data set of the first group is used as the training set in comparison to the second group (PCR-based: R^2 = 0.99,Q^2 = 0.67;LMO = 0.60,y-rand = -0.29; cell-based: R^2 = 0.66; Q^2 = 0.56; LMO = 0.52, y-rand = -0.09). We suggested such a distinction is associated with the multiple factors which may influence on the IC_{50} estimation in the experiment when cell lines are used as a material (in cell-based methods of testing). The models with the best accuracy and predictivity was obtained for data sets corresponded to the radioactivity assay (PCR-based method, R^2 = 0.96; Q^2 = 0.69; LMO = 0.71, y-rand = -0.30). The best results for the sub-sets corresponded to the cell-based assay were obtained for the data set corresponded to the antigen assay using mononuclear cells (blood), human (phytohemagglutinin-stimulated): R^2=0.97; Q^2=0.93; F=13.3; LMO=0.91; y_{rand}=-0.31. Twenty three models were built using sub-sets from CHEMBL data sets obtained according to the certain source of biological information (specific paper). We revealed that such preprocessing of the data allows obtaining better models in comparison of using CHEMBL data without any division onto the subsets. The combination of the data from CHEMBL and INTEGRITY database was not achieved due to the different data source used and absence of the structured data about material and method of biological testing in CHEMBL.

QSAR models obtained with more consistent and homogeneous training sets have better accuracy and predictivity in comparison with the initial data sets. However the combining of data from several different large-scale databases is open problem due to the absence of the unified terminology of the material and method of biological testing of chemical compounds in the available databases.

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DISINFECTION ACTIVITY COEFFICIENT OF SOLUTION - DACS IN RELATION TO MICROBIAL ACTIVITY OF DISINFECTANTS ON STAPHYLOCOCCUS AUREUS

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Knowing antiseptic activity of chemical disinfectant substances has great practical value. It is evidential that there is the need for defining parameter for comparing various chemical aqueous disinfectants. Phenol coefficient shows how many times bactericidal activity of examined disinfectant is greater or lower than bactericidal activity of standard phenol solution (5%). Suitability of phenol coefficient for evaluation of nonphenolic disinfectants is still opened question.

The aim of this study is to develop a new empirical coefficient which is capable to express the various physic-chemical properties of disinfectant solutions on bactericidal activity. The basic duty of this parameter (Disinfection Activity Coefficient of Solution - DACS) is to express capability for comparison and prediction of disinfectant activity. The DACS index, which is the sum of four terms (fluidity, surface tension, redox potential and osmolality), results in good correlation with the activity at different disinfectant aqueous solutions. The DACS index can be calculated using additive and statistical models. The usefulness of DACS is demonstrated for analyze of bactericidal activities on different disinfectant solutions containing boric acid, chlorhexidne, chlorhexidine with cetrimide, chloroxylenol, chlorophen, eosin, hydrogen peroxide, phenyl mercury borate, povidon-iodine, thiomersal, tosilchloramide and phenol. Results for bactericidal activities obtained from microbiological tests on Staphylococcus aureus was compared with activities predicted with DACS. As the conclusion, it is considered good correlation between experimental and calculated values for bactericidal activity.

BULK PROPERTIES OF HYPERCROSSLINKED POLYSTYRENE NETWORKS: A MULTISCALE SIMULATION

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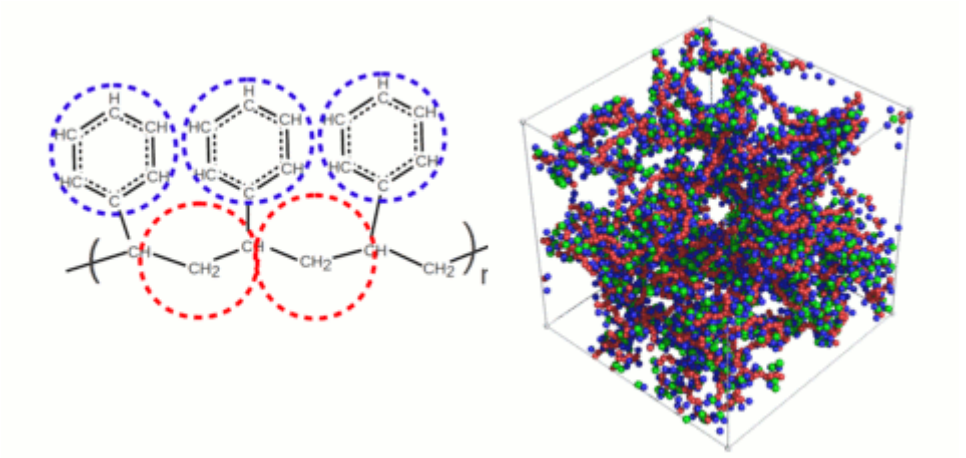
Hypercrosslinked polystyrene networks are known since 1970s [1-2]. Hypercrosslinked networks with extremely high density of crosslinks swell in any solvents, whether good or poor, polar or non-polar, and are capable to absorb virtually any substances and gases. The products based on hypercrosslinked polystyrene are available for commercial, scientific and medical applications. The hypercrosslinked gels are mainly formed by fast and multiple crosslinking of macromolecules swollen in a good solvent. Simultaneously formed links thus lead to formation of a quenched conformational state with a specific inner porous structure and large specific surface.

The influence of the synthesis conditions on the elastic modulus of hypercrosslinked polystyrene networks was studied by means of computer experiment. The framework of the multiscale simulation had been developed by the authors [3] and comprises the following consecutive stages: molecular dynamics atomistic simulation of a polystyrene solution, the mapping of atomistic structure onto coarse-grained model (Figure 1a), the crosslink formation, the reverse mapping, the relaxation of the structure and the measurements of the bulk properties. The synthesis of hypercrosslinked polystyrene was performed for different polymer concentrations and various degrees of cross-linking. It was shown that the calculated values of the elastic modulus are in reasonable quantitative correspondence with experimental data. The elastic modulus increases with increase of the number of crosslinks and the density of polymer.

A B



Figire 1. Coarse-grained model of polystyrene chain (a) and hypercrosslinked polystyrene network in coarse-grained representation (b).

This work was supported by the Russian Foundation for Basic research (project no. 14-03-31616).

The computations were performed using the resources of Supercomputing Center of Lomonosov Moscow State University [4].

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SELF-ASSEMBLY OF AN AMPHIPHILIC MACROMOLECULE UNDER SPHERICAL CONFINEMENT: AN EFFICIENT ROUTE TO GENERATE HOLLOW NANOSPHERES

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In general, bio-macromolecules are composed of hydrophilic and hydrophobic moieties and are confined within small cavities, such as cell membranes and intracellular organelles. We have studied the self-organization of macromolecules having groups with different affinities to solvents under spherical nano-scale confinement by means of computer modeling [1]. Fig. 1 depicts the diagram of state for a single amphiphilic macromolecule in poor solvent: ε_{AB} is parameter of incompatibility between units *A* of main chain and side groups *B*; *R* is the radius of spherical confinement, where the macromolecule is placed.

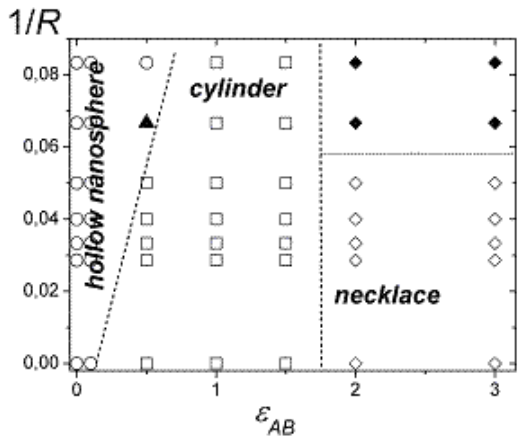

Fig. 1. Diagram of state of a single amphiphilic macromolecule in poor solvent.

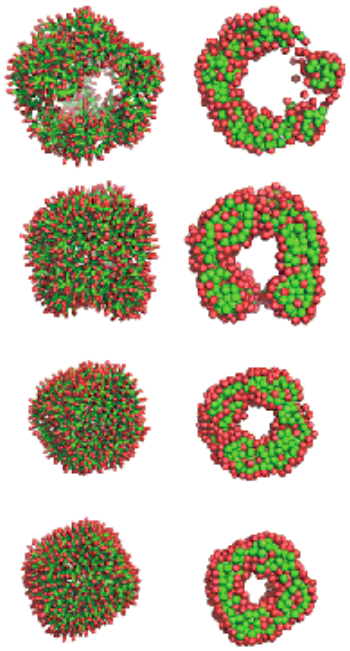

Fig. 2. Snapshots of a macromolecule inside a cavity and its cross-sections. The main-chain monomer units *A* are shown in green and the side-chain monomer units *B* are shown in red. $R = 12$, $\varepsilon_{AB} = 0.5$, $\varepsilon_{AA} = -2, -3, -3.5, -4$ (from top to bottom).

The most interesting structures for possible applications are hollow nanospheres (Fig. 2) – spherical globules with a hollow interior. They could serve as nanosized containers for transport of substances through an outer matrix, in which they are otherwise soluble. The hollow nanospheres are stable and should be simple in preparation and varying of their size and the size of their hollow interior.

The work was supported by Russian Science Foundation (project 14-13-00745). The computations were performed using the resources of Supercomputing Center of Lomonosov Moscow State University [2].

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QUANTITATIVE ANALYSIS OF STRUCTURE – FUNGICIDAL ACTIVITY FOR 1,2,3-THIADIAZOLES AND 1,2,3-TRIAZOLES

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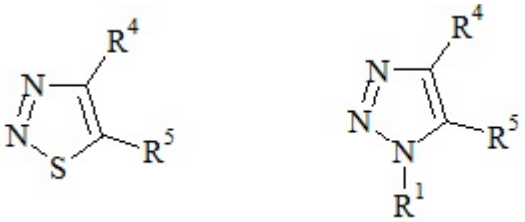
Abstract. Quantitative regularities between structure – fungicidal activity against *Verticilium dahlia* on cotton, *Fusarium oxysporum cucumerinum* on cucumbers, *Gibberella zeae* on wheat for synthesized library of 1,2,3-thiadiazoles and 1,2,3-triazoles had been found based on the QSAR-analysis. Revealed that topological descriptors determine a fungicidal activity for 1,2,3-thiadiazole while electronic descriptors play major role for 1,2,3-triazoles.

Tendency to increase of crop's loss by disease of plants are worldwide problem. 1,2,3-Thiadiazole cycle enters to composition of series of fungicidal [1], phytoactive [2], antiviruses [3] compounds and Systemic Acquired Resistance activators of plants («Bion» [4], «Tiadianile» [5]). The study of phytoactivity was found that 1,2,3-thiadiazoles under the action of sunlight degrade to form ethylene derivatives i.e. 1,2,3-thiadiazoles exert influence on the plants not only as cytokinins, but also as plant hormones of ethylene class.
5-Amino-1,2,3-thiadiazole derivatives easy rearrangements in 5-mercapto-1,2,3-triazoles [7-9], that is why these heterocycles can be classified as one scaffold.



In this study are presented comparative dates of quality regularities between structure – fungicidal activity for 1,2,3-thiadiazole and 1,2,3-triazole derivatives and QSAR equation for future prediction of fungicidal activity.

Fungicidal activity was studied against *Fusarium oxysporum cucumerinum* (cucumber root rot)*, Gibberella zeae* (Fusarium head blight of wheat), *Verticilium dahlia* (Verticillium wilt of cotton).

Fungicidal activity of compounds was evaluated used standard methods [10].

Method of regressive analysis was used for description of biological activity of molecules.
Picked regression parameters which determinated contribution of each descriptor were found used least square method.

Method of estimating cross was also used to develop the QSAR model.

It has been shown that different set of descriptors corresponds for 1,2,3-thiadiazoles and 1,2,3-triazoles. The most important topological descriptor for 1,2,3-thiadiazoles is quantity of chlorines in molecule.

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A 3D-QSAR PHARMACOPHORE MODELLING AND MOLECULAR DOCKING METHOD TO STUDY THE BINDING MECHANISM OF CYP17A1 INHIBITORS

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Prostate cancer (PC) has posed a serious threat in elder males because of its ability to grow and even progress through the androgen receptor (AR). CYP17A1 has emerged as a novel target for prostate cancer; as the inhibition of this enzyme decreases the production of androgens from all its sources. In this work, a 3D-QSAR pharmacophore model was performed on a diverse set (98 compounds) of steroidal and non-steroidal CYP17A1 inhibitors obtained from literature and 88 molecules were used for constructing the model after outlier removal. A six-point pharmacophore model with two hydrogen bond acceptors (A), one hydrogen bond donor (D), one hydrophobic group (H), and two aromatic rings (R) with unique geometrical arrangement was generated from a training set of inhibitors randomly selected, which was validated with a test set, providing adequate predictive statistics (R^2 = 0.9342 and Q^2 = 0.8874), respectively. A Density Functional Theory optimization procedure was employed to further calculate the electronic properties explaining the reactivity of highly-active and inactive inhibitors. Finally, docking calculations revealed hydrogen bonding and hydrophobic interactions as the main driving forces explaining the binding affinity of these inhibitors to the target enzyme.

Keywords: Prostate cancer, CYP17A1 inhibitors, Pharmacophore, Molecular docking

FRAGMENT-BASED SIMILARITY SEARCHING: INFINITE COLOR SPACE WITH REDUCED GRAPHS

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Fragment-based similarity searching and abstract representation of molecular features in terms of reduced graphs have widely, yet separately, been applied to virtual screening studies individually [1,2,3]. In this work, the potential of the combination of these approaches is investigated in a demanding retrospective manner: A new type of reduced graphs is introduced that does not suffer from information loss during its construction and bypasses the necessity of coloring the graph's nodes according to a predefined feature dictionary. The method allows similarity calculations within a continuous color space rather than be bound to a fixed numbers of labels or colors.

Our algorithm utilizes MCSS for determining topological congruency of pairs of molecules and enables multiple fingerprints to determine their similarity on the level of their chemical epitopes. The algorithm generates fragments from input compounds and translates them to their reduced graph representations. Each generated fragment is encoded in terms of a fingerprint, thus allowing a relaxed matching between the fragments of the reference and target graph, respectively (Figure 1A and B).

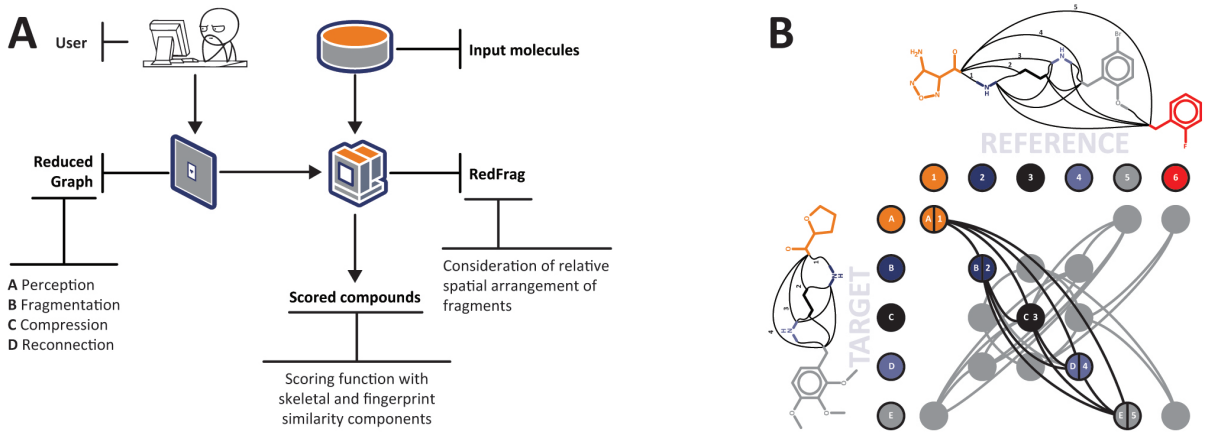

Figure 1: **A)** Outline of RedFrag's usage and functionality. RedFrag accepts a reference molecule, creates a reduced graph representation and screens a library for topological and chemical similarity. B**)** Maximum Clique Detection as key-step of similarity perception. Both graphs share a common topological arrangement of similar fragments.

Our validation procedure encompasses the MUV [4] dataset, consisting of 17 activity, a variety of nuclear receptors, GPCRs and kinases. We investigated our method's performance thoroughly with seven fingerprints, three fragmentation patterns and nine scoring function variations in order to reasonably discover the sweet spot for each activity class. Over all activity classes, we found the retrieval effectiveness to be competitive and even outperforming than a variety of global descriptors. For three different GPCRs we could observe high enrichment rates, reflecting the capability of recognizing common pharmacophore features arranged in a specific two-dimensional way. In the second phase of this project we will exploit the challenging endothiapepsin system in order to validate our approach prospectively. Both aspects, fragment-based and reduced-graph-support enable the algorithm to find and enrich structurally diverse compounds, leading to scaffold hops.

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DETERMINATION OF AMYLOID FORMATION MECHANISM AND CALCULATION OF PROTOFIBRIL NUCLEUS SIZE ON THE BASIS OF THE EXPERIMENTAL DATA OF KINETICS OF FIBRIL FORMATION

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Aggregation of peptides and proteins into amyloid structure is one of the most intensively studied biological phenomena at the moment. To date, there is no developed theory that would allow one to determine what kind of mechanism presents in given experiment on the basis of aggregation kinetic data. We attempted to create such a theory. Various kinetic models of amyloid formation process are considered. In addition to the primary nucleation stage, which is believed to be common among all the amyloid formation processes, considered models include the various regimes of growth of protofibrils. Following the nucleation stage regimes of growth can be divided into two types: "linear" growth regime of protofibrils where possible number of points of growth (the place where monomers can be attached) is proportional to the number of nuclei and the "exponential" regime of growth, where the number of points of growth in the course of aggregation may exceed the number of nuclei. Analysis of the kinetic curves of amyloid formation revealed the regime of exponential growth to be realized in the kinetic experiments quite often. Types of exponential growth of amyloid fibrils may vary, but, in general, all types can be reduced to three scenarios - fragmentation, the growth from the surface and bifurcation. In the case of fragmentation the number of points of growth increases due to breakage of fibrils. Deformations on the surface of fibrils might serve as new points of growth or they could serve as place where new secondary nuclei will be formed which will then give rise to new fibrils – such cases called bifurcation and bifurcation with secondary nucleation. Growth from the surface is the unusual scenario – in this case, the entire surface serves as point of growth and shape of the resulting aggregate will not be fibrillar, at the same time, such structures have been found experimentally, so the consideration of such scenario is justified. To separate experimental cases with linear growth regime from the cases with exponential growth regime we introduced a new value - L_{rel}, relative lag time. As it turned out, Lrel can be also used to calculate nucleus sizes of primary and secondary nucleation. On the basis of relations between the characteristic times T_{lag} (the lag period) and T_2 (the time when all monomers to be included in the aggregate) we concluded on the need and importance of the series of kinetic experiments where the only the variable would be a concentration of monomers. Such series of experiments allow one in some cases to determine the mechanism by which the aggregation goes, as well as to calculate sizes of the primary and secondary nucleation, if latter takes place to be. At the same time, the analysis showed that not all the results of kinetic experiments can be interpreted unambiguously to determine the mechanism of aggregation. In such cases, one should use additional experiments interpretation of which is able to uniquely identify the mechanism. At the same time the behavior of the quantities L_{rel}, T_{lag}, T_2 allows one to narrow down the possible mechanisms in such uncertain circumstances.

This study was supported in part by Russian Academy of Sciences (programs “Molecular and Cell Biology” (Grant Nos.01201353567 and 01201358029), “Fundamental Sciences to Medicine”) and Russian Science Foundation (№ 14-14-00536)

AN ALIGNMENT INDEPENDENT 3D QSAR STUDY ON A SERIES OF TNF-ALPHA CONVERTING ENZYME INHIBITORS

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Tumor necrosis factor-alpha (TNF-α) is a multifunctional cytokine mainly secreted by stimulated macrophages to regulate wide variety of signaling pathways within cells. Despite playing several physiologic roles, the elevated level of TNF-α is implicated in the pathogenesis of chronic inflammatory and autoimmune diseases. Activation of TNF-α is mediated by TNF-α converting enzyme (TACE). Therefore, inhibitors of TACE may serve as novel therapeutic agents useful in control and treatment of such diseases.Three dimensional quantitative structure-activity relationship (3D-QSAR) analysis based on alignment independent descriptors (GRIND) was performed on a set of TACE inhibitors. To this end, TACE inhibitors were docked into the active site of the TACE using GOLD program. 3D-QSAR model was generated by applying partial least square (PLS) and principle component analysis (PCA) methods implemented in Pentacle program. The reliability and validity of the proposed model was evaluated using both internal and external cross validation methods. The resulting 3D model (R^2=0.83, q^2=0.57) is capable of predicting inhibitory activity of the test compounds with a correlation coefficient of 0.71. The standard deviation on error of prediction (SDEP) and the mean absolute percentage error (MAPE) of prediction were 0.56 and 5.81, respectively. The binding mode was proposed based on interpretation of the PLS-coefficients from the 3D-QSAR analysis in terms of molecular interaction fields found important for the inhibitory activity. The results of this study can aid designing novel TACE inhibitors useful in the treatment of inflammatory diseases.

MAXIMISING RECOVERY IN VIRTUAL SCREENING USING INFORMATION ENTROPY

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An enormous variety of methods for virtual screening have been developed over recent years.[1] Over time different studies have arrived at different conclusions as to the relative performance of different tools or different methodologies in virtual screening (2D v. 3D, ligand v. structure-based).[2] A large number of methods have also been developed to fuse results from different virtual screening methods to maximise performance.[3] In this paper we present novel methods to assess the complementarity of structure-based VS and 3D ligand-based VS. We approach the problem from two different angles: comparing absolute performance of individual methods and their fused results using appropriate statistical methods and comparing the hits from different methods to quantitate their overlap. In attacking the latter problem we use both simple set-based approaches and a more sophisticated approach using information entropy.[4]

$$H(X) = \sum_i P(x_i)\, I(x_i) = -\sum_i P(x_i) \log_b P(x_i)$$

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INTERACTIONS OF STRONGLY AND WEAKLY BOUND WATER MOLECULES TO PROETIN BINDING SITES AND PROPENSITIES FOR REPLACEMENT

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Experimental evidence suggests that water molecules play a crucial role to mediate interactions between ligands and protein binding sites. Displacement of specific water molecules by ligand moieties is possible in some cases and could in addition favourably contribute to the free energy of binding. Therefore an understanding of the thermodynamic nature of these water molecules might guide further structure-based drug design. Here it is of critical importance to determine the propensity of such a structurally conserved water molecule within a macromolecular binding site to be replaced by a part of a novel ligand.

The nature of these water interactions in several protein binding sites was studied by using 3D-RISM calculations towards an understanding of their thermodynamic features and the possibility for replacement by ligand parts.

The 3D reference interaction site model (RISM) [1,2] constitutes an implicit solvent model that is based on classical density functional theory. It solves the converged H and O atom densities on a 3D grid (g-function) and directly provides equilibrium thermodynamic quantities. The results are equivalent to those of infinite Monte Carlo or Molecular Dynamics simulations at a fraction of the computational cost.

In our investigations, we are focussing on two types of water molecules in X-ray structures of relevant protein binding sites, namely streptavidin, COX-2, factor Xa and factor VIIa: Those which can be replaced by a part of the ligand and those, which are almost integral part of the receptor and cannot be replaced, but should potentially be targeted in structure-based design. Our approach allows the semi-quantitative assessment of whether some given structural water molecule indeed could potentially be targeted for replacement in structure-based design.

This approach was extended to describe ligands in their crystallographic conformation and to compute molecular interaction fields capturing information about Gibbs free energy of solvation (DG) factorization into respective enthalpic and entropic terms. PLS-based regression models from those solvation fields capturing thermodynamical properties of ligands fields are shown to provide a significant advantage to understand SAR features. This will be demonstrated for a congeneric series of serine protease inhibitions, for which several X-ray structures in addition provide insight into replacement structural water.

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IDENTIFICATION OF NOVEL POTENTIAL INHIBITORS OF IL-36 RECEPTOR SIGNALING

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IL-36 family cytokines (α, β and γ) have been implicated to play a key role in skin inflammatory diseases, such as psoriasis. Upon activation, IL-36 cytokines interact with their specific receptor IL-1rp2 and initiate the production of a range of pro-inflammatory cytokines and chemokines. Similar to most members of the IL-1 family, IL-36 cytokines require proteolytic processing for activation [1]. Thus, one therapeutic approach for blocking IL-36 activation is to inhibit the proteases responsible for activating IL-36 family cytokines, but unfortunately they are not identified yet. An alternative approach is to antagonize the interaction between IL-36 and the IL-36 receptor.

In current work in silico screening for small molecule IL-1rp2 antagonist identification was made with LeadFinder (LF) and AutoDock (AD) packages under default computation parameters. The D3 domain from 3O4O.pdb structure of the IL-1rp2 was used for screening (the structure is resolved by X-ray diffraction at 2.50 Å resolution). D3 domain is responsible for interaction with the processed part of IL-1 family proteins. The water molecules and co-crystallized anions were removed from the protein model. Hydrogens were added to the resolved structure and their positions refined using Gromacs software package. The 20×20×20 Å box centered to the coordinates of the IL-1−IL-1RII binding interface was used for energy grid maps calculation with 0.300 Å grid spacing. Small molecules were treated as flexible and protein − as rigid.

A set of approximately 50000 compounds from the high diversity St. Petersburg State Technological Institute library was screened using in silico method. The ligand protonation states were accounted at the pH 7.0. For the accuracy increase each compound was represented in 15 most favored conformations generated by Omega with mmff94 force field.

A set of 20 promising IL-1rp2 antagonist molecules were identified during VS with the calculated inhibition constant Ki in the range of 1÷8·10-8. The binding specificity and their physico-chemical properties of the representative compounds are discussed in the report.

Acknowledgements. The work has been supported by Ministry of Education and Science of the Russian Federation State Contract № 14.B25.310013.

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PLATE-BASED COMPOUND LIBRARY SELECTION USING FREELY AVAILABLE WORKFLOW COMPONENTS

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While cherry-picking subsets of compounds from large compound libraries usually is the desired method for biased selection of screening sets or compounds for purchasing, this may not always be feasible due to laboratory-technical limitations. Furthermore, cherry-picking will in the long term lead to uneven depletion of compound plates. Screening or purchasing of all plates may not be possible due to resource constraints. Thus, when resorting to plate-based compound selection, access to an intelligent selection algorithm ensuring maximal coverage of chemical space is desirable. Inspired by a recent publication describing plate-based diversity subset screening (1), we sought to develop a similar approach using freely available components. Here we describe a workflow for performing tailored plate-based selections of compound libraries using integrated freely available software components, including Python scripts, Knime and MarvinBeans applications. The workflow can be applied to any plate-based selection problem, from selecting screening plates to selection of plated compounds for purchasing. The performance of the workflow will be illustrated with practical examples, applied to the 145K compound screening collection of the Chemical Biology Consortium Sweden.

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MOLECULAR SIMULATIONS FOR NETWORK PHARMACOLOGY

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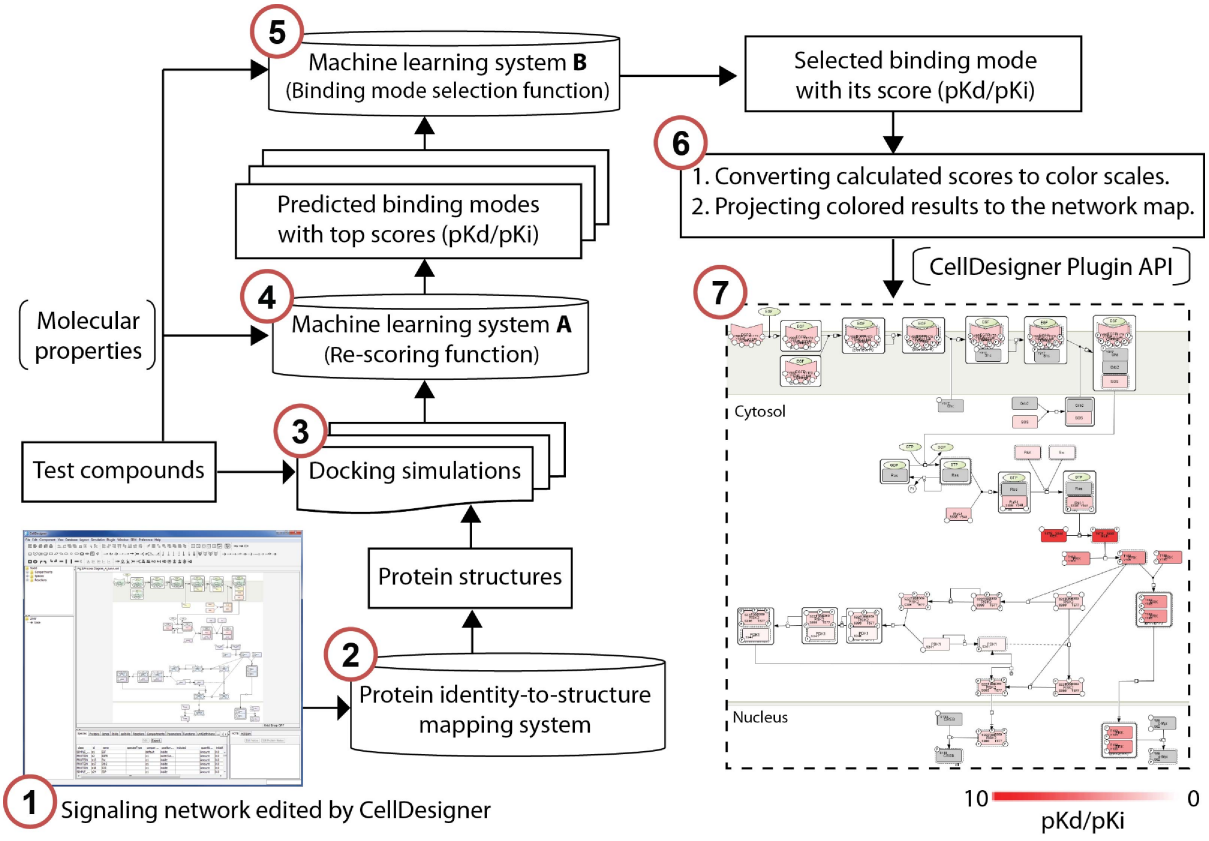
Increased availability of bioinformatics resources is creating opportunities for the application of systems pharmacology to predict drug effects and toxicity led by multi-target interaction. Together with specialized bio- and cheminformatics data, technologies including molecular interaction network description, structure-based drug design, high-throughput screening methods and statistical analysis help investigate the polypharmacology of a given drug or candidate. To achieve a comprehensive assessment of pharmacological effect, we propose a network-based screening approach for rapidly predicting the binding interactions between a given compound against proteins involved in a complex network. The screening approach mainly integrates the facilities of a curated molecular interaction network map and molecular docking simulation conducted by two elaborately built machine learning systems. Results from a series of benchmark validations and a case study show that the docking simulation equipped with the machine learning systems possesses a competitive performance in predicting the binding potential compared with the state of the art, as well as an adequate capability of identifying either primary or off-targets. The application of such a network-based screening approach along with a reliable docking simulation provides a feasibility to systematically understand the network-dependent effects upon the presence of a drug or candidate to address drug safety issues.



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BIOLOGICAL ACTIVITY AND ISOMERIC STATE RELATIONSHIP OF 3-ALKYLIDENEOXINDOLE DERIVATIVES

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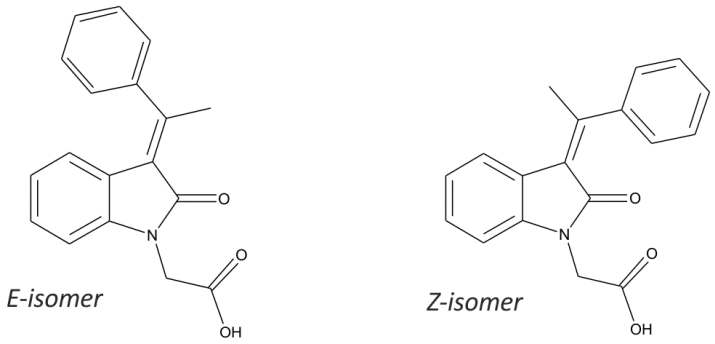
In recent years AMP-activated protein kinase (AMPK) has considered as a potential target in drug development for treatment of diabetes type II, obesity, metabolic syndrome, cardiac ischemia, stroke and even cancer. Increased interest in AMPK is expressed in various publications revealing new modulators of its activity.

One of the directions in AMPK modulators search is design of AMPK activators acting by blocking autoinhibitory domain of kinase. The best known of these activators are 3-alkylideneoxindole derivatives, they include Compound 24 – the most potent in this series, whose activity has been shown as well in mouse model [1].

By computer modeling, previously, we have defined a region presumably responsible for interaction of autoinhibitory domain with the kinase complex. Using these data and the structural similarity of 3-alkylideneoxindole derivatives we managed to construct a series of new compounds and validate them in the site of interest through molecular docking.

One of the target protein features is restricted size of the active site which leads to a strong dependence of binding energy against geometry characteristic of the molecule. To develop compounds using SBDD (Structure Based Drug Design) and FBDD (Fragment Based Drug Design) methods isomeric state, in which active molecule may exist, must be considered.



It is known that 3-alkylideneoxindole compounds may be in two isomeric forms (*E*- or *Z*-) [2], but there are no evidence in literature whether the form of the compound affects the AMPK activity. According to our calculations affinity of *E*- and *Z*-isomers to AMPK active site differs significantly.

Currently, we have isolated a number of individual isomers of 3-alkylideneoxindole derivatives. Primary data indicates that there is a correlation between calculated and experimental activity of the compounds.

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MOLECULAR MECHANISMS OF INTERACTION OF ORTHOPOXVIRAL CrmB PROTEINS WITH TUMOR NECROSIS FACTOR

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TNF hyperproduction causes the development of chronic inflammations, including those of autoimmune nature. Recombinant viral proteins inhibiting Tumor Necrosis Factor (TNF) activity could be used for development of new drugs for the inflammatory diseases treatment. To analyze the mechanisms of the interaction between human (hTNF), mouse (mTNF) and the cowpox virus N-terminal binding domain (TNFBD-CPXV), also the variola virus N-terminal binding domain (TNFBD-VARV) and to define the amino acids most importantly involved in the formation of complexes, computer models, derived from the X-ray structure of a homologous hTNF/TNFBD II complex, were used together with experiments. For analysis of binding free energy molecular dynamics simulations (Amber 12) were conducted followed by MM/GBSA protocol. MM/GBSA free energy decomposition protocol was used to identify key residues involved in complexes formation. It was shown that mouse TNF binds stronger with TNF-Binding Protein CrmB of variola virus or cowpox virus in comparison with human TNF. TNF-Binding Protein CrmB of variola virus had higher affinity to TNF of both organisms than CrmB of cowpox virus. The results of MM/GBSA free energy calculation were confirmed experimentally by surface plasmon resonance measurements. The MM/GBSA free energy decomposition protocol allowed us to reveal the key amino acid residues involved in the formation of the protein complexes, also to explain the observed difference in their formation free energy. Aminoacid substitution ASP63->ASN63 in the sequence of TNF-Binding Domain of CrmB of variola virus was revealed to be energetically favorable. The current work gave a deeper insight into the molecular mechanisms of the interaction of the TNF-binding protein of variola virus and cowpox virus with TNF.

IDENTIFICATION OF DRUG TARGETS RELATED TO THE INDUCTION OF VENTRICULAR TACHYARRHYTHMIA THROUGH SYSTEMS CHEMICAL BIOLOGY APPROACH

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Ventricular tachyarrhythmia (VT) is one of the most serious adverse drug reactions which often leads to death. *In vitro* assessment of interaction of lead compounds with HERG potassium channel as a main known reason of VT induction [1] is obligatory test during the drug development. However, experimental and clinical data reveal that inhibition of ion channels is not a single possible mechanism of VT induction [2]. Therefore identification of other protein drug targets contributing to the induction of VT is crucial. We have developed a systems chemical biology [3] approach for search of such targets which involves the following steps: (1) Creation of special sets of VT-causing and non-VT-causing drugs with data on their structures; (2) Prediction of drug-target interaction (DTI) profiles for these drugs using a special version of PASS (Prediction of Activity Spectra for Substances) software [4-7]. This version was trained on ChEMBL [8] and DrugBank [9] data and predicts interactions with 1738 human protein targets with average AUC values of 0.97, as calculated through the leave-one-out cross-validation procedure; (3) Statistical analysis of predicted DTI profiles for VT-causing and non-VT-causing drugs allows identifying potential VT-related targets; (4) Gene ontology and pathway enrichment analysis of these targets with subsequent analysis of literature allows identifying biological processes underlying drug-induced VT etiology; (5) Creation of cardiomyocyte regulatory network (CRN) based on general and heart-specific signaling and regulatory pathways with a special emphasis on identified VT-related pathways and processes; (6) Simulation of changes in behavior of CRN caused by inhibition of each node or their combinations [10] allows identifying additional VT-related targets which cannot be found by analysis of DTI profiles. Based on this approach, we revealed 311 potential VT-related protein targets and classified them into three confidence categories based on supporting experimental data from literature: (1) high (proteins are known to be associated with induction of VT by interactions with chemical compounds or deletion/over-expression of corresponding genes; 56 proteins); (2) medium (protein are known to participate in VT-related pathways and processes which were determined by our analysis; 156 proteins); (3) low (proteins without any supporting information; 99 proteins).

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INTERACTION OF DOXORUBICIN WITH DOUBLE, POLY(rA)•POLY(rU), AND TRIPLE, POLY(rA)•2POLY(rU), RNA HELICES

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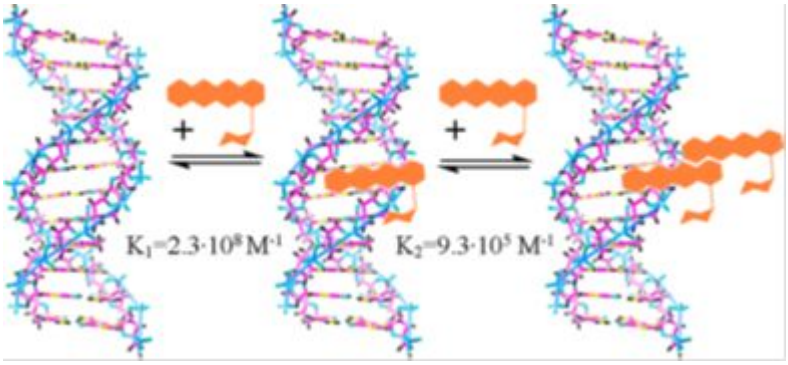
Doxorubicin (DOX) is an important fluorescence anthracycline currently in use for the treatment of different cancers.[1]

We have reported recently that, in the presence of ct-DNA, DOX may react with great affinity to form two different types of complexes according to the scheme shown below.[2] The first complex is bifunctional, that is, it operates by both intercalation and binding to the groove, whereas the second is an aggregate formed at the expense of the first complex.



Given the growing interest aroused by this drug, we report here on the interaction of DOX with the double, Poly(rA)•Poly(rU), and triple, Poly(rA)•2Poly(rU), RNA helices. Absorbance, fluorescence, circular dichroism and viscometry measurements have demonstrated much less affinity with RNA than with DNA. The double helix of RNA (conformation A) permits intercalation of only the DOX aromatic moiety, yielding the partially intercalated monofunctional complex.

As to the triple helix, only an external complex has been observed, most likely bound to the minor groove. This feature has enabled us to conclude that the intercalation in the A conformation of the double helix occurs through the major groove occupied by the third strand in the triplex structure, thus preventing from intercalation of the latter.

Acknowledgement. The financial support by the Spanish Obra Social “la Caixa” OSLC-2012-007 and Junta de Castilla y León (Fondo Social Europeo, project BU-299A12-1), Spain, is gratefully acknowledged.

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DEVELOPMENT OF QSAR MODEL FOR 1,2,3-THIADIAZOLE DERIVATIVES

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Abstract. Fungicidal activity against 9 biological objects for synthesized library of compounds contained 1,2,3-thiadiazole in structure was determinated. QSAR models were developed based on these data. Structure – biological activity was analyzed.

Modern technology of medications and agricultural compounds construction are aiming to develop of reliable methods to predict biological activity of different organic compounds. First way to identify these compounds is screening of the synthesized compounds. The second way is establishment of quantitative and qualitative dependence of biological activity and structure.

Compounds included a 1,2,3-thiadiazole ring in the structure have different spectrum of biological activity. Various derivatives of 1,2,3-thiadiazole have been synthesized.

Fungicidal activity was investigated on the following sites: *Alternaria solani* on tomato, *Cercospora rachidicola* on peanuts, *Gibberella zeae* on wheat, *Physalospora piricola* on apples , *Botrytis cinerea* on cucumber, *Sclerotinia sclerotiorum* on rapeseed, *Rhizoctonia cerealis* on wheat, *Pellicularia sasakii* on rice, *Phytophthora infestans* on potato.

The aim of our study was to determine the dependence of the activity - structure based on the library of synthesized compounds. Linear regression model depending on the activity of the structure was built in each case of activity against certain fungi. Optimal number of descriptors *n* was defined by step through the correlation coefficient changes depending on changes in the number of considered descriptors. Selected biological activity data were used to construct the corresponding QSAR-equations. In developing QSAR models we have also used the method of cross-validation.

QSAR equation was compiled with regard to eight descriptors, they are the most significant, because the presence of other factors in the equation does not lead to a significant change of parameters depending on quantitative. Using less than seven descriptors does not give satisfactory correlation coefficient. Increase of descriptors number to 9-10 may adversely affect to the reliability of the equation.

Twofold purpose have been pursued in the QSAR equation. On the one hand, to identify compounds with the greatest fungicidal activity - the classical problem performed to pick up the structural elements corresponding to this activity. On the other hand, to determine a substance with lower and fungicidal activity even zero, since such compounds are more likely to manifest the true systemic acquired resistance.

In addition, there is always an opportunity to improve the equation obtained by checking the new synthesized compounds, further amendments and the selection of new descriptors for refinement and the calculation of new data.

The structure of the novel compounds for the synthesis and biological checking with predetermined biological activities depending on the structural elements can be simulated based on the QSAR equation.

The research was carried out in terms of Ural Federal University development program with the financial support of young scientists. The reported study was partially supported by Russian Foundation for Basic Research, research projects No. 13-03-00137.

EFFECT OF THE MEMBRANOTROPIC SUBSTITUENTS ON THE ABILITY OF ISOINDOLINONES TO INHIBIT P53 - MDM2 INTERACTION

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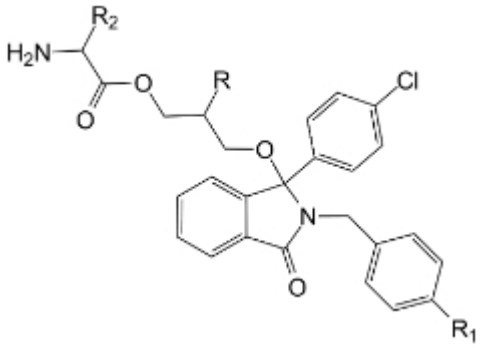
Increasing of an active molecule membrane permeability can increase efficiency of a drug by improving its bioavailability. Our task is to modify inhibitors of p53-MDM2 protein interaction that plays important role in cell death [1] to increase their membrane permeability without losing target activity.

Virtual screening of a database that contains isoindolinones [2] substituted with groups that can improve membrane permeability such as lipophilic amino acids or skeletal carbon cages was performed. Gibbs energy and scoring were used to analyze results of interaction modeling of small molecule ligands and MDM2 region containing a cavity that is responsible for interaction with p53.



As a result we have established that presence of membranotropic substituents not only increases ability of the molecule to penetrate membranes without losing target activity and solubility but also increases this inhibitory activity. For example, etherification of the free hydroxyl group with valine leads to change Gibbs energy and scoring more than one unit (ΔG=-9.2, VScore=-11.1 for modified molecule and ΔG=-8.1, VScore=-10.1 for original compound, that according to preliminary estimates corresponds to enhances the inhibition efficiency on the order) and use of substitute adamantyl groups is even more effective.

Moreover albeight these compounds have two chiral centers (R,R-, R,S-, S,R- and S,S- enantiomers) comparison of different isomers clearly showed that although such isomers is differently located in the MDM2 cavity they all are more efficient to inhibit protein-protein interaction than original unmodified compound and the spatial arrangement of the spacer has a greater value for the bond strength than the direction of terminal amino acid. For example, in case of valine that has a limited effect, VScore of the valine-substituent molecule with R- or S-linker differs by 0.4, while change of terminal substituent direction causes a change of less than 0.1.

Thus, it was found that modification of MDM2 inhibitors structure with membranotropic fragments results in a parallel increase in the efficiency of inhibiting the protein-protein interaction by increasing the binding strength of small molecule ligands with p53-binding domain of MDM2.

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FRAGMENT-BASED LIGAND IDENTIFICATION USING HIGH-THROUGHPUT MOLECULAR DYNAMICS SIMULATIONS

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Fragment-based drug design is becoming a widely used strategy in lead generation. However, characterization of binding kinetics, energetics and poses of chemical fragments inside protein cavities remains challenging. Here, we use high-throughput molecular dynamics to completely reconstruct the fragment-protein binding process of a focused library containing 34 fragments designed to probe human Factor Xa. For each fragment the expected binding pose is shown together with its kinetics and binding pathway and we are able to recover the four most potent binders identified by NMR screening. In addition to provide the fragment pose within the binding cavity, data on the kinetics and energetics of those fragments help explaining some of the results obtained from inconclusive competition assays. This in-silico approach shows great potential for designing and screening libraries of a few hundred fragments in a routinely manner.

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PREDICTION OF THE MUTAGENICITY OF NITROBENZENES IN THE AMES TEST BY MEANS OF THE JSM METHOD AND USING THE QUANTUM CHEMICALLY CALCULATED PARAMETERS

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Background and Motivations

Genotoxicity is one of the most harmful toxic effects of chemicals. The prediction of mutagenic activity using the Ames test is a tool for preliminary screening for genotoxic activity of chemicals.

Methodology

A learning model called JSM method [1] followed by the analysis of the hypotheses (structural fragments) generated were used for the prediction of the mutagenicity of nitrobenzenes in the bacterial Amestest. In the intellectual computer JSM system the chemical's structures are automatically transformed into lines of the FCSS (Fragmentary Code of Substructure Superposition) language [1]. Datasets on mutagenicity (yes/no) of nitro substituted benzenes toward strains TA100 and TA98 of *S. typhimurium* with and without activation by the microsome fraction of rats liver cells (S9) were used. In the largest dataset, containing 256 chemicals, those chemicals that show mutagenic activity toward at least one of the strains were considered as mutagenic. Then the method was applied separately for the data on mutagenicity toward strains TA100 and TA98. Two variants of the JSM method were used subsequently in the course of leave-one-out procedure. This enabled us to make predictions for 75% of the set.

Results and Conclusions

The results enabled one to determine the structural features crucial for the activity toward the two bacterial strains. The automatically generated hypothesis were compared with the "structural alerts", determined by the experts on the basis of covalent DNA binding mechanisms. Many coincidences were found and some new alerts and brakes were .defined. In the cases of an ambiguous or wrong JSM prediction the read-across prediction of the mutagenicity of a test compound was made. We used the parents of a hypothesis generated in the course of leave-one-out procedure as members of a category. The parameters characterizing the probable reactions of these compounds or their metabolites with nucleophilic centers of biomolecules were calculated by DFT or semiempirical methods and used for read-across. The different mechanisms of the nitro group reduction by nitroreductases were took in consideration. The use of the quantum chemically calculated parameters enables one to diminish the number of ambiguous or erroneous predictions made using JSM method. The carcinogenicity in the series of nitrobenzenes is better characterized by the results of the Ames test on the TA100 strain.

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PYRAZOLE-5-CARBOXAMIDES, NOVEL INHIBITORS OF RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS (RAGE) AS POTENTIAL AD THERAPEUTICS

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In an effort to develop novel inhibitors of receptor for advanced glycation end products (RAGE) for the treatment of Alzheimer's disease, a series of pyrazole-5-carboxamides were designed, synthesized and biologically evaluated. Analyses of the extensive structure-activity relationship (SAR) led us to identify a 4-fluorophenoxy analog that exhibited improved in vitro RAGE inhibitory activity and more favorable aqueous solubility than the parent 2-aminopyrimidine. Surface plasmon resonance (SPR) and molecular docking study strongly supported the RAGE inhibitory activity of pyrazole-5-carboxamides. The brain Aβ-lowering effect of the analog is also described.

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IMPACT OF DISTANCE-BASED METRIC LEARNING ON CLASSIFICATION AND VISUALIZATION MODEL PERFORMANCE AND STRUCTURE-ACTIVITY LANDSCAPES

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This study concerns large margin nearest neighbors classifier and its multi-metric extension as the efficient approaches for metric learning which aimed to learn an appropriate distance/similarity function for considered case studies. In recent years, many studies in data mining and pattern recognition have demonstrated that a learned metric can significantly improve the performance in classification, clustering and retrieval tasks [1-4].

This study describes application of the metric learning approach to in silico assessment of chemical liabilities. Chemical liabilities, such as adverse effects and toxicity, play a significant role in drug discovery process, in silico assessment of chemical liabilities is an important step aimed to reduce costs and animal testing by complementing or replacing in vitro and in vivo experiments. Here, to our knowledge for the first time, a distance-based metric learning procedures have been applied for in silico assessment of chemical liabilities, the impact of metric learning on structure–activity landscapes [5-7] and predictive performance of developed models has been analyzed, the learned metric was used in support vector machines. The metric learning results have been illustrated using linear and non-linear data visualization techniques in order to indicate how the change of metrics affected nearest neighbors relations and descriptor space.

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MINING WITH IMBALANCED DATA: MODELING STRATEGIES FOR CLASSIFICATION AND VISUALIZATION

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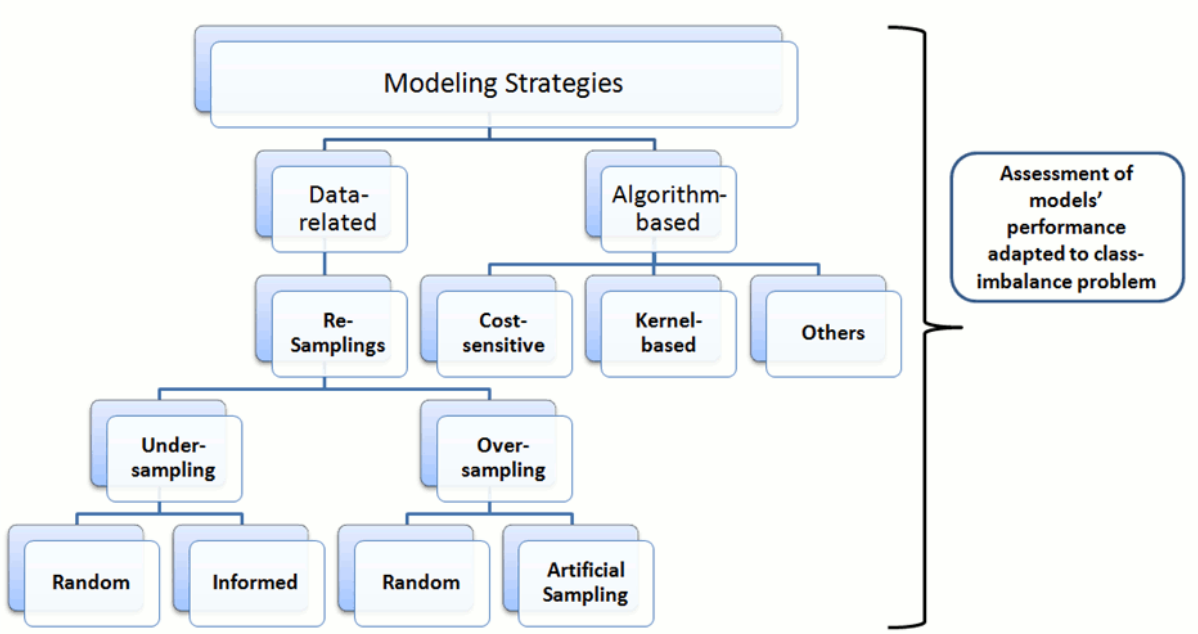
Class imbalance learning has received considerable attention in machine learning and chemoinformatics as current algorithms tend to be focused on majority classes and do not provide acceptable classification performance in case of data imbalance. In this study, to our knowledge for the first time, we present the comparative study of several strategies to solve the imbalanced data problem considering both visualization and classification purposes in chemoinformatics. Involved approaches are directed to solve the imbalance learning problem both at the data and algorithmic levels using different types of descriptors. The quantitative parameters of the assessment of model performance adapted to imbalanced learning problem have been involved. The performance of developed models has been assessed on external test set.



PREDICTION OF TRANSPORT PROPERTIES OF ELECTROCERAMIC OXIDE SYSTEMS FOR SOFCS USING CHEMOINFORMATICS APPROACHES

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Our research focuses on the development of chemoinformatics methods and algorithms to discover electroceramic materials and the application of these methods to materials for energy technologies.

Ceramic materials are widely used in electrochemical devices such as oxygen separation membranes and solid oxide fuel cell (SOFC) cathodes. Solid oxide fuel cells are of great interest as economical, clean and efficient power generation devices. Fuel cells have several advantages over conventional power generation techniques. They characterized by high-energy conversion efficiency and high power density. Due to the difficult and time consuming process of conventional compound synthesis, the development of materials are turning from experimental synthesis efforts to *in silico* design. The study of the materials with a complex phase structure, as well as the prediction of the properties of materials obtained under different conditions are of particular interest.

In this study we propose the descriptors efficient for the assessment of "composition-structure-ion diffusion" relationship and taking into account porosity, grain size, used measurement methods and equipment. Involved approaches include complementary machine learning methods encompassing chemography, regression, data imputation and metric learning techniques. Obtained results provide guidance for future searches of materials suitable for applications in SOFCs. Developed materials informatics approaches can be used in related fields.

Acknowledgements:

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DISCOVERY OF NEW SYNTHETIC MOLECULES FOR VECTOR CONTROL OF AEDES AEGYPTI AND ANOPHELES GAMBIAE TO COMBAT INFECTIOUS DISEASES

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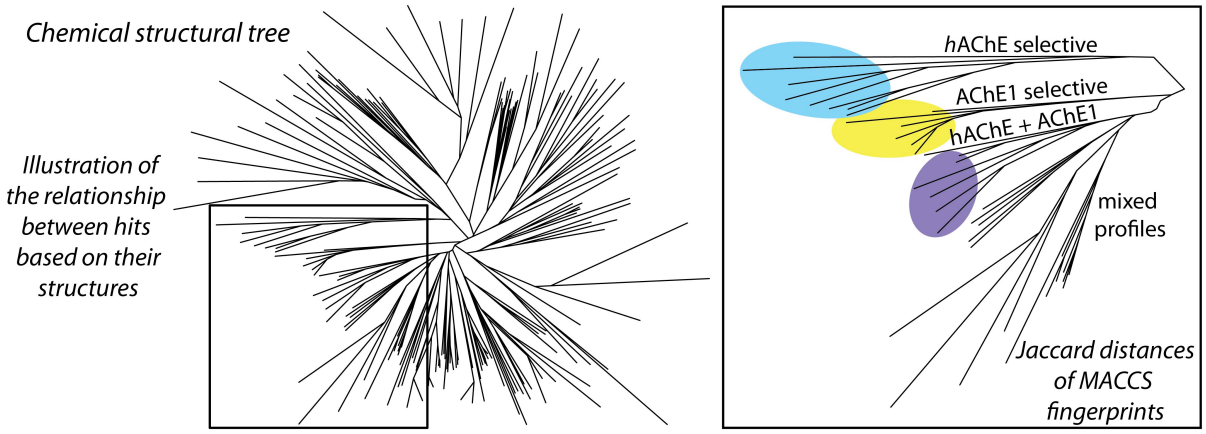
Vector-borne diseases are the cause of great suffering and misery that hinder economic development and poverty eradication in many low- and middle-income countries. Hundreds of millions of people are annually affected by parasitic- and viral infections via bites of *Aedes* or *Anopheles* mosquitoes.[1] Vector control by use of insecticides is a powerful tool to prevent disease transmission. Due to increasing resistance development and generic toxicity of currently used compounds, development of new safe, effective, and sustainable insecticides is urgent.[2]

We aim to develop novel insecticides by selectively targeting an iso-form of acetylcholinesterase (AChE1), not present in vertebrates. Chemical starting points have been discovered by high throughput screening (HTS) using AChE1 derived from disease transmitting mosquitoes *Aedes aegypti* (dengue and chikungunya) and *Anopheles gambiae* (malaria). HTS evaluation, including comparison with human AChE inhibition data[3] and chemical structural trees, has enabled us to identify diverse AChE1-hits belonging to several different compound classes. Many of these classes contain a basic amine that can form cation-arene interactions typical for AChE, but also neutral or negatively charged compounds have emerged. Importantly, we have found classes displaying different selectivity profiles and structural analysis has revealed clear trends for the compound classes that exhibit selectivity . The identified hits form an important basis in our work and will be used for design and synthesis of new insecticides to combat infectious diseases.



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PROTEIN INTER-CONFORMATIONAL MOVEMENT MODELING BASED ON MASS TRANSPORTATION PRINCIPLE

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One of the most essential and widespread problems of structural biology is to predict how a protein moves from one given conformation to another. A number of methods based on different protein representations have been proposed. An approach based on a coarse-grained protein model is presented and studied. The aim of the study is a construction of long-term conformational movements for further dynamic docking and protein functional research.
A movement of a protein is presented as a series of protein conformations. The first and the last conformations in the series correspond to the given ones. The intermediate conformations are constructed on the basis of the first and the last ones. Protein atoms are supposed to move at kinked curves that connect positions of the atoms in the conformations. The kinked curves approximate well the true trajectories of the atoms as the number of intermediate conformations grows. The cost of a transformation presented in the described way is a function of a sum of distances passed by each atom between adjacent conformations multiplied by corresponding atomic masses. In other words, a movement cost is calculated in accordance with the mass transportation principle. Given the model described above, the protein movement is derived by minimizing its cost as a function of torsion angles of intermediate conformations. Using torsion angles for conformation specifying ensures that bond lengths and planar angles remain unchanged. Also a number of constraint functions to restrict inadmissible movements like backbone self-intersections are introduced and included in the presented model.

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TRAPP- A TOOL FOR THE DETECTION AND ANALYSIS OF PROTEIN CAVITY DYNAMICS AND THE PREDICTION OF TRANSIENT BINDING POCKETS.

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The neglect of protein flexibility is one of the most critical limitations of currently available methods for designing new protein inhibitors. In our presentation, we will introduce TRAPP (TRAnsient Pockets in Proteins)[1] - a new software platform and webserver designed for exploring the dynamics of binding pockets, the identification of transient pockets, and for tracing their physicochemical properties.

The TRAPP workflow includes several independent procedures: (i) modeling of the binding site flexibility; (ii) analysis and classification of the binding site conformational variations; (iii) detection of transient and conserved pocket regions from available or generated protein trajectories or ensembles of protein structures. To enable the exploration of slow pocket dynamics in a reasonable computational time, we developed and implemented a new non-equilibrium molecular dynamics (MD)approach in the TRAPP workflow that facilitates the crossing of the energy barriers between the original and alternative structures and thus facilitates fast exploration of large-scale conformational changes of a binding site.

The details of the TRAPP workflow as well as its application to several targets will be summarized in our presentation. The TRAPP approach may open up new possibilities for the design of novel ligands for known protein structures and enable a more comprehensive assessment of protein druggability by exploring protein conformations beyond those available from protein crystallography. This can be of great value for the design of specific inhibitors that exploit so far unknown transient binding sites.

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IN SILICO PREDICTION OF ANTITUMOR CYTOTOXICITY OF PHARMACOLOGICALLY ACTIVE SUBSTANCES FOR HUMAN COLORECTAL CANCER AND NORMAL CELL LINES

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Currently, bio- and chemoinformatics methods, and mathematical modeling are widely used for the detection of pathogenic mechanisms of cancer and quest for potential drug-targets and their ligands. Regulatory network analysis based on signaling pathways and cell cycle regulation data combines in a single system the genomics and proteomics data. Development of computer-aided methods to personalize existing therapy using proteomic data obtained directly from patients is an important aim of modern computational biology.

The present work was focused on the development of approach for *in silico* prediction of cytotoxic effect of chemical compounds in normal and colorectal cancer cell lines based on the prediction of their cytotoxicity and action on human proteins, regulatory networks modeling and gene expression.

We have created the cell cycle regulatory networks models[1] including 2603 regulatory interactions between 1504 colorectal cancer genes/proteins and hypo- and hyperexpressed genes for 10 colorectal cancer cell lines (Caco-2, COLO 320DM, HCT-8, HCT-116, HT-29, LS174T, SW48, SW480, SW620, WIDR-UP) and 2 normal cell lines (HaCaT, WI-38). In the colorectal cancer cell cycle regulation modeling, several known and new pharmacological targets were found.

Modeling of cell cycle regulatory networks for colorectal cancer cell lines and search for potential therapeutical targets was performed based on proteomic data given for biopsy samples of normal colorectal tissue and colorectal tumor to estimate applicability of the developed approach to proteomic data of individual patients. So, proteomic data of cancer and normal intestinal epithelium tissue of patients were used as initial states of hyperexpressed genes for the cell cycle and apoptosis simulation.

The targets found in virtual experiment on cell lines converge with those found for real patients. As a result of applying the method for modeling used proteomic data both general (CDK4, CDK6, CYCLIN D1, AKT-1, CDK2, etc.) and specific (RAF-1, CYCLIN B1:CDK1, CYCLIN A:CDK2, MKK4, VDAC-2) targets for patients with colorectal cancer were obtained.

The computer program PASS[2,3,4] (Prediction of Activity Spectra for Substances) was used to develop the structure-activity relationships models. The appropriate training sets were created based on the information from ChEMBLdb 16 database (www.ebi.ac.uk/chembldb/) on cytotoxicity and interactions of chemicals with 661 proteins involved in human cell cycle regulation. The average prediction accuracy calculated by a leave-one-out cross-validation procedure was approximately 96% for cytotoxicity prediction for 24 colorectal cancer cell lines and 31 normal cell lines and 97% for protein-ligand interactions. While screening libraries of commercially available samples of chemical compounds (Asinex, ChemBlock, ChemBridge, InterBioScreen), we have selected few dozen promising compounds for which the interactions with identified targets, the cytotoxicity for colorectal cancer cell lines, and the absence of cytotoxicity for 31 normal human cell lines. Several selected compounds are currently under experimental testing.

Thus, the developed approach allows revealing compounds possessing antitumor activity for colorectal cancer cell lines and action on proteins responsible for the cell cycle arrest and apoptosis. Also the applicability of proteomic data to find promising targets for personalized approaches to treat patients has been showed.

This work was supported by Ministry of Education and Science of the Russian Federation (contract № 14.512.11.0093).

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DEVELOPMENT OF SUBSTITUENT CONVERSION DATABASE AND SEARCHING SYSTEM FOR MEDICINAL CHEMISTS

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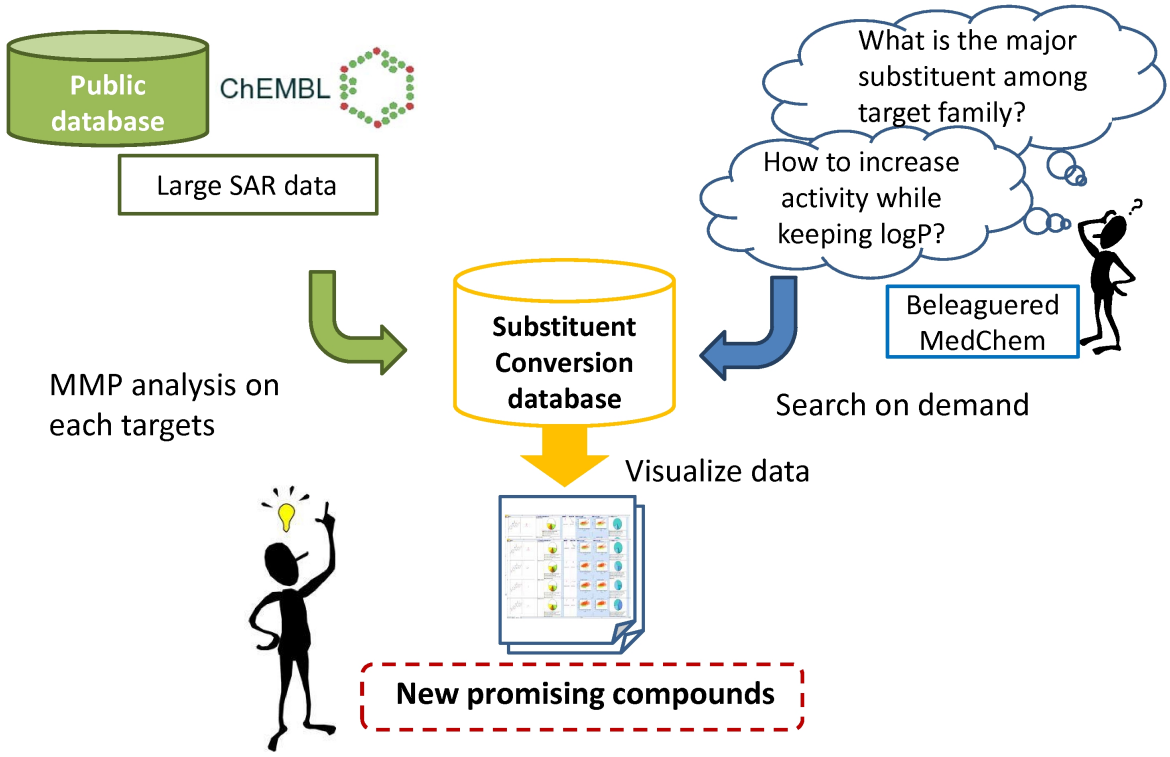
Large chemistry data sets have become easily available as Public Database. The data is accumulation of Medicinal Chemists' experiences and is to be utilized for drug design. Matched Molecular Pair Analysis is one of the useful methods to analyze such large chemistry data sets. Various suggestions of promising or unexpected chemical transformations could be extracted from large databases.

In this study, we have developed a substituent conversion database by Matched Molecular Pair Analysis of SAR data from ChEMBL in order to propose or analyze statistically preferable substituents. Each conversion entry has the data such as activity ratio between before and after the conversion, frequency, the name of target protein and their family. We expect that this database would be helpful for Medicinal Chemists to design new compounds without any omission. Furthermore, from the chosen substituent candidates, more detailed and accurate predictions such as docking and QSAR models can be applied to select more promising synthetic candidates.

The substituent conversion database and searching system is aiming to be a good molecular design partner for Medicinal Chemists. To promote Medicinal Chemist's intuitive understanding, how to extract and visualize the data are the key issues. But it is challenging. In this symposium, our approaches considering medicinal chemists usage and future directions will be discussed.



IMPOSSIBLE IS NOTHING: USING UNIFIED DESCRIPTION METHODS FOR BULK AND NANO MATERIALS

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In more than 50 years of active development, the field of quantitative structure-activity relationships (QSAR) modeling has grown tremendously with respect to the diversity of both methodologies and applications [1]. Researchers solved a lot of different tasks starting from prediction of solubility of phenolic compounds and finishing with nanoparticles characterization.

To make QSAR theoretical modeling, each particle should be described by numerical parameter, called descriptor. Chemical descriptors are at the core of QSAR modeling, and so many different types of chemical descriptors reflecting various levels of chemical structure representation have been proposed so far [1].

Unfortunately, modeling of nanoparticles is challenging because of the high complexity. They consist of great number of individual molecules and properties of nanoparticles dramatically differ from analogous properties of individual molecules. It is clear, that traditional QSAR approaches seem to be much more problematic than in case of “classical” chemicals.

In the current study it was shown that developed in-house Simplex Representation of Molecular Structure (SiRMS-based descriptors) [2] and “Liquid Drop” model (LDM-based descriptors) [3] are useful for QSAR investigation of different properties of different types of materials from bulk to nano-sized materials.

In addition, another studies presenting nano-QSAR models were analysed. Special nano-oriented descriptors and regular methods of structural representation were compare.

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CAUSAL DISCOVERY AND CLASSIFICATION MODELS FOR TOXICITY OF METAL OXIDE NANOPARTICLES TOWARDS BEAS-2B CELLS AND RAW 264.7 CELLS

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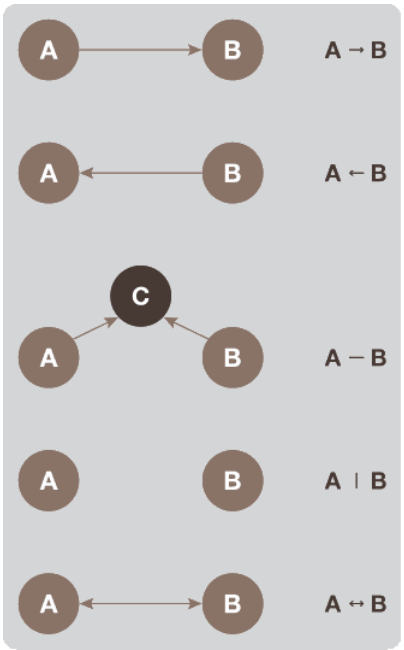
The knowledge of the toxicity of nanomaterials and factors responsible for it is important issue related to the human health and safety risks associated with nanotechnology.

In this study, the structure-toxicity relationships or nano-QSARs for toxicity of nanoparticles towards BEAS-2B cells and RAW 264.7 cells models are established.

In the present study it was shown that the proposed combination of descriptors and statistical approach is the convenient tool for the prediction of toxicity nano-sized metal oxides. We have utilized a computational modeling methodology to build computational classification models for quick predictions of ranks of toxicity. The developed nano-QSAR models were validated and reliably predict the toxicity for studied metal oxide nanoparticles. The obtained results reveal some new aspects of the biological action. We assume that the presented method is very promising not only for modeling of biological activity, but also for a variety of other properties of nanoparticles due to the peculiarities of nanostructures.

It was demonstrated that causal inference methods are able to show underlying structure of nanoparticles' properties. Causal structures can be described with graphical models. An example of a graphical model is the directed acyclic graph model.



QSPR ANALYSIS OF SOME ADME PROPERTIES OF DRUG SUBSTANCES USING ROC CURVES

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Exploring pharmacokinetic (or ADME) properties plays the great role in drug discovery. Among most important ADME properties are bioavailability, elimination half-life, total body clearance and volume of distribution.

Bioavailability is typically defined as a fraction of an administered dose of unchanged drug that reaches the systemic circulation. Oral bioavailability is usually less than 100% due to incomplete absorption in the gastrointestinal tract and first-pass metabolism in the liver.

Elimination half-life of the drug is the time during which the concentration of drug in the body is reduced by 50%.

Total body clearance is the volume of plasma cleared of the drug per unit time and describes how quickly drugs are eliminated, metabolized or distributed throughout the body.

The volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly approach distributed to produce the desired blood concentration of a drug.

Thus, the aim of the present work is developing binary classification QSPR models of different ADME characteristics of various drugs. The modeling dataset included about 600 structurally diverse drug substances, e.g. ibuprofen, amprenavir, aspirin, lorazepam, butabarbital, theophylline, alprenolol, etc.

In this study, we have developed classification 2D QSPR models using simplex representation of molecular structure (SiRMS) [1] and Random Forest (RF) statistical approach. All compounds from the dataset were divided into two (high and low) classes. For choosing optimal thresholds we have used ROC (Receiver operating characteristic) curves which are widely used in medicine, biometrics, machine learning and many other areas.

As a result, for each pharmacokinetic property we have obtained binary classification models with satisfactory error of prediction.

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2.5D - QSAR/QSPR STUDIES OF CHIRAL COMPOUNDS BASED ON SIMPLEX REPRESENTATION OF MOLECULAR STRUCTURE

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Nowadays, more than a half of commercial drugs consist of only one stereoisomer. Thus, importance of stereochemical features for organic compounds becomes obvious. A study of their influence to biological activities and chemical properties is a very important problem. In chemoinformatics stereochemical attributes are taken into account only by direct description of dimensional structure via 3D-QSAR approach. It is important to develop of 2D-QSAR approach considering stereochemical features of studied compounds (2.5D-QSAR)

This work represents development of an approach of Simplex Representation of Molecular Structure (SiRMS), which is based on description of molecular structure by 2D simplexes. Fragments which reflect stereochemical features are described by respective 3D conformation-independent simplexes.

To evaluate applicability of this approach, we have solved some QSAR-tasks. In the first one, we had to describe relationship “structure- chromatographic retention” for 16 compounds (8 couples of enanthiomeres). Developed models had good statistical characteristics (R^2>0,97, Q^2>0,94)

We were able to compare results of two other QSAR-tasks with 3D-QSAR models obtained earlier.

Our approach allowed to develop model of drosophila cell line for 71 ecdysteroids. Statistical parameters and predictive ability of that model were better than respective characteristics of 3D-CoMFA model. As a matter of fact, chiral descriptors showed quite big relative influence .

For 50 CCR2 receptor antagonists, developed “structure-affinity” models were comparable to those developed via HQSAR-approach with chiral labels. Chirality showed relatively small importance for this activity; wherein, presence of chiral descriptors was the only factor differing values of predicted affinity for enanthiomeres.

Thus, application of Simplex Representation of the Molecular Structure with described modification considering chirality is relatively simple and universal approach for obtaining adequate QSAR-models of chirality-dependent properties

CAUSAL ANALYSIS FOR QSAR

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The interest towards in silico prediction of nanoparticles' toxicity is growing. The main purposes of modeling nowadays, however, are not only QSARs that will obtain predictive power, but also models maintaining the ability of mechanistic interpretation. According to well-known paradigm "Correlation is not causation", traditional approaches towards the interpretation cannot show existing 'cause-effect' relationships. To obtain underlying structure of existing nano-data we referred to methods of causal discovery [1, 2], which are based on conditional probabilities and directed acyclic graphs.

The pairs with well-known causal connections, i.e. zeta-potential – size, pH – zeta-potential and size – electrophoretic mobility, were used as 'golden standard' to test the causal methods. Further 'golden standard' was broadened by data on nanoparticles' stability.

For further analysis variety of nanotoxicity data was taken, such as acute aquatic toxicity towards Daphnia magna and Paramecium multimicronucleatum, data on oxidative stress in bronchial epithelium cells and cytitotoxicity towards E. coli.

For each of the datasets consensus directed acyclic graph (DAG) was built. For some data the dependencies, previously guessed during QSAR analysis was confirmed.

To summarize all of the above, causal discovery method proved to be useful tool to undercover hidden'cause-effect' relationships in nano-data. These methods can be applied as a useful addition to nanoQSAR modelling to obtain rational and much less ambiguous interpretation.

The funding through the European Commission 7th Framework Program NanoBRIDGES (FP7-PEOPLE-2011-IRSES, Grant Agreement no. 295128) is gratefully acknowledged.

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STRUCTURAL AND FUNCTIONAL INTERPRETATION OF 2D QSAR MODELS OF STRUCTURE-BLOOD-BRAIN BARRIER PERMEABILITY RELATIONSHIP OF ORGANIC COMPOUNDS

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Analysis of influence of different structural features on blood-brain barrier (BBB) permeability was the goal of the present work. Brain penetration is one of the major parameters which are taken into consideration in chemical toxicological studies and in the process of creating of new drugs. The investigation of blood-brain barrier permeability is necessary for construction of new medicinal preparations, and also for more effective treatment of brain diseases. The blood- brain barrier separates the brain from the blood stream and limits the transport of substances from the systemic circulation into the brain tissue. The ability of an organic compound to penetrate the brain can be estimated by measuring its brain-to-blood concentration ratio (BB) which is defined as the ratio of drug concentration in brain tissue to the drug concentration in blood and usually expressed as $\log(C_{brain}/C_{blood})$ or log BB[1].

At present time the theoretical methods (QSAR/QSPR) widely used for estimation of the permeability of substances through the BBB. The known models are inherently additive and do not take into account mutual influence of atoms in a molecule. In addition, the structurally or functionally homogeneous dataset of compounds were used for development of these models. Thus, the development of models with satisfactory predictive power for structurally diverse datasets is quite actual task. But even more important task is interpretation of obtained QSAR models in terms of structure and atomic properties. This information can be used for compounds design and fast filtering of undesirable compounds.

In this work we have built 2D QSAR models using simplex representation of molecular structure (SiRMS) [2] and Random Forest method. The obtained consensus model is characterized by a satisfactory predictive ability ($R2_{oob}$= 0.62, $RMSE_{oob}$ = 0.44). Structural and functional interpretation of the obtained model revealed that the presence of highly polar groups (carboxyl, carbonyl, phenolic hydroxyl) decrease the ability of substances to penetrate though brain tissue, and the presence of halogen atoms and aromatic fragments mainly increases the efficiency of the molecule transport through the BBB.

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USING HIT-QSAR METHOD FOR MODELING OF WIDE SPECTRUM OF ANTI-INFLUENZA ACTIVITY

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The goal of this study is to design novel selective anti-influenza agents by means of Quantitative Structure-Activity Relationship (QSAR) modeling of antiviral activity of the diverse set of chemical compounds. The development of QSAR models was carried out using Hierarchic QSAR Technology (HiT QSAR) [1] based on Simplex representation of molecular structure (SiRMS) and random forest statistical method [2]. The set of adamantane derivatives, crown and aza-crown ethers, and known antiviral drugs was tested against the following activities:
- inhibition of reproduction of the influenza strain H1N1 (A/PR/8/34) in experiments in CAM tissue culture (41 compounds);
- inhibition of reproduction of the virus strain H1N1 (A/PR/8/34) in cell culture MDCK (21 compound);
- inhibition of the reproduction for the strain H5N3 (54 compounds) (expressed in lgTID50 - and reflected suppression of viral replication in “experimental” samples to “control”);
- inhibition of the reproduction for the virus (H3N2) A/Hong Kong/1/68 (34 compounds)
toxicity against the Colpoda steinii culture (85 compounds);
- Chemical-Therapeutical Index for H1N1 strain (27 compounds).
We succeed to develop robust and predictive QSAR models. Then we used developed models for the virtual screening and molecular design of new antiviral agents with increased anti-influenza activity and selectivity, and reduced toxicity. Four benzodiazol derivatives has been recommended for further experimental testing. Compounds has been synthesized by chemists. The results of experimental testing confirmed predicted values of antiviral activity chemical-therapeutical index, and cytotoxicity.
This work is partially supported by Science and Technology Center in Ukraine (Project P407)

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QSAR ANALYSIS OF ANTVIRALS AGAINST INFLUENZA A (H1N1) VIRUS FOR ANGELICIN DERIVATIVES

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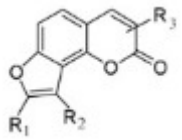
Viral infections are widespread, they comprise more than 95 % of all known human infectious diseases. Influenza epidemic and pandemics in the past century had caused serious impact on global morbidity, mortality and economy. Search for promising compounds - agents against influenza A virus is a very important and urgent task.

The development of QSAR models on the base of simplex representation of molecular structure (SiRMS) [1] and the analysis of influence of different structural features on influenza A (H1N1) virus was the goal of the present work.

A set of 63 organic compounds derivatives of angelicin [2] was the object of this study.

The general structure of angelicin derivatives:



where:

R1: -Ph, -OH, -H, -CH3, -2-furanyl, -2-thienyl, -3-thienyl, -2-pyridyl, -4-CH3-Ph, -4-OCH3-Ph, -4-NO2-Ph, -4-Cl-Ph, -3-CH3-Ph, -2-CH3-Ph, -3-OCH3-Ph, -2-OCH3-Ph, -3-NO2-Ph, -3-Cl-Ph, -3-F-Ph, -3-OH-Ph;

R2: -Ph, -H, -CH3, -n-C3H7, -n-C6H13, -n-C10H21, -1-naphthyl, -2-naphthyl, -2-thienyl, -2-furanyl, -4-CH3-Ph,
-4-CH3O-Ph, -4-NO2-Ph, -4-Cl-Ph, -4-Br-Ph, -3-Br-Ph , -2-Br-Ph, -3,5-diBr-Ph, -3-CH3-Ph, -3-NO2-Ph, -3-Cl-Ph, -3-CN-Ph;
R3: -4-Ph, -H, -OC(O)CH=CHCH3, -3-CH3, -4-CH3, -5-CH3, -4-C2H5, -4-C3H7, -3-CH2CH2CH2CH2-4.

In the present work, only 2D simplex descriptors were used for molecular structure representation. Not only atom type but also other physical-chemical characteristics of an atom such as: partial charge, lipophilicity, refraction, Van-der-Waals interactions and the ability for an atom to be a donor or acceptor in hydrogen bond formation were used for atom differentiation. The usage of sundry variants of differentiation of simplex vertexes (atoms) represents the principal feature of the simplex approach [1]. QSAR models were created using PLS approach (Partial Least Squares.).

Obtained consensus model, which describes structure-activity relationships, has following statistical characteristics: determination coefficient R2 = 0.78; cross-validated determination coefficient Q2 = 0.62; determination coefficient for the test set R2test = 0.62. The relative influence of physical-chemical parameters and
molecular fragments on influenza A (H1N1) virus for angelicin derivatives was calculated.

By using PASS the spectrum of biological activity was calculated for investigated compounds. Probability of influenza activity for angelicin derivatives was less than 30%, i.e. similar compounds are not included in the database, as compounds, which are having influenza activity. Thus, angelicin derivatives are new perspective compounds for the study of influenza activity.

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TYPE II TOPOISOMERASES AS TARGETS FOR RATIONAL DRUG DESIGN IN ORDER TO IMPROVE CURRENT ANTI-BACTERIAL AND ANTI-CANCER THERAPIES

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Nowadays we are experiencing an enormous increase in computational power and in its availability to many users even with a limited budget. Advances in GPU and Cloud computing as well as the development of novel methods in Molecular Dynamics and ligand binding simulations are making possible what we could only dream about only a few years ago. This is especially a good timing for these advances considering the constant increase in drug resistance of pathogens, limited number of the newly developed remedies and a growing need for new drugs and treatments. As such, rational drug design is becoming a more and more important scientific and medical topic. However, no computational experiment can be done without the prior investigation of the system to be studied using experimental biophysical and biochemical techniques.

Here we present what we believe to be ground work for the future rational drug design and development both in anti-bacterial and anti-cancer therapy. Our focus of efforts is on the structural analysis of topoisomerases from different organisms. Topoisomerases are ubiquitous enzymes present in both prokaryotes and eukaryotes. They are responsible for maintaining the desired level of supercoiling of DNA in order to allow other cellular machineries to operate. Our focus is on the type II topoisomerases which create a temporary break in one double-stranded DNA and guide the other double-stranded DNA through the break in the ATP-facilitated process, thus changing the linking number in steps of 2. Also, in bacteria, type II topoisomerases are required for daughter chromosomes segregation upon cell division. Bacterial type II topoisomerases are targeted by fluoroquinolones which stabilise the cleavage protein-DNA complex, stalling the mechanism and eventually leading to the creation of the double stranded DNA breaks in the chromosomes which are lethal to bacteria. In human, type II topoisomerases are targeted by anti-cancer drugs such as etoposide or doxorubicin in a way somewhat similar to the action of quinolones in bacteria.

Our best studied system to date is topoisomerase IV from *Streptococcus pneumoniae*, a known pathogen causing pneumonia, bacteraemia, meningitis, otitis etc., for which we solved the first cleavage complex of topo IV with its DNA target stabilised by fluoroquinolones [1]. Since then we extensively probed the active site of the topo IV using different quinolones and also quinasoline dione PD 0305970 produced by Pfizer [2]. Recently we expanded our efforts into other organisms (such as *Klebsiella pneumoniae*) and also solved the cleavage complex of gyrase and a full-length ParE-ParC55 protein-DNA complex of topo IV from *S. pneumoniae* thus extending our knowledge of the composition of the active site of type II topoisomerases as well as providing further insights into the overall structure of topoisomerases and their mechanism of action consequently extending the potential drug target search areas.

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MULTIVARIATE CONSENSUS FACTORS OF DIOXIN-LIKE COMPOUNDS AS AN AID IN THE REEVALUATION OF TEFS - AN IN SILICO APPROACH USING AN EXTENSIVE HUMAN AND RODENT IN VITRO SCREENING OF AHR MEDIATED EFFECTS

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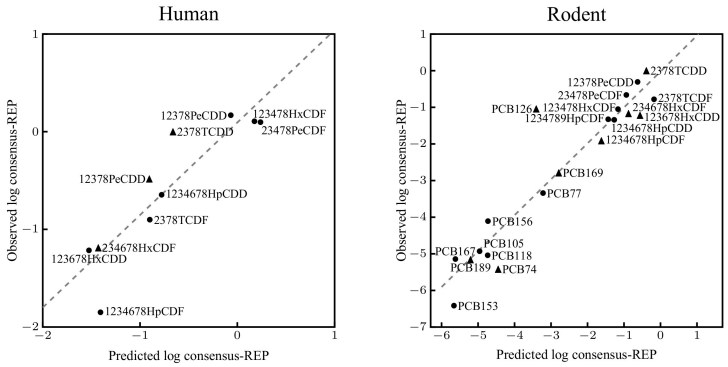
Polychlorinated dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs) and biphenyls (PCBs) are omnipresent and persistent environmental pollutants. Congeners among these chemical classes whose toxic effects are similar to those of 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD) - e.g. their toxic effects are known to be mediated via the aryl hydrocarbon receptor (AhR) - are of special concern and their health risks are evaluated using toxic equivalency factors (TEFs). The TEF system provides a unique tool to assess mixture effects of these three classes of chemicals based on the assumption of additivity where the concentration of each compound times its TEF factor together sum up the risk of a sample (Toxicol. Sci. 93: 223-241, 2006). Today human cell lines are being frequently used to aid in the risk assessment of human's exposure of dioxins and dioxin-like compounds. It is suggested that humans are among the most dioxin-resistant species, but in the latest reevaluation of the TEFs, it was concluded that more research on human systems is needed to say whether rodent studies are valid for humans.

In this study, human and rodent bioassays (17 measured AhR related responses) were studied and compared using a selected set of dioxin-like compounds covering 18 TEF assigned compounds and two reference PCBs. For each assay and compound, relative effect potency values (REPs) - compared to TCDD - were calculated and used for the analysis. In order to condense the information from the battery of tests completed for the studied compounds, two principal component analysis (PCA) models based on the data from the rodent and human cell assays, respectively, were calculated. Here the data was summarized to reach a score explaining 97% (rodent) and 91% (human) of the variation. The scores from the PCAs of rodent and human REP data were used to numerically define consensus-REPs. The score value was multiplied with the loading value for each biological response (REPs) as a means to reach a factor scaled as the original responses. These consensus factors were used to predict the consensus-REPs of the untested TEF assigned compounds by QSAR modeling. The QSAR models and their predictions showed good statistics; Q^2=0.83 & RMSEP=0.96, and Q^2=0.71 & RMSEP=0.47, for the rodent and human model, respectively. The properties that influenced the models were quite different, in the human case relying more on atom-specific electronic properties (of lateral positioned carbons in the molecular structure) compared to a mixture of electronic properties, shape- and surface characteristics for the rodent model.



NOVEL KINASE INHIBITORS FOR PKA AND PKB TARGETING THE PHOSPHATE-LOOP

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The wide occurrence of more than 500 kinases in the human genome and their important roles in diseases such as cancer and diabetes make kinases to an attractive target in drug design.[1] Protein Kinase A (PKA) and B (PKB, also called akt) play important roles in the regulatory processes of glycogen, sugar, and lipid metabolism, and are furthermore involved in signal transduction processes. Selectivity for one specific kinase has been extensively discussed in antitumor strategies and is of high interest for the pharmaceutical use.[2,3] PKA is a widely used model for many kinases, as it is a well known enzyme with good availability and handling properties. To study PKB affinities a PKA triple mutant, a so called PKAB3[4] is often used as a model to mimic the active pocket.

In our research, we have used structure-based design and 3D modeling as tools for inhibitor design. The novel inhibitors show single-digit-nanomolar affinity against PKA and the recently resolved co-crystal structures enable us to obtain insights into the P-loop of PKA and PKB to investigate the interactions. All tested inhibitors (n = 32) were ATP-competitive inhibitors, interacting with the hinge-region of the active pocket, reaching the ribose pocket and targeting the phosphate-loop.

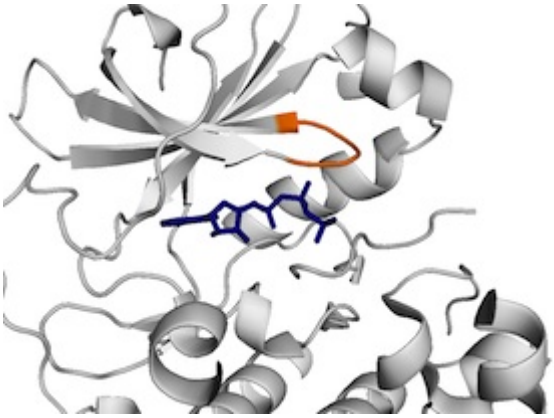

Fig. 1: co-cristal structure of PKB (grey) with AMP-PNP (blue). In orange the glycine-rich loop is indicated. PDB-code: 106K[5]

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DESIGN YOUR CHEMICAL UNIVERSE: MINING FRAGMENT SPACES FOR NOVEL MOLECULES

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The necessity for medicinal chemists to continually design novel molecules demands for efficient and innovative computational tools to support their effort. Due to the enormous extent of the chemical universe mining for novel molecules with desirable properties proves difficult. The common strategy is to limit search space by considering only those molecules with suitable physicochemical and topological properties. In addition to methods and data structures for efficiently modeling this chemical subspace, user-friendly tools to access this functionality are strongly required. Here, we present an efficient method for exhaustively enumerating all molecules within certain subspaces, i.e., molecules with specific physicochemical properties. Although, a complete enumeration of the chemical universe is not feasible, enumeration with stringent physicochemical constraints is possible[1]. Furthermore, our new approach is combined with other previously published methods for searching chemical space and can be access via a user-friendly graphical tool.

As the underlying model we use a *fragment space*, i.e., a combinatorial chemical space consisting of molecular fragments and connection rules. Each fragment has at least one reaction site that corresponds to an open valence. These sites are modeled as artificial atoms with a defined type, called *link atoms*. The connection rules determine compatibility of such link atoms. When two fragments are connected, the link atoms are removed and a bond in accordance with the connection rule is introduced.

In the past, fragment spaces have been subject to query-based search methods utilizing molecular similarity[2] and substructure search[3-4], these algorithms only retrieve molecules with high structural similarity. Our new approach for constraint-based enumeration complements these algorithms by searching for new molecules based on common physicochemical properties rather than structural similarity. The identified molecules therefore exhibit a much greater variety of structural features and possibly new scaffolds that have not been considered before.

Beside our constraint-based enumeration approach we combined the aforementioned query-based search methods into one user-friendly application. This enables the visualization of the contents of a fragment space (fragments and connection rules), as well as novel molecules. In addition to retrieving molecules, a user is enabled to design their own fragment spaces. A couple of scenarios have been published in the past: A new fragment space can be generated from a set of molecules[5], while an existing one can be manipulated in order to tailor it to a specific problem[6]. By providing an easy to use interface to create, manipulate, and search fragment spaces, our tool allows interactively navigating through the chemical universe.

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HETEROCYCLE-LINKED CONSTRAINED PHENYLBENZYL AMIDES, NOVEL ANTAGONISTS OF TRANSIENT RECEPTOR POTENTIAL CATION CHANNEL, VANILLOID SUBFAMILY MEMBER 1(TRPV1)

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Research on TRPV1-mediated pain transmission has progressed dramatically over the past several years.A series of phenylbenzyl amides with constrained heterocyclic linkers were found to be TRPV1 antagonists with promising in vivo profiles. In particular, one of the analogues containing a furan linker exhibited excellent TRPV1 antagonistic activity and in vivo analgesic efficacy. In addition, the binding modes of dibenzyl thiourea, benzylphenethyl amide, and furan-linked phenylbenzyl amide were examined by using the flexible docking study within the rTRPV1 homology model.

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STRUCTURE-ACTIVITY RELATIONSHIP STUDY OF MULTI-TARGET INHIBITORS

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The discovery of multi-target drugs has recently attracted much attention, because multi-target drugs are able to interact with several targets simultaneously and lead to new and more effective medications for a variety of complex diseases. There is a lack of elegant methods for *de novo* multi-target drug design and optimization, especially for multiple targets with large differences in their binding sites, even though a few methods have been developed for rational multi-target drug discovery. And there are not popular rules about structure-activity relationship (SAR) study of multi-target inhibitors.

We have been focused on developing multi-target inhibitors. Recently we have reported *de novo* multi-target ligand design method with an iterative fragment-growing strategy and used this method to design highly integrated inhibitors for proteins with dissimilar binding pockets[1]. For inflammation-related arachidonic acid (AA) metabolic network, we have designed dual-target inhibitors and studied QSAR of these dual-target inhibitors. 1) Dual-target inhibitors against 5-lipoxygenase (5-LOX) and prostaglandin E synthase (PGES). A comparative model for 5-LOX closed- conformation were built and used in virtual screening[2]. Several unique chemical structures compounds showed moderate inhibition activities in human whole blood (HWB) assay. Two of them showed good inhibition to the production of PGE2 in HWB assay. Both were also confirmed to inhibit 5-LOX and PGES in cell-free assay. Furthermore, structure activity relationship study was also performed to verify the binding modes of the lead scaffolds[3]. 2) Dual-target inhibitors against cyclooxygenase 2 (COX-2)/ leukotriene A4 hydrolase (LTA4H). We use our multi-target ligand design method to design COX-2/LTA4H dual-target inhibitor, one kind potential inhibitor is obtained by several rounds of 'design–synthesis–bioassay' studies and structure activity relationship is studied. We have also designed and synthesized a series of COX-2/LTA4H dual inhibitors by adding groups from known COX-2 inhibitors to LTA4H inhibitor backbone[4]. Two compounds showed dual inhibition activities in the enzyme assay, as well as in the HWB assay. Furthermore improvement is under investigation.

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UNDERSTANDING THE NON-CATALYTIC BEHAVIOUR OF HUMAN BUTYRYLCHOLINESTERASE SILENT VARIANTS: A MOLECULAR DYNAMICS APPROACH

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Prolonged apnoea following injection of the myoralaxant succinylcholine was first described in 1953. Because a large part of administered succinylcholine is shortly hydrolyzed by plasma butyrylcholinesterase (BChE), prolonged apnoea was attributed to deficiency in BChE. It was found that BChE deficiency is due to genetic variation. About 70 natural mutations of human BChE have been documented so far. Most of them cause alteration in BChE activity. This may result either from point mutations effect on catalytic functioning, or from point mutations that affect protein expression or cause truncations in the protein sequence. The most common and well-studied mutation affecting catalytic efficacy of BChE is Asp70Gly, leading to the so-called “atypical” BChE [1].

Recently, two novel BChE “silent” variants, Val204Asp [2] and Ala34Val [3] causing prolonged neuromuscular block after administration of the myorelaxant mivacurium were reported. To understand how these mutations disrupt the enzyme catalytic triad and determine a “silent” phenotype, we performed molecular dynamics (MD) simulations. To validate applicability of the approach for modelling the impact of point mutations on BChE catalytic machinery, we selected two BChE mutations previously studied experimentally: the silent variant Ala328Asp was compared to the catalytically active mutant Ala328Cys and the wild-type enzyme. During 100ns MD simulations, catalytic triad of the wild-typeenzyme stayed operative. Catalytic triad of Ala328Asp mutant was disrupted due to formation of new hydrogen bond between catalytic His438 and Asp328 instead of catalytic Glu325. Catalytic triad of Ala328Cys mutant was disrupted only during a short part of MD trajectory while His438 interacted with Cys328. This interaction was rather weak and shortly after His438 returned back to the triad in full accordance with experimental observations.

Two different mechanisms for disruption of BChE catalytic triad in novel mutants were discovered:

(1) Due to introduction of negatively charged amino acid, Val204Asp mutation leads to disruption of local hydrogen bonding network. The overall effect of the mutation on the protein structure is disruption of hydrogen bonding between Gln233 and Glu441 (this H-bonding brings the α/β-unit turn carrying the catalytic Ser198 close to the loop carrying the catalytic His438). This leads the catalytic Ser198 to move away from the catalytic His438, which in turn disrupts the functional catalytic triad. Additionally, this causes an increase in the enzyme volume, suggesting that enzyme is in a pre-denaturation (molten globule) state.

(2) Ala34Val mutation leads to an increase in the mobility of the Ω-loop. In this mutant, the Ω-loop residues involved in the peripheral anionic site and vicinal residues show increased fluctuations. This increased mobility is subsequently transmitted down to the active site gorge to key active site residues: Trp82 (the π-cation binding site) and catalytic His438. Increased fluctuations of these 2 residues cause disruption of the catalytic triad: catalytic His438 no longer interacts with Ser198, but instead freely moves, forming hydrogen bonds either with residues Glu197 and Trp82, or peripheral site residue Tyr332.

Kinetic study of Ala34Val with butyrylthiocholine as the substrate demonstrated that in the presence of substrate excess, the enzyme catalytic activity is restored. Steered MD simulations with butyrylcholine showed that the substrate moving down the gorge may lug off the loop carrying His438, and bring it back close to the other catalytic residues in functional conformation.

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ASSESSING TIGHT BINDING OF 6-METHYLURACIL DERIVATIVES TO ACETYLCHOLINESTERASE: BINDING FREE ENERGY AND LIGAND TRAFFICKING MOLECULAR MODELLING STUDIES

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Previously reported compound called C-547, a derivative of 6-methyluracil, tightly binds to acetylcholinesterase (AChE), acting as a non-covalent inhibitor [1]. Kinetic measurements provided K_I value of 80 pM. However, after 20 min of incubation of AChE with C-547, the enzyme was irreversibly inhibited.

We performed a molecular docking study for the binding of the C-547 to AChE active site and within the gorge. This provided ΔG_{bind} value of -13.72 kcal/mol in good agreement with the measured K_I value, and showed interaction of the ligand groups with AChE amino acids side chains all along the gorge, from the active site at the bottom to the peripheral anionic site (PAS) and the gorge rim. Interactions of the inhibitor with the enzyme residues include hydrogen bonds, hydrophobic, π-π and π-cation interactions. Alanine screening study provided that the major binding contributions are interactions of ligand groups with side chains of Trp86 of cation-binding site, Tyr341 in the middle of the gorge, Trp286 of PAS and Tyr124 in the middle of the gorge (amino acids listed in order of decreasing contribution).

To include the contribution of protein-ligand complex dynamics to the free energy of binding, we performed molecular dynamics free energy calculations, using alchemical route algorithm. This provided a ΔG_{bind} value of -12.2 kcal/mol. This value is also in agreement with the measured K_I value. However, it doesn't explain the apparent irreversible binding of the inhibitor observed after 20 min incubation.

To investigate the binding process, we performed steered molecular dynamics of the enzyme-ligand association and dissociation. Simulation of the binding process showed that ligand moving across the gorge bottleneck (Tyr124 and Tyr341 residues) needs a great increase in force value to go deeper down the gorge. This step is considerably impaired because the inhibitor nitrophenyl ring and tetraethylammonium group have to pass the bottleneck. Pulling the ligand out of the gorge is accompanied by enzyme conformational changes: protein loops lining the gorge are everted outside the enzyme as the ligand is expelled from the gorge. Restraints applied to keep integrity of the native protein structure resulted in extremely high pulling force values needed to move the inhibitor out of the gorge. The first peak corresponds to the energy needed to move out nitrophenyl ring and tetraethylammonium group from the active site, and the second peak reflects the energy needed to move these ligand groups across the Tyr124–Tyr341 bottleneck. Umbrella sampling technique was used to estimate binding free energy.

Steered molecular dynamics study showed that inhibitor trafficking along the gorge involves crossing the bottleneck barrier. When this gate is passed, the ligand becomes tightly bound both to the AChE gorge and the active site, but it is trapped, what makes this non-covalent binding irreversible. In conclusion, this ligand appears to be a tight slow-binding inhibitor.

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MOLECULAR DOCKING STUDY OF SPECIFICITY OF N,N-DISUBSTITUTED 2-AMINOTHIAZOLINES AS INHIBITORS OF BUTYRYLCHOLINESTERASE AND CARBOXYLESTERASE

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Serine hydrolases play important roles in many physiological processes. Selective inhibitors of some serine esterases have been approved as drugs for treatment obesity, type 2 diabetes, microbial infections and neurodegenerative disorders. Searching for new inhibitors of this class of enzymes is of great interest. In particular, inhibitors of acetylcholinesterase (AChE, EC 3.1.1.7) contribute to the improvement of cognitive functions in dementia of various origins. Inhibitors of butyrylcholinesterase (BChE, EC 3.1.1.8) also improve cognitive function, that is especially important for severe stages of Alzheimer's disease when the activity of AChE is decreased and its function, hydrolysis of acetylcholine, is implemented by BChE. BChE inhibitors do not have dangerous side effects such as acute cholinergic toxicity and other adverse effects of AChE inhibitors. Carboxylesterases (CaE, EC 3.1.1.1) play major roles in the activation, detoxification and biodistribution of numerous drugs including esters, thioesters, carbamates, and amides. Application of selective CaE inhibitors to increase bioavailability and/or extend the half-life of drugs may represent a viable therapeutic option.

Synthesis of new derivatives of 2-aminothiazolines (Fig. 1), their biological evaluation as inhibitors of three serine esterases AChE, BChE and CaE was reported recently. Some effective inhibitors of BChE and CaE have been found in this series which have a low anti-AChE activity. To gain more insights into the molecular determinants responsible for the observed ability to inhibit the BChE and CaE activity, a modelling study was undertaken through molecular docking of the most active and selective compounds.

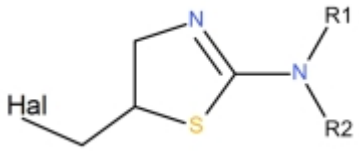

Figure 1. General structure of 2-amino-5-halomethyl-thiazoline derivatives.

In the present study we calculated binding energies of 31 N-substituted 2-amino-5-halomethyl-thiazolines with two target enzymes, BChE and CaE, using Autodock 4.2 and FlexX programs. An influence of the method of determining the atomic charges on the ligands and proteins on modeling results was studied. It was demonstrated that use of atomic charges derived from quantum-mechanical calculations helps to improve significantly the results of molecular docking. Different protonation states of the ligands were considered and several popular programs for pKa estimation were tested. Also, geometry of the enzymes was partially optimized by means of semi-empirical quantum chemistry methods for improvement of the crystallographic structures traditionally used for molecular modeling. The results explain the observed inhibitor selectivity of N-substituted 2-amino-5-halomethyl-thiazolines. It was shown that these compounds bind preferably with the active site of BChE, while in CaE they are preferably located at the mouth of the enzyme gorge. Obtained results allow us to make recommendations for their focused modification.

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DESIGN, BIOLOGICAL ACTIVITY PREDICTION, SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NEW AMINO ACID DERIVATIVES OF 2-CHLORO-N-(9,10-DIOXO-9,10-DIHYDROANTHRACENE-1-YL)ACETAMIDE

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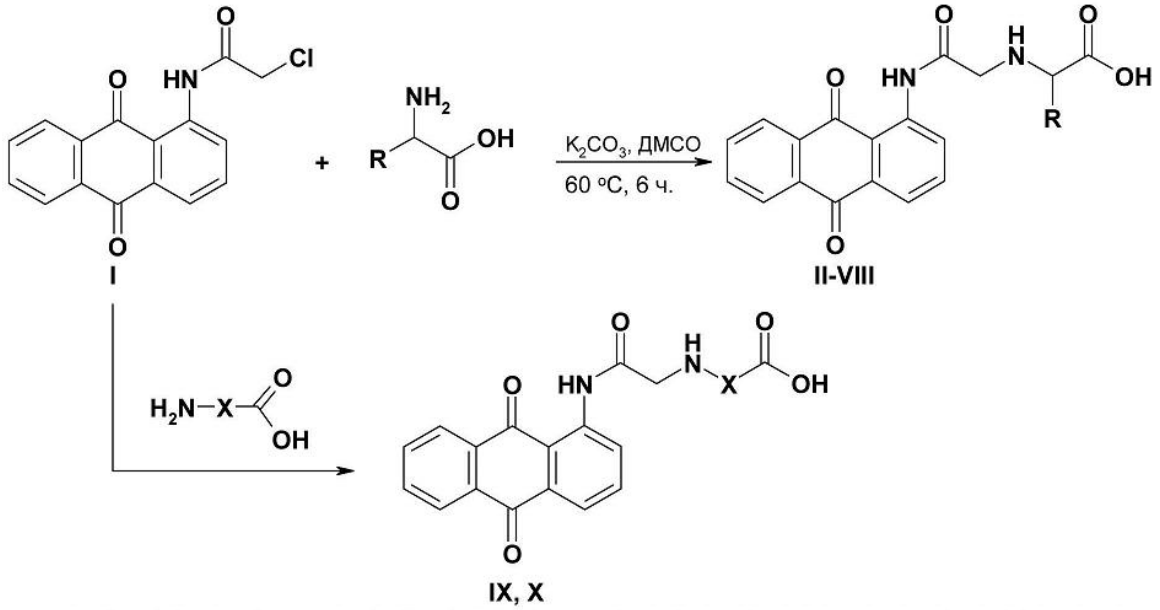
Due to their biological activity 9,10-anthraquinone derivatives are widely used by pharmaceutical, cosmetic and food industries. However, information about biological activity of compounds contained antraquinone core modified by chloroacetamide fragment is still very limited. We performed design, computational bioactivity prediction, chemical synthesis and biological testing of new amino acid derivatives of 2-chloro-N-(9,10-dioxo-9,10-dihydroantracene-1-yl)acetamide (**I**).

Prediction of biological activity spectra of the designed compounds were carried out using computer program PASS [1-3]. Currently PASS predicts over 6000 biological activities on the basis of structural formula of compound with average accuracy about 95% based on SAR analysis of the training set containing information about almost 1 mln known biologically active compounds.

According to the PASS predictions, some designed derivatives may exhibit antimicrobial, antineoplastic, antioxidant, antiviral and immunostimulating activities. The most promising compounds were synthesized (Figure 1) and their antimicrobial activity was tested. For some compounds the results of computational prediction corresponded to the experimental data [4]. In accordance with the prediction, the further studies of antineoplastic and antioxidant activities of the synthesized compounds are under way now.



R = -H (II); -CH_3 (III); -$CH_2C_6H_5$ (IV); -$CH(CH_3)_2$ (V); -$CH_2CH(CH_3)_2$ (VI); -$(CH_2)_2SCH_3$ (VII); -$(CH_2)_2COOH$ (VIII)
X = $(CH_2)_2$ (IX); $(CH_2)_3$ (X)

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PREDICTION OF TAUTOMER EQUILIBRIUM CONSTANTS USING THE CONDENSED GRAPHS OF REACTION APPROACH

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Chemical reactivity, spectral and physico-chemical properties of compounds are highly dependent on equilibrium between tautomeric forms. Typically, in chemical databases or QSAR/QSPR modeling the most populated in water form is considered. On the other hand, many experiments are carried out in non-aqueous media or water-organic solvent mixtures and, therefore, prediction of the tautomers' population as a function of solvent represent a real challenge for chemoinformatics.

In this work, we report QSPR modeling of tautomer equilibrium constants ($\log K_T$) taking into account solvent effects. A dataset containing $\log K_T$ values for 744 tautomer equilibria in 13 pure solvents and 7 types of water-organic solvents mixtures has been compiled from the literature. These data cover 11 types of tautomer transformations. 2-3 tautomeric equilibria of each type (32 in total) in different solvent and temperatures were selected to external validation set. Each equilibrium has been transformed into Condensed Graph of Reaction (CGR) representing a pseudo-molecule characterizing by both conventional chemical bonds (e.g., single, double, aromatic, etc) and dynamical bonds (e.g., single transformed to double) [1, 2]. For the ensemble of CGRs, the ISIDA fragment descriptors were generated [3]. Solvents were encoded by 15 descriptors representing solvent polarity, polarizability, H-acidity and basicity [2]. QSPR models were built using SVM, Random Forest and Gaussian Processes methods. Both "universal" (for the entire dataset) and "specific" (for each transformation type) models were obtained. They display reasonable predictive performance: In 10 x 5-fold cross validation, RMSE ≈0.9 and 0.15-1.34 $\log K_T$ units for universal and specific models, respectively. Relative populations are predicted with RMSE ≈19% in cross-validation with the universal model. The most stable tautomer is assigned correctly in 81% of cases. Using fragment control applicability domain RMSE 1.44 $\log K_T$ units were obtained on external validation set.

For the comparison purpose, $\log K_T$ values for some selected equilibria in pure solvents were also assessed in quantum chemical (QC) calculations at semi-empirical and ab initio levels. In the first series of calculations, some 600 equilibria in pure solvents were calculated using PM6 semi-empirical method using IEFPCM model for solvent description with SMD non-electrostatic corrections. Prediction was far worse than the null model, in which all predicted values are equal to the average property value on the training set. For the external validation set of 32 equilibria, both DFT B3LYP/6-311++G(d,p) and CBS-4M methods were applied. They involved the same continuum solvation model as in semi-empirical calculations. Both methods poorly predict $\log K_T$: RMSE is 8.99 and 12.67 $\log K_T$ units respectively. Thus, our QSPR models perform much better than any type of QC calculations.

Tautomeric equilibria in water at temperature about 25°C were selected to test the quality of predictions made by ChemAxon/Tautomerizer plugin. Surprisingly, ChemAxon predictions were worse than the null model, whereas our models yields rather reasonable predictions.

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STRUCTURE-ACTIVITY RELATIONSHIPS AND MOLECULAR DOCKING FOR CARBAMOYLATED 1-HYDROPERFLUOROISOPROPANOLS AS NEW SELECTIVE INHIBITORS OF CARBOXYLESTERASE

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Carboxylesterases (EC 3.1.1.1, CaE) have key roles in the metabolism and pharmacokinetics of a wide variety of ester-containing clinical drugs. CaE inhibitors potentially have dual roles in modulating drug action by both reducing induced toxicity and/or increasing molecule half-life. Selective CaE inhibitors could be used as co-drugs to improve the efficacy of clinically approved agents.

We have synthesized a number of carbamoylated 1-hydroperfluoroisopropanols of general formula $RNHC(O)OCH(CF_3)_2$ where R = CH_3 (**1**), *n*-C_3H_7 (**2**), *n*-C_4H_9 (**3**), *n*-C_6H_{11} (**4**), *tert*-C_4H_9 (**5**), *cyclo*-C_6H_{11} (**6**), *cyclo*-C_7H_{13} (**7**), C_6H_5-CH_2 (**8**), C_6H_5 (**9**), Ar-X (**10;** X = 3-Cl; 4-Cl; 3,4-Cl) [1]. The inhibitor activity against three esterase targets: human erythrocyte acetylcholinesterase (AChE, EC 3.1.1.7), horse serum butyrylcholinesterase (BChE, EC 3.1.1.8) and porcine liver CaE was studied. IC_{50} values at 10 min incubation and k_i ($M^{-1}min^{-1}$) values were determined. It was shown that the carbamates did not inhibit AChE, weakly inhibited BChE and most effectively inhibited CaE. For compounds with linear R, inhibitor activity against BChE and CaE enhanced with hydrophobicity increasing. Carbamate (**5**), R = *tert*-C_4H_9, showed only a weak anti-CaE activity. Inserting the cyclic R substituents resulted in a significant increase in the anti-CaE activity: for (**6**) IC_{50} = 0.39±0.05 μM, k_i = (1.42±0.20) x10^5 $M^{-1}min^{-1}$; for (**7**) IC_{50} = 0.24 ± 0.037 μM, k_i = (2.10 ± 0.30) x10^5 $M^{-1}min^{-1}$; while anti-BChE activity of these compounds was dramatically decreased. Therefore, carbamates with R = *cyclo*-C_6H_{11} (**6**) and *cyclo*-C_7H_{13} (**7**) were effective and high selective inhibitors of CaE: selectivity CaE/BChE was 436 and 288 respectively. On the other hand, replacement of cyclic R substituent with C_6H_5-CH_2 (**8**) significantly reduced anti-CaE activity; N-aryl carbamates (**9-10**; R = Ar, Ar-X) did not inhibit CaE.

The structural aspects of inhibition of CaE and BChE by carbamoylated 1-hydroperfluoroisopropanols were studied by the method of molecular docking using program AutoDock 4.2. X-ray structures (PDB ID 2H7C for CaE and 1P0I for BuChE) were saturated with water molecules and optimized by means of molecular mechanics. Docking to CaE was carried out for normal R-containing compounds (**2**) – (**4**), *N-cyclo*-alkyl carbamates (**6**), (**7**); carbamates with R = C_6H_5-CH_2 (**8**), and R = C_6H_5 (**9**). Docking to BChE was performed for *N-cyclo*-alkyl carbamates (**6**) and (**7**).

The docking results for *N*-alkyl carbamates demonstrated that normal R elongation led to increasing hydrophobic interactions in the CaE active site. Binding energies of CaE-inhibitor complexes enhanced with R elongation: -3.55 (**2**), -3.85 (**3**), -4.43 (**4**) kcal/mol that agreed with rising anti-CaE activity in this series. The most active CaE inhibitors, *N-cyclo*-alkyl carbamates (**6**) and (**7**) have favorable hydrophobic interactions in the CaE active site; a high flexibility of (**7**) allows it to change the position during reaction of carbamoylation. The complexes CaE - *N-cyclo*-alkyl carbamates have the highest binding energies: -6.38 (**6**), -4.92 (**7**) kcal/mol; whereas the binding energy of BChE - *N-cyclo*-alkyl carbamate complexes was rather low that agreed with low anti-BChE activity of cyclic carbamates.

The docking simulation were performed to clarify differences in anti-CaE activity of carbamates (**6**) R = *cyclo*-C_6H_{11}, (**8**) R = CH_2-C_6H_5 and (**9**) R = C_6H_5. The following binding energies have been shown for the three enzyme-inhibitor complexes: -6.38 (**6**), -4.74 (**8**) and -3.27 (**9**) kcal/mol, and favorable distance for nucleophilic attack between the carbonyl carbon atom of the inhibitor and the oxygen atom of Ser221 of CaE. The most active compound (**6**) has an optimal orientation for carbamoylation of the active Ser221. The inactive compound (**9**) has very low energy of binding with CaE, which explains that its inhibitory activity was not observed experimentally. Weak inhibitory activity of the compound (**8**) is associated, apparently, with steric hindrances in carbamoylation of Ser221. Thus, the results of molecular docking confirm and explain the experimental data.

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THE ACID/BASE PROFILE OF THE HUMAN METABOLOME

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The acid/base profile of drugs is known to greatly affect their biopharmaceutical characteristics. This study will compare the acid/base profiles of human small molecule metabolites (the human metabolome) against a set of natural products and established drugs. The comparison will also focus on a selected set of physicochemical properties. A further set of analyses will be presented on time related differences in the acid/base profile of drugs approved for human use before and after 1982.

The acid/base profile of the non-lipid component of the human metabolome was found to be similar to both drugs and natural products. In contrast, and as expected, the lipid component of the metabolome displayed considerable differences to the other datasets. An inspection of the physicochemical properties of the non-lipid set showed that they had lower average ClogP values and more H bond donors than the other compound sets. Overall however, the non-lipid set shared similar distributions of physicochemical property values with the drug set. Given then the non-lipid metabolites represent biochemicals that interact with at least one macromolecular target, their profiles are of interest to drug discovery scientists. [1]

The distribution of acid/base property values for drugs approved before and after 1982 were similar, however, there was a trend for molecules with more complex arrangements of acids and bases, as well as showing a greater number of compounds containing basic groups with pK_a values below 7.0.

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USE OF MLR-QSARS TO EVALUATE NEW CINNAMIC ACID-BASED ANTIMALARIAL DERIVATIVES AS POTENTIAL ANTITUBERCULAR AGENTS

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Tuberculosis (TB) is the second leading cause of death from an infectious disease (1). 8.6 million new cases and 1.3 million deaths are the alarming TB figures recently reported by WHO for 2012 (1). The rise of multidrug-resistant (MDR-TB) and extensively drug resistant (XDR-TB) forms of TB has urged the need to find new and more effective antitubercular drugs. From the various strategies being used with this purpose, one of the most successful has been the repurposing for TB of compounds used to treat other conditions. This is the case of gatifloxacin and moxifloxacin, both in phase 3 of the clinical TB pipeline.

In this context, four series of cinnamic acid derivatives, previously synthesized as antimalarials, were analyzed as potential anti-TB drugs. (2) Starting with a set of cinnamic acid derivatives collected from literature with reported activity against *M. tuberculosis* (*Mtb*), (3) multiple linear regression (MLR)-based QSAR models have been derived. (4) The robustness and predictive ability of these models have been assessed by rigorous internal and external validation procedures. In particular, their predictive power was evaluated using the most stringent validation criteria to date and precautionary threshold values, along with visual inspection of scatter plots (5). The possibility of chance correlation was precluded by *Y*-randomization techniques, and the applicability domain of the models gauged by various filtering methods. The best derived model, found to predict *p*MIC with an *SD* of 0.25 log units, was used to estimate the anti-TB activity of the 95 synthesized antimalarials. From these, 19 exhibited high predicted anti-TB activities (MIC = 0.2-0.8 μM), comparable to that of the reference drug, isoniazid (MIC = 0.3 μM) and the most promising compounds were selected to be tested *in vitro* against *wt Mtb.*

Acknowledgements

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A SUCCESSFUL QSAR STRATEGY FOR THE DEVELOPMENT OF NEW ANTITUBERCULAR COMPOUNDS

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Tuberculosis remains a widespread infectious disease of global proportions with over 1.3 million deaths and 8.6 million new cases as reported by WHO in 2012 (1). The upsurge of multidrug resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) has significantly limited the number of available drugs for treatment, making the quest for new and effective drugs a major challenge. In this work we describe the QSAR-oriented design, synthesis and *in vitro* antitubercular activity of 13 isoniazid (INH) derivatives against H37Rv and two resistant TB strains, one carrying only a *katG* S315T mutation and the other resulting from a full deletion of the *katG* gene (Δ*katG*) (2, 3). QSAR studies were developed on the basis of classification (RFs and ASNNs) and MLR approaches and rigorous validation procedures were applied to ensure the models' robustness and predictive ability. Five of the newly synthesized INH derivatives showed activities against H37Rv higher than that of the referenced compound, INH (*i.e.*, MIC ≤ 0.28 μM) and, surprisingly, one compound exhibited a six fold decrease in MIC against the *katG* S315T resistant strain, by comparison with INH (6.9 μM vs. 43.8 μM). This finding seems to question the relationship between the increased resistance of *katG* (S315T) to INH and a putative larger steric constraint in the access channel to the heme active site in the mutated strain. Additionally, the new derivatives were ineffective against the Δ*katG* strain, hence corroborating the importance of KatG in the activation of INH-based compounds. The most potent compounds were also found not to be cytotoxic against VERO cells being thus promising scaffolds for drug development.

Acknowledgements

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ESTIMATION OF THE DIFFUSION COEFFICIENTS OF MOLECULES USING MOLECULAR MODELING

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Diffusion is an important physicochemical phenomenon in molecular transport and the life sciences. Following the administration of a drug, molecules of the drug are transported via the bloodstream and distributed to organs by active and passive transport. Because diffusion is the driving force behind passive transport, information on drug diffusion is useful for analyzing drug delivery systems and pharmacokinetics. The extent of molecular diffusion is regulated by the diffusion coefficient of a molecule. When a molecule is approximated with a sphere of radius r, its diffusion coefficient D is expressed by the Stokes-Einstein equation: $D = k_B T/6\pi r\eta$. Here, k_B, η and T are the Boltzmann constant, the viscosity of the solvent, and the absolute temperature, respectively. Using this equation, the diffusion coefficient D can be determined from an approximated molecular radius. Recently we have demonstrated that this approach provides reasonable estimation of the diffusion coefficients of several sugars[1].

In this study, we have farther estimated diffusion coefficients of some amino acids and molecules with hydroxyl groups. First, stable conformations of some sugars were calculated based on the molecular modeling approach using the MOE system[2]. The approximated or effective radii of molecules were calculated based on the radius of gyration of each molecule in order to take molecular shapes into account. Finally, diffusion coefficients were estimated from the Stokes-Einstein equation. Table 1 shows some results of our approach, including those obtained before. It shows number of conformers of molecules with ΔE less than 3 kcal/mol. The effective radii (r_e) of those molecules and the estimated diffusion coefficients (D_e) as well as reference values (D_0) are also listed in Table 1. For example, the diffusion coefficient of fructose was estimated to be 6.8×10^{-6} cm^2/s while the experimentally determined diffusion coefficient was reported to be 6.86×10^{-6} cm^2/s. The results presented in Table 1 indicate that our approach accurately estimates the diffusion coefficients of sugars. As for amino acids, however, the agreements of the estimated and observed values of diffusion coefficients are not so good as those of sugars. To our knowledge, few experimental values of diffusion coefficients have been reported. Our approach for estimating the diffusion coefficients of small molecules provides an alternative to the experimental measurement of diffusion coefficients, although more improvement might be desirable.

Table 1 Stable conformers, effective radii, and diffusion coefficients of molecules

compound	no. of conformers[a]	r_e	diffusion coefficient ($\times10^{-6}$cm^2/s)	
			D_e [b]	D_0 [c]
glycerol	5	2.9	8.5	-
xylose	14	3.4	7.2	7.50[5]
fructose	4	3.6	6.8	6.86[3], 7.00[4]
glucose	10	3.4	6.7	6.79[3], 6.75[4]
sucrose	15	4.8	5.1	5.23[3], 5.23[4], 4.85
maltose	24	5.0	4.9	5.18[5]
glycine	1	2.7	9.1	10.4
alanine	1	2.9	8.4	8.99

a. No. of conformers with $\Delta E < 3$ kcal/mol.
b. D_e are calculated by our work.
c. D_0 are reported values extrapolated to infinite dilution.

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PREDICTING BSEP INHIBITION BY DRUGS

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The bile salt export pump (BSEP) is an ATP-binding cassette (ABC) transporter that mediates bile salts secretion across the canalicular membrane of the hepatocytes. Inhibition of this transporter causes the intracellular accumulation of bile salts, leading to acquired cholestasis [1]. Some approved drugs like cimetidine, verapamil or chlorpromazine are known to inhibit BSEP, which is an important risk factor for drug-induced cholestasis [2]. Therefore, detection of such inhibitors at early stages of the drug development process can save time and efforts.

In this work, we trained predictive models for BSEP inhibition using a dataset of 838 drug-like compounds provided by AstraZeneca. Simple exploratory analysis revealed the importance of hydrophobicity and aromaticity for BSEP inhibition. The best performing model in terms of predictivity by both 10-fold cross-validation and external set validation [3][4] was then used to screen the DrugBank database for potential BSEP inhibitors. Top-ranked molecules were carefully checked for known BSEP inhibition. Out of the 59 top-ranked molecules, 17 have been reported as BSEP inhibitors either in Drugbank or in the literature. Given these encouraging results, 10 top-ranked diverse compounds were purchased and tested for their ability to inhibit BSEP. Of these 10 compounds, the three drugs bromocryptin, nelfinavir and montelukast are reported with an IC 50 below 30μM in a taurocholate efflux inhibition assay. The positive control, cyclosporin A, is measured with an IC50 of 7μM.

This work received financial support from the University of Vienna, doctoral programme Biopromotion, and from the Innovative Medicines Initiative Joint Undertaking under grant agreement n°115002 (eTOX), resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in-kind contribution. We also acknowledge financial support provided by the Austrian Science Fund, grant F03502.

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BEYOND OVERTON's RULE - QUANTITATIVE MODELLING OF PASSIVE PERMEATION THROUGH TIGHT CELL MONOLAYERS

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Passive permeation of drugs through tight endothelia is a fundamental step that determines their bioavailability at the target tissue. This is generally rationalized in terms of drug hydrophobicity, based on Overtons's rule, but the severe limitations of this simplistic approach lead to poor predictive value. The lack of adequate predictors for the rate of passive permeation through tight endothelia is limiting the development of drugs targeted to the brain and generates significant economic and human costs.

In this work we have modeled the rate of passive permeation of a homologous series of amphiphiles across a tight cell monolayer to obtain rules relating the amphiphile structure and its rate of permeation. The amphiphile enters the system from the serum (equilibrated with serum albumin and lipoproteins) and its sequestration by serum components, interaction with the endothelium and accumulation in the tissue is followed over time. The overall processes is quantitatively described by a mechanistic model that takes into account the kinetics and equilibrium parameters for interaction of the amphiphiles with each barrier and binding agent [1-4]. Contrary to the common expectation, we observe a decrease in the characteristic rate of accumulation in the tissue with the increase in the amphiphile hydrophobicity for ClogP higher than 2.9, Figure 1. A sensitivity analysis was performed to identify the effect of each step in the overall permeation of the amphiphiles. The extent of sequestration in the serum strongly influences the observed permeation rate for all amphiphiles although its importance is not monotonically depend on the solute hydrophobicity, Figure 1. A single rate limiting step was identified for amphiphiles with low or high hydrophobicity, corresponding to the translocation through the membranes or desorption from the apical outer leaflet, respectively. For amphiphiles with intermediate hydrophobicity both steps influence significantly the overall rate of permeation observed. The analytic equations that describe the rate of entry into the tissue for processes limited by a single step are also given.

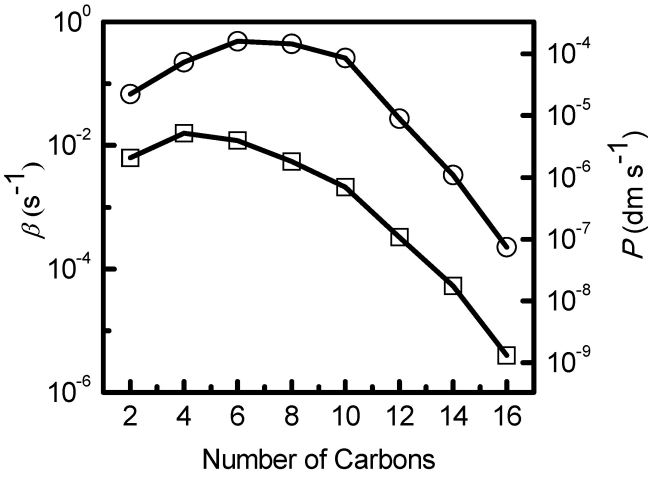

Figure 1 - Dependence of the characteristic transfer rate constant, β, and Permeability coefficient, P, with the number of carbons for the NBD-C_n homologous series, for a complete transfer of amphiphile from the blood into the tissue. The results shown are for a model including sequestration of the amphiphile by albumin and lipoproteins in the blood (□) and in the absence of sequestration (○).

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COMPUTATIONAL PREDICTION OF LIVER TOXICITY WITH QSPR BASED ON A LARGE DATASET

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Liver toxicity is still a major concern of pharmaceutical development accounting for costly clinical failures. Computer models can help to reduce attrition by identification of liabilities early in Discovery. However, a recent review on the prediction of liver injury[1] shows, that available computational models often fail to predict novel chemotypes, i.e. a set of structural features not well sampled in the model training set. Low sensitivities (~50%) are of highest concern to many models, and better computational models are eagerly awaited.

Liver toxicity is multi-facetted, thus our QSPR approach started with a clean definition of the pathology. Liver-related adverse findings were categorized hierarchically into seven pathology classes. Human and preclinical animal data were kept separately. A large data repository of >4000 compounds from public-domain literature and in-house data sets was compiled and classified accordingly. Detailed information on species, study type, findings and dosing was recorded for evaluation.

All published compounds, excluding 269 Sanofi drug candidates, were randomly assigned to training (80%), test (10%), and internal validation sets (10%) keeping the ratio of active to inactive compounds constant. For each species and pathology class a support vector machine model was trained. Each model was consecutively optimized using a genetic algorithm for feature selection from a large pool of diverse descriptors selected from fingerprints (MACCS keys) as well as physical properties and topological and pharmacological features (MOE, CATS, VolSurf+). Validation on the internal validation sets showed a good performance both for human and preclinical endpoints with areas under the ROC curve (AUC) of 0.71 to 0.77, indicating a good separation of active and inactive compounds. Additionally, we applied a statistical analysis to define a confidence parameter for each prediction. This parameter depends on the local enrichment (predictivity) and serves the purpose to identify uncertain predictions to define the model applicability domain.

Finally, in a rigorous setup the preclinical models were applied to 269 very diverse internal and non-published compounds with 28 day rat study data. Neglecting model applicability domains, the AUC values were quite low (0.56 to 0.67). In contrast to that, the previously established confidence domains increase sensitivity (>80%) and positive predictive value (up to 49%) as compared to commercially available models (Leadscope and DEREK) for human endpoints (sensitivity < 20%; positive predictive value < 25%; considering applicability domain). Nevertheless, applicability of our models to ~55% of our data set is retained. This clearly underlines the need for well-defined and optimized model applicability domains in QSPR models for hepatotoxicity.

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UNDERSTANDING TLR2 ANTAGONISM BY SMALL MOLECULES

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Toll-like receptors (TLRs) play an essential role in the initiation of the immune response upon recognition of pathogens (1). Recently, the development of chronic inflammatory diseases like rheumatoid arthritis has been linked to abnormal TLR signaling (2). Therefore, targeting the receptors has been suggested as a promising strategy to treat these conditions. We present the successful rational design of TLR2 antagonists through molecular modeling and virtual screening.

The development of TLR2 antagonists is especially challenging due to the small amount of data available. To overcome these difficulties we developed and performed a combined structure- and ligand-based approach. In the ligand-based part of our work, a two-stepped shape- and feature-based similarity search was performed using known TLR2 modulators as query structures. In the structure-based part of the study, a 3D pharmacophore derived from molecular interaction fields (MIFs) of the TLR2 binding site was employed to identify potential TLR2 binders. Virtual screening hits were selected for biological validation, which resulted in the identification of several small molecule TLR2 antagonists with IC_{50} values in the low micromolar range (3).

Next, we performed an extensive study to identify plausible binding modes for novel small molecule TLR2 antagonists. Virtual hits confirmed to be active were first classified into structural categories and analyzed for potential activity cliffs necessary for binding. Docking studies were performed for each individual structural class leading to the elucidation of plausible binding modes. The gained knowledge was integrated into a 3D pharmacophore collection that contains all currently available information on TLR2 antagonism induced by small molecules.

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MOLECULAR DOCKING STUDIES OF ACRB TRIMERIC MULTIDRUG EFFLUX PUMPS

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Multidrug resistance (MDR) has become a growing problem in the medical treatment of pathogenic bacteria (1). RND family efflux pump proteins are generally showing an important role for MDR in Gram-negative bacteria and most of the clinically used antibiotics are the substrates of this bacterial efflux RND pump family (2). An important group of RND pump family is based on a tripartite assembly, which is composed of an outer membrane exit duct of the TolC family, an energized inner membrane transporter (AcrB), and a periplasmic adaptor protein (AcrA), also known as a membrane fusion protein (3). The transporter AcrB, which presumably captures the drug molecules mainly from the periplasm (4), shows an extremely wide substrate specificity.

The goal of this research was that predictions from the structure activity relationships of some novel benzothiazole derivatives possibly would lead to design new AcrB inhibitors that would not be pumped out quickly and better inhibitors of these pumps by using a docking protocol in Discovery Studio 3.5 (5).

Key words: Efflux pumps, AcrB, MDR, Docking, Molecular Modelling

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NOVEL APPROACH FOR NAVIGATING THE BIOLOGICALLY RELEVANT CHEMICAL SPACE OF SCAFFOLDS AND R-GROUPS. PART 1: SCAFFOLDS

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We will describe a novel approach for guiding medicinal chemists in i) identifying bioisosteric ring systems for *scaffold hopping* and selecting diverse chemotypes [1,2] and ii) analyzing the biologically relevant chemical space covered by R-groups [3,4]. These tools are available as interactive web-based applications and will be presented in two posters.

In this first poster, we present our approach for mining and analyzing scaffolds.

Scaffolds are described using a novel 2D alignment-independent descriptor, Scaffold Fingerprint (SFP). This fingerprint encodes information on the topology, shape, sp3 carbons and their chirality, pharmacophoric features as well as the position and atom type of the diversity point(s) of the scaffold. SFP is very simple to calculate, fast and easily interpretable.

It was implemented in a tool designed for:

1. Interactive visual inspection of the chemical space of the available fragment rings. The analysis of ring contents of databases will be presented: DrugBank, ChEMBL, Zinc, natural products and target-focused sets. [1]
2. Scaffold bioisosteric replacement using a database of over 150000 ring fragments extracted from commercially available and bioactive compounds. Very good enrichment factors and recall values were obtained in two different retrospective study cases: MCH-R1 antagonists and PDE-5 inhibitors. [2] This approach was compared with gold-standard ECFP_6 fingerprints.

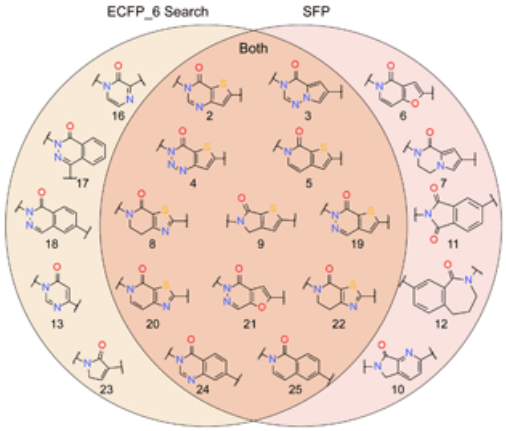

Figure 1. MCH-R1 scaffolds found among the 500 top ranked scaffolds. Overlap between SFP and ECFP_6 fingerprints.

3. Chemotype-based diverse selection of compounds for acquiring commercial libraries or for selecting representative internal compounds for screening campaigns. [2]

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NOVEL APPROACH FOR NAVIGATING THE BIOLOGICALLY RELEVANT CHEMICAL SPACE OF SCAFFOLDS AND R-GROUPS. PART 2: R-GROUPS

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In this second poster, we present our approach for R-groups navigation [1,2].

R-group analysis is based on a descriptor accounting for ligand-receptor interactions (LiRIf) that enables the definition of a reference-independent space. The most populated ligand-receptor interactions across different target families (GPCR, Kinases, nuclear receptors) are quickly identified. Using a real project-based data set [2], we will show the impact of this system on four key navigation strategies for the drug discovery process:

1.Competitor's patents analysis: comparison of patents coverage and identification of the most frequent fragments.

2.Structure-activity relationship (SAR) analysis: identification of critical ligand-receptor interactions, substructural frequent patterns and activity cliffs.

3. Compounds acquisition: selection of commercially available molecules that complement unexplored spaces or areas of interest.

4. Design of new analogues: selection of commercially available reagents based on reaction types and according to the exploration purpose (focused or diverse).

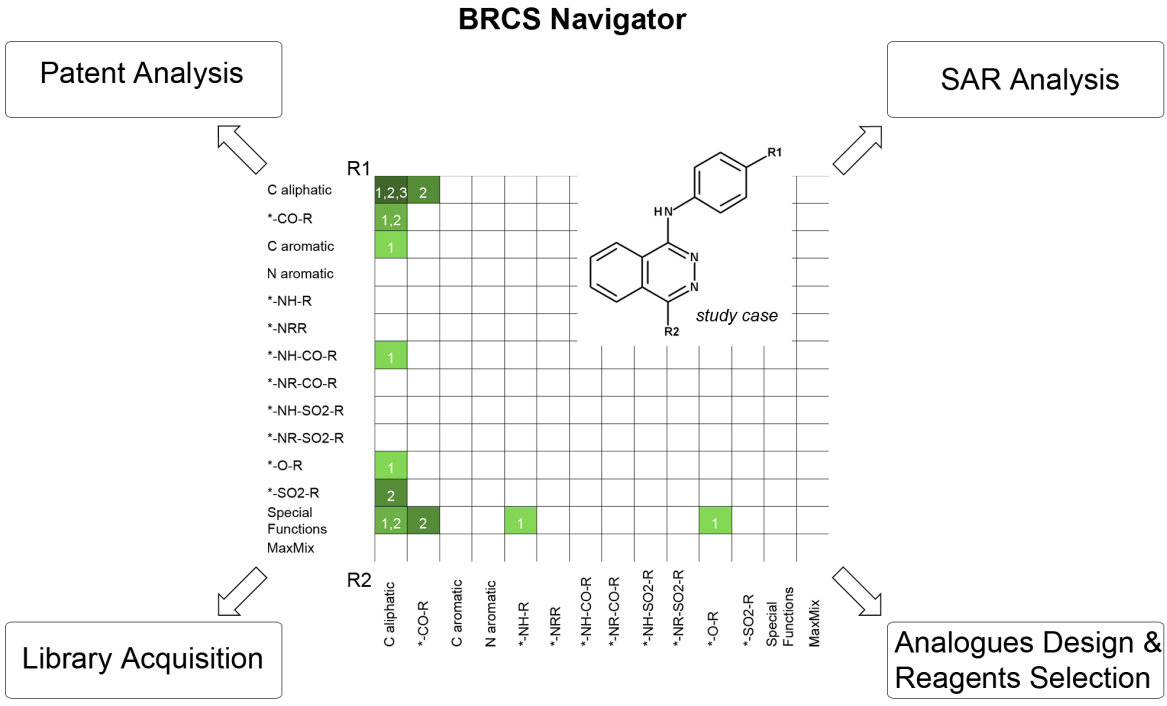

Figure 1. Schematic representation of our interactive tool for R-group navigation.

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DEVELOPING QSAR MODELS FOR MEMBRANE PERMEABILITY FOR DIFFERENT CHEMICAL CLASSES AT VARIOUS pHs

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Human absorption is important ADME property for orally administered drugs. Drugs can be transported across intestinal epithelium using two ways: active and passive transport. It has been predicted that around 80-90 percent of drugs is transported passively and making prediction of passive transport is important in early stages of drug discovery. Passive transport can be measured using parallel artificial membrane permeability assay (PAMPA). So far published PAMPA measurements have been carried out at one (near neutral) pH, while intestinal has wide pH-range (3 to 9). Therefore it can be hypothesized that using neutral pH alone cannot give acceptable prediction for all compounds. It is also supported by the known fact that mostly only neutral molecules move across the membrane. This means that for predicting membrane permeability by acids, the best pH should be acidic and for bases basic. This allows concluding that in order to get better prediction models for membrane permeability, it is necessary to study different chemical classes individually at optimal pH, suitable for these chemical classes.

The purpose of current work is to develop permeability QSAR models for different chemical classes (acids, bases, ampholytes and neutrals) at appropriate pHs. For this the PAMPA measurements were performed for around 200 compounds at 4 pHs (3, 5, 7.4 and 9). The dataset includes approximately 50 acids, 85 bases, 70 ampholytes and 15 neutrals, which were divided to individual datasets. The experimental values were analyzed and used for *in silico* modelling. Every dataset was used to develop 5 different models: all four pHs and best membrane permeability by four pHs. Multi-linear QSAR models were developed using stepwise forward selection of molecular descriptors. In results different models were compared and found best suited pHs for every chemical classes.

The result shows that obtained descriptive and predictive models for membrane permeability are highly depend on chemical classes. For the acids, the optimal pH for the modelling is pH 3, because of highest amount of neutral species is at this pH and most of the acids have highest membrane permeability at this pHs. For the bases optimal pH is 9, because of highest amount neutral species is at this pH. For the ampholytes, the situation is much more complicated, because these compounds do not have universal pH, where all compounds have highest membrane permeability. Because of this it is appropriate to use the best membrane permeability from all four pHs. For the neutral compounds, membrane permeability does not depend on pH and consequently all pHs give comparable result. Present work shows that for different chemical classes it is good to use specific pHs to get more precise results for maximum membrane permeability.

COMPUTATIONAL AND EXPERIMENTAL STUDIES OF FLAVIVIRUS ENVELOPE PROTEINS AS PROMISING DRUG TARGETS

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Given the mutation rate of the viruses and severity of viral diseases, constant search for novel targets of antiviral drugs becomes the fate of medicinal chemists working in this field. A perfect antiviral drug should be selective enough to interact only with a virus, leaving biological macromolecules of humans and their symbiotic microorganisms intact, and at the same time it should affect as many viral variants as possible to be generally applicable against a certain disease. Thus, such a drug should target the most conserved regions of the virus. Deep understanding of the virus life cycle machinery is required to achieve this goal.

Envelope (E) protein of the viruses belonging to *Flavivirus* genus is one of such promising targets. These proteins, along with underlying membrane (M) proteins, form the outer shell of the viral particle and mediate key early stages of the infection, namely, interaction with the host cell receptors and viral and cellular membranes fusion, leading to viral genome release into cytoplasm. Fusion prevention is a widely recognised strategy of antiviral drug discovery, and the conservation of this mechanism along the *Flavivirus* genus makes it very attractive.

In our studies we focus on the most epidemiologically important flaviviruses for Russia and Europe, namely, tick-borne encephalitis virus (TBEV) and West Nile virus (WNV), taking into account also the most studied flavivirus, dengue virus (DENV), for which a significant amount of structural data is available.

With the help of docking-based virtual screening of small molecule compounds against a homology model of E protein, several potent inhibitors of TBEV replication were identified. Then a molecular dynamics simulation was performed for complexes of E proteins and these inhibitors to identify putative biologically active conformations for further ligand-based virtual screening.

Further insights into the fusion machinery were obtained from massive molecular dynamics simulations of envelope building blocks consisting of 2 E and 2 M protein subunits. Explicit solvent and membrane were utilised, and 500 ns trajectories were achieved for neutral pre-fusion and protonated prefusion states. Changes in interaction pattern of histidine residues upon their protonation clearly illustrate the 'histidine switch' hypothesis of flaviviral fusion. Movement patterns of surface residues provide valuable information for understanding the interaction of flaviviruses with cell receptors and their recognition.

Another viable scheme of targeting E proteins suggests the interaction of antiviral compounds with a trimeric post-fusion state of the protein. That was successfully proved for anti-DENV peptides derived from the 'stem' region of the E protein. We have rationalised these literature data through the development of a peptide-protein docking scheme allowing the discrimination between the active and inactive peptides. Molecular dynamics simulation of the peptides suggests the most favoured conformation. Design of anti-TBEV peptides was performed.

IN SILICO DRUG DESIGN OF SELECTIVE INHIBITOR OF SHIP2 AS A NOVEL THERAPEUTIC AGENT FOR DIABETES

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The prevalence of type 2 diabetes is increasing worldwide. Although the number of anti-diabetic drugs is also increasing, their therapeutic outcome remains insufficient. Recently, SH2 domain-containing inositol 5'-phosphatase 2 (SHIP2) and phosphatase and tensin homologs deleted on chromosome 10 (PTEN) have been identified as endogenous negative regulators of insulin signaling, and thus the inhibitors of them are considered to have great potential of treating obesity and type 2 diabetes. Of these, selective inhibitors of SHIP2 are more promising since PTEN has a tumor suppressive activity and its inhibition might lead to severe side effects. We had previously developed several inhibitors of SHIP2 with new scaffolds using *in silico* ligand-based drug design (LBDD)[1)], but the validation and improvement of the target selectivity of these compounds were difficult in LBDD approach. In this study, we aimed to develop the selective inhibitor of SHIP2 using *in silico* structure-based drug design (SBDD), based on the 3D coordinates of both SHIP2 and PTEN.

First, compounds with similar functional groups to the 3D pharmacophore of SHIP2-inhibitor complex were retrieved from the database containing approximately four million compounds (Namiki Shoji) by using the UNITY search module in SYBYL-X 1.3 (Tripos). Compounds fulfilling Oprea's criteria were selected, and then we performed docking calculations with the SP mode of Glide 5.8 in Schrödinger Suite 2012 (Schrödinger) against the representative structures of SHIP2 and PTEN, respectively. Compounds were ranked by their Glide scores, and those with higher Glide scores to SHIP2 and lower to PTEN were selected as the candidates of the selective inhibitors of SHIP2. These candidates were then clustered according to their 2D similarity, and the representative compounds in each cluster are chosen. Activity measurements and structural optimizations of them are currently under investigation.

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INHIBITORS OF THE OXYTOCINASE SUBFAMILY OF M1 AMINOPEPTIDASES THAT DEMONSTRATE POTENT TARGETED ANTI-INFLAMMATORY PROPERTIES

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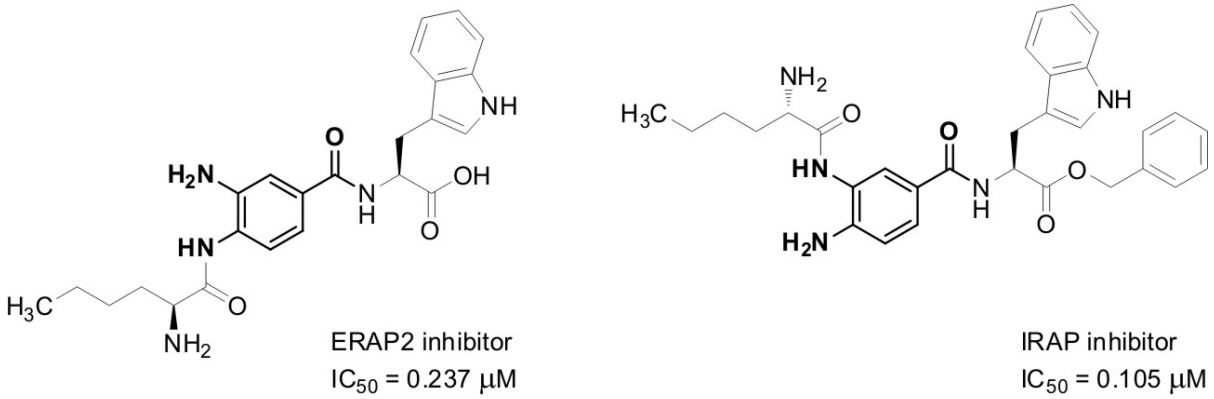
Members of the oxytocinase sub-family of M1 aminopeptidases (ERAP1, ERAP2 and IRAP) play important roles in both the adaptive and innate human immune responses. Their enzymatic activity can contribute to the pathogenesis of several major human diseases ranging from viral and parasitic infections to autoimmunity and cancer. Antigen processing and presentation assays in cells showed that designed phosphinic pseudopeptide transition state analogs can induce increased cell-surface antigen presentation of transfected and endogenous antigens and enhance cytotoxic T-cell responses [1]. By exploting the recent biochemical and structural analyses of ERAP1 and ERAP2 we have developed a novel class of selective aminopeptidase inhibitors based on the 3,4-diaminobenzoic acid scaffold with low micromolar activity for ERAP1 [2].

Structure-based optimization yielded several sub-micromolar inhibitors for ERAP2 and IRAP, some of which displayed remarkable selectivity profiles for these three, highly homologous aminopeptidases. Cell-based analysis indicated that this class of inhibitors is effective in down-regulating macrophage activation induced by lipopolysaccharide and interferon- γ, as well as cross-presentation by bone marrow-derived dendritic cells. Our results indicate that this class of inhibitors may be useful as novel targeted anti-inflammatory compounds.



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SYNTHETIC POLYMER STRUCTURES PROGRAMMING FOR THE ANTIVIRAL ACTIVITY AND DRUG RESISTANCE PREVENTION

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The polymeric compounds are general molecular basis for origin and evolution of biological life. Just and exclusively the biopolymers are capable of providing the genetic programming through the nucleic acids (**NA**) and the most relevant structure-functional self-organization from lipids, proteins, saccharides … to great diversity of biological organisms in norm and in pathologies. The viruses (simplest, but highly danger genetic parasites) in form of pre-infecting *virions* can be considered as the *unique polymer-accumulating complexes* (NA genome cores in protein capsides +/- lipid envelopes) maximally free from small molecule ballast. Any virion appears as lifeless-like nano-particle until it penetrates into the permissive cell via the entry-allowing cell's receptor(s). Inside the cell the viral components reintegrate with cell molecular system, switching the biosynthesis to the viral reproduction, where small molecule metabolites are involved too. But again just the polymers (viral and cellular NA, protein-based enzymes …) play a key role in this infective rearrangement toward parasitic replication, self-assembly, maturation, and delivery of next viral posterity (followed by depletion/dead of the host cell). Therefore, no antiviral prevention/therapy can be completely-efficient if the antiviral drugs are based on small molecules exclusively, i.e. without a macromolecular basis. The synthetic and/or hybrid polymeric compounds, as the drug capable tools for adequate counter-intervention in viral life cycle, are required cardinally [*1*]. Against the viral genetic evolution (that is many folds faster than the natural evolution of human immunity) we oppose a counter-evolution of synthetic/hybrid polymer-scale antivirals designed in searching for SAR- principles of partial nature-mimicking but mainly artificial (non-genome) programming these structures to the antiviral functionality [*2*].

The first phase of this research work was focused on SAR-searching the most effective polymeric adjuvants for antiviral immunity, first of all, through the interferon-inductive antiviral prophylaxis. The structural parameters responsible for the required functionality become known from other authors and own *in vivo* results analysis as a structural similarity to viral NA backbone (with alteration of furan-derived and acidic units). Among the most effective synthetic imitator with the required SAR the alternating copolymer of divinyl ether with maleic acid (**DVEMA**) was selected. In-depth study of free-radical synthesis of DVEMA reveals an ambiguity of cyclo-isomery in the polymeric chain grows with possible formation of five- (furan-der.), six- (pyran-der.) and seven-membered cycles, that allows of some biofunctional irregularity. To solve this problem the quantum chemistry modeling of the competitive routs of the isomery was performed, and the best (solvent-dependent) conditions for selective synthesis of the most effective "furan" modification of DVEMA (**DVEMA-5**) were cleared.

The second phase of research is scope for next generation of DVEMA-5 (and related polymers) derivatives. The selected polymeric backbones were modified by side-groups/anchors/chains species in searching the SAR-algorithms (similarly to the genetic coding of proteins via side-chain variable sequences). Particularly, a direct antiviral blocking in addition to the immune stimulation was programmed by variations at least 5 groups of side-chain modulators: (1) electrostatic-selective vectors; (2) hydrophobic pendant anchors; (3) cholesten-related anchors to raft-portals of viral entry on cell's membranes; (4) peptide fragments of virus-sensitive cell's receptors; (5) polypeptide fragments of virions themselves. Numerous polymeric inhibitors of human immunodeficiency (HIV) and other viruses were discovered. Stepwise-variable docking-co-molecular dynamics methodologies were improved to be adequately introduced in study of specific binding interactions between the synthetic and biological polymers. The polymer level advantages and SAR-parameters for amplified antiviral activity and drug resistance prevention were found in good correlation with *in vitro* experimental data, opening promising prospects to a novel SAR-based drug design development [3,4].

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IDENTIFICATION OF INDUSTRIAL CHEMICALS INTERFERING WITH THE THYROID HORMONE RECEPTOR USING MOLECULAR MODELING METHODS

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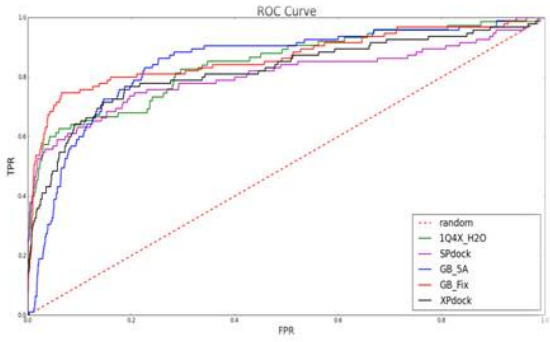
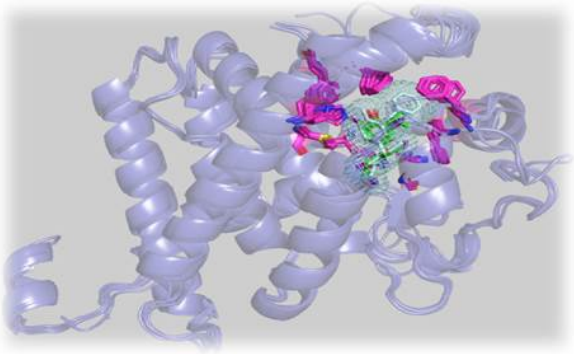
Thyroid hormones (THs) play a vital role in CNS development, body growth and regulating other hormones production. Some exogenous compounds have been report to interfere with physiological functions of THs, which causes endocrinal related diseases and developmental disorders, especially in infants and children. Identification of these thyroid disrupting chemicals (TDCs) could be laborious and time-consuming by conventional *in vitro* and *in vivo* approaches. *In silico*-based methods provide means to decrease the number of animal tests and reduce costs. Here we present a virtual screening protocol, using ensemble docking and MM-GBSA (Molecular Mechanics-Generalized Born Surface Area) rescoring methods, to identify TDCs among UV absorbers—an example of industrial chemicals.

UV absorbers are widely utilized in plastics and cosmetics to prevent products from UV-light induced degradation. Recent reports have proved their presence in beverage containers, pharmaceutical packaging, household dust and human serum. Exposure to these chemicals might pose threats to human health.

In this developed protocol, 18 human TH receptor complex structures were clustered based on their co-crystalized ligands. DUD-E (a Directory of Useful Decoys-Enhanced) TH receptor subset[1] was docked into six representative complexes using Glide. We assessed the docking result of each single complex structure and their best combination was selected as an ensemble docking model to achieve the best performance in number of hits identified among the top 20% highest ranked compounds. The ensemble docking result was then rescored using MM-GBSA minimization that further improved the virtual screening performance of the ensemble model. OpenEye SZMAP[2]was also utilized to characterize the bridging water molecules within the ligand binding pocket.





In this study, we screened 80 UV absorbers together with their metabolites generated by ChemAxon Metabolizer [3] using the established protocol. For identified potential hazardous compounds, molecular dynamic simulations were utilized to elucidate their thyroid disrupting mechanism by investigating their interaction with the TH receptor. Some representative compounds will be tested in a TH receptor luciferase-based (TRE-Luc) assay in the future.

The study provides us a computational means to identify potential TDCs from fairly large chemical libraries. The outcome will serve as a guidance of chemical selection for further *in vitro* and *in vivo* studies. Moreover, it also allows us to visualize the interactions between hazardous chemicals and the TH receptor. This would help us to reach a better understanding of the mechanism-of-action (MoA) of thyroid disruption.

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THE USE OF NEW MOLECULAR MODELLING METHOD FOR INVESTIGATION OF STRUCTURAL WATER

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It is known that water plays an important role in forming of the conformation of biomolecules, in particular, has a great influence on the ligand binding in the active site of the protein. Positions of water molecules in the crystal structure of the protein can be determined experimentally (by the X-ray spectroscopy), however, the crystal structures often contain incomplete data about the water environment, and may also contain artifacts. Most of the structural-oriented methods of drug development and docking do not take into account the presence of structural (tightly bound water molecules) in the active site of the protein, but this approach is not efficient enough, since it does not consider the energy contribution of such water in the formation of bridging ligand - protein bonds.

We analyzed the crystal structures of different proteins in the representative set of human ATPases and discovered that many of the structures have a voids in the active sites, which can be filled with water. The presence of these voids, in particular, may be due to the presence of solvent molecules other than water, which for some reason were not included in the crystal structure. The results of molecular dynamics in the water box also suggest a much greater degree of hydration of the ligand in the active site. In this regard, we examined the methods of filling in the active site of the protein with water on the example of the utility aquaFlood implemented in the software package molecular modeling ICM-Pro [1]. The result of the work of this tool is not suitable for the docking, so we developed another utility for simulation of the positions of the structural and bridge water in the active site of the protein (AquaBridge).

This utility includes a calculation of the main parameters of the hydrogen bond (bond length, donor and acceptor angles), the structural water is considered, with at least two hydrogen bonds with protein, bridge - water that forms hydrogen bonds with protein and ligand at the same time. The work of this tool was tested on a representative set of ATPases (51 crystal structure of high-resolution from PDB - Protein Data Bank [2]). In many cases utility has found besides the positions of the crystal water some positions of the water, which is not present in crystal structure.

We investigated hydration motives of different ATPases from a representative set and produced cluster analyses that allowed for the identification of two groups of proteins, with very similar active sites construction. Also in this paper, we studied the influence of structural water on the effectiveness of the docking procedure of small ligands in the active site of the protein and demonstrated improvement of docking results. Accounting of the structural water in the active site of the protein contributes to obtaining more accurate ligand conformations, as well as to increase selectivity of searching ligands using docking.

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SEQOPT: NEW METHOD AND WEB SERVER FOR DE NOVO DESIGN OF STABLE ALPHA-HELICES IN PEPTIDES AND GLOBULAR PROTEINS

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α-Helices is one of the most abundant element of protein secondary structure. Numerous studies of α-helical peptides not only contributed to better understanding of the protein folding but also represent an increasing pharmacological interest as practical utility for development of novel therapeutics modulating protein-protein interactions in vivo (1). A large body of information has been accumulated regarding the factors which govern the stability of α-helices in proteins and the helical behavior of both isolated protein fragments and designed helical sequences in solution. These factors include interactions between amino acid side chains, interactions between charged or polar side chains and the helix macrodipole and terminal capping. Many of these factors have been applied separately in attempts to increase the conformational stability of α-helices in peptides and in natural proteins.

In this work we developed a new method (SEQOPT) for the design of peptide sequences with the optimal implementation of all these factors (2,3). The method is based on AGADIR, the statistical mechanical theory for helix-coil transitions in monomeric peptides and the Tunneling Algorithm of global optimization of multidimensional functions for optimization of amino acid sequences. Unlike traditional approaches that are often used to increase protein stability by adding a few favorable interactions to the protein structure, this method deals with all possible sequences of protein helices and selects the best one from them.

SEQOPT showed high efficiency in designing the amino acid sequences of α-helical peptides up to 20 amino acid residues which requires ~1 hour of computing time on a modern personal computer. For shorter sequences required optimization time decreases rapidly. The method showed high correlation between the theoretical predictions of conformational stability of α-helices with optimized sequences and the experimental data obtained with CD spectroscopy (R~0,9). It is shown that the maximum achievable alpha-helical content of short peptides using only the 20 standard amino acids at 5°C is about 70-75% (2). Under certain conditions the method can be a powerful practical tool not only for design of highly stable peptide helices but also for protein engineering. Publicly available SEQOPT web server is located at our WEB site http://mml.spbstu.ru/services/seqopt/ where one can optimize peptide sequences with arbitary fixation of functionally important amino acids.

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MINING PHYSICOCHEMICAL FEATURES THAT CONTRIBUTE TO ORAL BIOAVAILABILITY IN PEPTIDE MIDDLE SPACE

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Landmark studies[1,2] on small molecule drugs that are orally bioavailable identified key physicochemical limitations of low molecular weight, low polarity and low-medium hydrophobicity that determine intestinal uptake and plasma concentrations. This report addresses some observations on so-called peptide "middle space", where many of the rules-of-five appear to breakdown and may need revision since these compounds are larger and more polar yet in certain cases are orally bioavailable. Our interests have been in developing constrained cyclic peptides that can mimic small, defined, bioactive surfaces of proteins,[3] and in learning how to make them orally bioavailable. Nature has produced some macrocyclic peptides like cyclosporin A that may hold important clues to confer sufficient bioavailability for compounds to reach intracellular targets.[4] Understanding how to harness these and other molecular and structural features might transform current approaches to designing and developing orally available peptide therapeutics.[5]

Using a dataset of 50+ cyclic peptides with oral absorption (F%) in rats, we established conformational analyses in $CHCl_3$ through torsional sampling (MCMM, Macromodel, Schrodinger Suite 2014). We further calculated a range of selection features that influence bioavailability such as 3D-molecular descriptors (e.g polar surface area, logP), energy potentials like $\Delta G_{dehydration}$ and structural features (e.g. N-methylation) for each conformer. We present here preliminary results correlating these and new features that appear to influence oral absorption and bioavailability.

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PREDICTING BLOOD-BRAIN BARRIER PERMEABILITY OF MARINE-DERIVED KINASE INHIBITORS FOR NEURODEGENERATIVE DISORDERS THERAPIES

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Neurodegenerative disorders affect more than 25 million patients worldwide leading to irreversible brain damage. The correlation between deregulated kinases and human diseases has led to the pursuit of protein kinases inhibitors. However, validated kinase inhibitor drugs (KDs) used for oncological treatments often fail to translate into neurodegenerative disorders due to their low/poor blood-brain barrier (BBB) permeability.[1]

Over the last 30 years, marine biodiscovery has delivered numerous potent inhibitors of therapeutically relevant kinases; the so-called marine-derived kinase inhibitors (MDKIs), offering underexploited chemical wealth.[2] Using a publicly-disclosed database of 448 CNS-penetrant small molecules, we designed statistical classifiers to predict BBB permeability in property space with 83-84% correctness. Applying the best models to MDKIs and KDs has confirmed previous experimental observations and returned interesting hits that include Phase II lead candidate; *bryostatin 1*, for the treatment of Alzheimer's disease (Blanchette Rockefeller Neurosciences Institute). [3-4]

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PHARMACOPHORE AND QSAR MODELS ON COUMARINS AS FXIIa INHIBITORS

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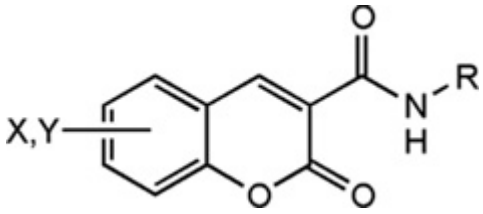
Thrombotic disorders are a major concern in public health. Anticoagulants used to address these diseases have proven their efficacy but they are still associated with bleeding risks. Therefore, novel strategies are requested to overcome such a limitation. In this perspective, the inhibition of the activated coagulation factor XII (FXIIa) emerges as an attractive approach for the development of safe antithrombotic drugs[1].

Among the compounds targeting the FXIIa, the 3-carboxamide coumarins (figure) have been described as selective inhibitors with IC50 values in the μM range[2]. Unfortunately, they lacked of activity in an *in vivo* model of thrombosis[3]. Thus to improve their activity and *in vivo* potency, new pharmacomodulations should be introduced.



To achieve this purpose and to improve our knowledge on the structural requirements needed to inhibit FXIIa, we used computational chemistry approaches. The three-dimensional structure of our target is not available meaning that virtual model can only be built from the ligands whose structure is known. Since these coumarins are the only small molecular-weight inhibitors described, we have decided to generate a pharmacophore model. We have also developed a 3D-QSAR model. These models features will be fully discussed.

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APPLICATION OF HETEROGENEOUS PUBLIC DATA FROM CHEMBLDB FOR TRAINING PASS SOFTWARE

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Millions of chemical compounds have been evaluated as protein's function modulators in thousands assays under various conditions to date. Scientists can get access to a considerable part of this data throw different internet resources like ChEMBL [1]. It is important to know how correctly use the data when experimentally determined activity of chemicals may vary from one experiment to another depending on experimental conditions and type of determined activity. In our work we evaluated a possibility of data application from ChEMBL_18 as a training set for building SAR models in PASS software [2-4]. A special data filtration for removing unreliable data was performed. An assessment of possibility of joint use for data records with experimentally determined diverse activity types was also executed. A training set including data on activity against protein targets from various organisms for more than 500 000 unique low molecular weight chemical compounds was created as a result. Average accuracy of prediction estimated by leave-one-out cross-validation and 20-fold cross-validation was about 98%. We suggest that the important way to improve prediction power of (Q)SAR models and to expand their applicability domain lies across the implementation of large datasets for training. And that's why it is necessary to learn about joint use of diverse activity data from public source. Results of correct application such data give us a valuable opportunity for *in silico* prediction wide spectrum of protein targets from various organisms for chemical compounds. Predicted spectrum could be implicated for preliminary assessment of possible side effects and planning experimental testing during development of new drugs as also for rational drug repositioning and for explaining mechanisms of adverse reactions for existing drugs.

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COMPUTATIONAL DISCOVERY OF BROAD-SPECTRUM BIOFILM INHIBITORS

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Biofilms are defined as bacterial communities enclosed in a self-produced polymeric matrix. Within biofilms, bacteria are much more protected against stress factors, such as metal toxicity, antimicrobials and the host immune system and therefore extremely difficult to combat. We propose to use ligand-based and protein target-based computational strategies to develop non-toxic specific biofilm inhibitors with broad-spectrum activity as a new generation of antibacterial agents.

By *in vitro* screening, our collaborating groups have identified a series of 2-aminoimidazole-based compounds with broad spectrum, preventive activity against biofilm formation. Microarray analysis and gene reporter assays indicate that these compounds inhibit biofilm formation by activating a specific bacterial two-component system, shown to negatively regulate biofilm formation. Therefore, Ligand-based approaches, such as QSAR modeling, similarity searches and ligand-based pharmacophore modeling, and receptor-based approaches, such as target protein-based pharmacohore modeling and docking simulations, are being used to screen commercial compound databases for discovering novel biofilm inhibitors with broad-spectrum activity and low toxicity. In addition, we will use molecular dynamics simulations to study the affinity of protein-ligand interactions for the further selection of biofilm inhibitors.

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DOCKING AND QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP STUDIES FOR 3-FLUORO-4-(PYRROLO[2,1-F][1,2,4]TRIAZIN-4-YLOXY)ANILINE, 3-FLUORO-4-(1H-PYRROLO[2,3-B]PYRIDIN-4-YLOXY)ANILINE, AND 4-(4-AMINO-2-FLUOROPHENOXY)-2-PYRIDINYLAMINE DERIVATIVES AS C-MET KINASE INHIBITORS

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c-Met is a receptor tyrosine kinase that is expressed in endothelial and epithelial cells. In normal cells, c-Met is activated by its ligand hepatocyte growth factor (HGF)/scatter factor [1]. When HGF binds to c-Met [2], causes receptor dimerisation and autophosphorylation of tyrosines 1234 and 1235. Under normal conditions, the pleiotropic effects of the HGF mediated c-Met activation is essential for normal physiological events, such as placental development and liver regeneration [2]; however, in cancer, both HGF and c-Met have been closely linked to the regulation of the metastatic process [3]. In this sense, c-Met has recently attracted considerable interest as a therapeutic target based on the discovery that aberrant c-Met activity is related with the occurrence of various cancers including lung, prostate, renal, ovarian, gastric, and liver cancers. According to the role of c-Met signaling in cancer progression and metastases, the c-Met receptor is considered a potential target for cancer therapy. c-Met tyrosine kinase inhibitors are able to block autophosphorylation of the c-Met kinase, thereby interrupting its downstream signaling pathways. In this research, we have performed docking of 3-fluoro-4-(pyrrolo[2,1-f][1,2,4]triazin-4-yloxy) aniline (FPTA), 3-fluoro-4-(1H-pyrrolo[2,3-b]pyridin-4-yloxy) aniline (FPPA), and 4-(4-amino-2-fluorophenoxy)-2-pyridinylamine (AFPP) derivatives complexed with c-Met kinase to study the orientations and preferred active conformations of these inhibitors. The study was conducted on a selected set of 103 compounds with variations both in structure and activity. Docking helped to analyze the molecular features which contribute to a high inhibitory activity for the studied compounds. In addition, the predicted biological activities of the c-Met kinase inhibitors, measured as IC50 values were obtained by using quantitative structure–activity relationship (QSAR) methods: Comparative molecular similarity analysis (CoMSIA) and multiple linear regression (MLR) with topological vectors. The best CoMSIA model included steric, electrostatic, hydrophobic, and hydrogen bonddonor fields; furthermore, we found a predictive model containing 2D-autocorrelation descriptors, GETAWAY descriptors (GETAWAY: Geometry, Topology and Atom-Weight AssemblY), fragment-based polar surface área (PSA), and MlogP. The statistical parameters: cross-validate correlation coefficient and the fitted correlation coefficient, validated the quality of the obtained predictive models for 76 compounds. Additionally, these models predicted adequately 25 compounds that were not included in the training set [4].

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MOLECULAR FIELD TOPOLOGY ANALYSIS OF ESTERASE PROFILE OF THIAZOLINE-BASED INHIBITORS OF SERINE ESTERASES

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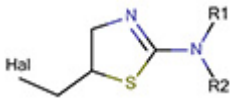
The term “esterase profile” describes the activity profile of anticholinesterase compounds as inhibitors of several pharmacologically important serine esterases: acetylcholinesterase (EC 3.1.1.7, AChE – cognition improvement and anti-target responsible for acute cholinergic toxicity), butyrylcholinesterase (BChE, EC 3.1.1.8 – cognition improvement, modulation of metabolism of ester-containing drugs), carboxylesterase (CaE, EC 3.1.1.1 – modulation of metabolism of ester-containing drugs) and neuropathy target esterase (NTE, EC 3.1.1.5 – anti-target responsible for delayed neurotoxicity) [1]. Determination and analysis of esterase profile of the compounds by means of the QSAR methods allows us to get a more complete view on biological effects of a compound and thereby evaluate its therapeutic potential and possible side effects.

Earlier we have successfully applied the Molecular Field Topology Analysis (MFTA) to the investigation of the inhibitor activity and selectivity of two large groups of organophosphorus compounds as irreversible covalent inhibitors of AChE, BChE, CaE and NTE [2, 3]. In the present work, the MFTA approach is used to analyse the structure – esterase profile relationships for the reversible inhibition of serine esterases (AChE, BChE and CaE) in a series of 41 new thiazoline-based compounds [4]. As a result of kinetic studies, some effective inhibitors of BChE and CaE have been found in this series which have a low anti-AChE activity. The compounds are of interest as drug candidates for the Alzheimer’s disease treatment and as co-drugs for the modulation of drug toxicity and/or their half-life.



In the MFTA approach [5, 6], the bioactivity model is based on the values of local molecular descriptors (e.g., atomic properties). A common frame of reference for their meaningful comparison and analysis for different compounds is provided by the so-called molecular supergraph resulting from the topological superimposition of the structural formulas. In addition to the predictive partial least squares regression (PLSR) model relating these properties at all positions of the molecular supergraph to the bioactivity, a graphic activity map is obtained summarizing the effect of properties on activity. The following local descriptors were considered: effective atomic charge *Q* estimated by the electronegativity equalization technique; the effective van der Waals radius of atom environment *Re* taking into account the steric requirements of the central non-hydrogen atom and other atoms bound to it; group lipophilicity *Lg* taking into account the contributions of the central non-hydrogen atom and the attached hydrogen atoms; hydrogen bond donor ability *Hd* and hydrogen bond acceptor ability *Ha* of an atom. The optimal model was selected using the Q^2 values obtained in the stabilized cross-validation procedure by averaging over many random reshufflings of the cross-validation subsets, thus providing a more robust and reliable estimation of the model predictivity. Using the MFTA models, the focused libraries of potential selective BChE and CaE inhibitors were designed.

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AN INTEGRATED ONLINE SERVICE FOR ADMET PROPERTIES PREDICTION

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The pharmacokinetic properties such as absorption, distribution, metabolism and excretion (ADME), as well as the toxicity of drugs and drug-like compounds, have a profound influence on their activity, pharmacological profile, and mode of use. Thus, the optimization of the ADMET properties is an important part of the drug discovery and development workflow wherein the ability to predict the relevant parameters for new structures and to analyze the structural features controlling the behavior of a compound is very useful in order to achieve better speed and efficiency.

In the previous decades, substantial work has been devoted to the modelling and prediction of these properties. However, the applicability and usefulness of the available models is often diminished due to limited data sets, inaccurate data, insufficiently validated modelling approaches, and/or inconvenient prediction procedures.

We have attempted to develop an integrated Web-based software for the prediction of a number of important ADMET properties applicable to diverse drugs and drug-like compounds. It employs a uniform modelling methodology based on the fragmental descriptors in the conjunction with back-propagation neural networks (BPNN) and double cross-validation procedure [1, 2]. Since the quality of raw data is critical for the accurate and predictive model, in most cases the data sets were verified and significantly extended over the largest previously published sets. Currently the prediction of the following properties [1, 3-7] is implemented:

- lipophilicity (LogP)
- blood-brain barrier permeability (LogBB)
- human intestinal absorption (HIA)
- plasma protein binding (PPB)
- mutagenicity
- hERG-mediated cardiotoxicity
- aryl hydrocarbon receptor (AhR) affinity
- cytotoxicity

Prediction of additional properties is planned in the future. For each parameter, the predicted value as well as qualitative and quantitative characteristic of the compound is provided.

The predictor software is available online at http://qsar.chem.msu.ru.

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A QUASI-SISTEMATIC MOLECULAR ALIGNMENT STRATEGY FOR 3-D QSAR MODEL DEVELOPMENT. THE KEY STEP FOR A 3-D QSAR SERVER

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Quantitative structure–activity relationships (QSARs), are ligand-based (LB) methods aimed to develop mathematical/statistical models which attempts to find a statistically significant correlation between structure and bioactivity using chemometric techniques. Three-dimensional (3-D) QSAR is a broad term encompassing all QSAR approaches, which correlate measured biological affinities with computed atom-based descriptors derived from the spatial representation of the considered molecular structures.
In its simplest form the development of a 3-D QSAR model comprises several steps: training and test sets selection (molecules active against a given target), conformation generation and superimposition (alignment rules), molecular interaction field calculation (MIF), correlation of bioactivity and MIF, graphical analysis.
When no target structure information are available and hence the binding site of the training set molecules, the alignment rules definition is the most critical step, especially if the training set is composed of flexible molecules.
In continuing our search in the 3-D QSAR field [1-6] in this report we focus on the developing an automatic procedure to build LB 3-D QSAR models whose alignment rules are defined through pruning hundreds of models with different alignment approaches. The 3-D QSAR engine of the process rely on our recent 3-D QSAutogrid/R [6] procedure which with its implemented multi-probe approach allows the definition of quantitative pharmacophore models.[3]
In this report, we focus on a sort of systematic alignment search by using several automated small molecule automated alignment programs to derive different alignment rules on pre-existent training sets. The final 3-D QSAR model is then selected based on the statistical parameters such as r2, q2 and SDEP and on the lack of chance correlation as measured by a y-scrambling procedure.
To the best of our knowledge, until now, there is no report of a quasi-sistematic molecular alignment approach for the optimization of the alignment rules during the development of a 3-D QSAR model.
Details will be presented and discussed.

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APPLICATION OF INFORMATION TECHNOLOGIES FOR XENOBIOTIC CONTAMINATION OF WATER BODIES HAZARD ASSESSMENT

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Humanity knows a huge number of chemical compounds. Already by 1986 has been known for about 7 million. Currently their number according to the International Registration of chemicals database CAS is nearby 88 million [3]. At the same time, Russia has developed about 2000 MPCs (maximum permissible concentrations) and TCLs (target concentration level). However, given the multi-component water pollution, where chemicals are affected physical, chemical and biological transformations it becomes clear the position on environmental insolvency of the system of maximum permissible concentrations.

Xenobiotics are a group of chemical substances alien to living organisms that naturally-not occurring in the biotic cycle. The increase in their concentration in the environment is most often associated with human activities. They can cause a number of adverse effects from allergic reactions to cancer. However, by virtue of their amount experiments to investigate all the activity of each compound are impossible [1].

In such cases, the computational technologies can narrow down the possible activity of a compound that reduces the cost and time to carry out research and experiments. In addition, it is worth noting that if there is information about the certain activities that reduces the number of experimental animals immediately.

All the results were carried out using the program of prediction biological activity spectra of organic compounds PASS (Prediction of Activity Spectra for Substances), originally used in pharmacology for the design of new drugs and GUSAR (General Unrestricted Structure-Activity Relationships) that can allow to predict LD_{50} values [4]. Also a list of priority pollutants, domestic regulations and international databases were used.

The work was conducted in three ways. First, the xenobiotic contamination of water bodies that are water sources of Moscow were investigated. Thus in 2009-2013 in the studied water bodies were found: active ingredients of pharmaceuticals - 50; excipients of pharmaceuticals - 11; metabolites of known pharmaceuticals - 43; substances of vitamin complexes and nutraceuticals- 5; degradation products of pharmaceuticals - 9. In addition, xenobiotics that are carcinogens, mutagens, teratogens, embryotoxicants, neurotoxins, nephrotoxicants were found.

Second way of researching was HELCOM (Baltic marine environment protection commission) list of hazardous substances [2]. All the substances were searching in databases and were exposed to calculations of LD_{50} and biological activities. Eight contaminates were found to be carcinogenic according prediction and no information about them was found in the databases(2,4-dichloro-4'-aminodiphenyl either; 2-chloro-4-nitroaniline, etc).

The third way of the research was devoted to chlorinated organics (chlorinated phenols and their derivatives, PCDD, PCDF, PCBs) that were found in one of the typical rivers of Europe part of Russia. According to LD_{50} value every class of substances was ranged. So top-10 from each class was identified.

As a result of this work it can be concluded that computational methods "structure-activity" can be effectively used to predict the biological activity of xenobiotic contaminants due to their adequacy to the experimental data. As a result of the calculations for the test substances have been identified certain types of activities, for which experimental data weren't found in the literature. In addition, for some compounds that are not carried out the experiments and were not found evidence of their toxicity the results of the calculations can become the basis of experiments on the identified activities. Also due to computational methods indicators of toxicity for any compound can be calculated and then the substances can be ranked according to their priority toxicity that will allow to conduct targeted research on the predicted activities of the most toxic compounds.

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MOLECULAR GEOMETRY, ELECTRONIC PROPERTIES, MPO METHODS AND STRUCTURE ACTIVITY/PROPERTY RELATIONSHIP STUDIES OF 1,3,4-THIADIAZOLE DERIVATIVES

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The resistance towards available drugs is rapidly becoming a major worldwide problem. The need to design new compounds to deal with this resistance has become one of the most important areas of research nowadays.

Heterocyclic compounds hold a special place among the major pharmaceutical natural products and synthetic drugs having different biological activities [1]. 1,3,4-thiadiazole and its derivatives have a considerable attention to enhance the antibacterial and antiparasitic activity particularly against trypanosomes [2-4]. It has been estimated that around 18–20 million people are infected and over 40 million individuals are threaten to be infected by the hemoflagellated protozoan Trypanosoma cruzi, the responsible agent of American trypanosomiasis (Chagas' disease) [5].

Drug discovery activities are producing ever-larger volumes of complex data that carry significant levels of uncertainty; multi-parameter optimization methods enable this data to be better utilized to quickly target compounds with a good balance of properties [6]. Therefore, we can use the multi-parameter optimization (MPO) methods to predict the best balance of properties, among these methods we carry out rules of thumb and calculated metrics.

The process of drug discovery balances a relentless search for molecules that have structural features that produce:

1. Strong target binding, using SAR; known as structure-based design.

2. High performance at in vivo barriers, using SPR; known as property-based design.

How a medicinal chemist goes about balancing these often disparate processes is a matter of experience and strategy [7]. Here we carry out the Structure Activity/Property Relationship (SAR/SPR) studies which are attempting to give us the correlation between molecular structures and properties that are taking place in the target activity.

In the present work, we started with a comparison between different calculation methods at Ab-initio and DFT levels employing several basis sets, than by studying the effect of radical substitution in R_1 and R_2 positions of 1,3,4-thiadiazole, through electron-donating and attracting groups. Our work is subsequently focused on the study of molecular geometry and electronic properties which are largely responsible for binding of a drug to its active sites; this allowed us to predict the influence of certain structural modifications on the biological activity. The present study, offers the ability to guide design and selection to quickly identify compounds from the 1,3,4-thiadiazole derivatives series that are likely to achieve outcome in the clinic and occupy a strong market position. Also it provides a discussion of several qualitative approximations of the structure activity/property relationship to search the preferred conformations and comparing the antitrypanosomal activities against cruzain to establish correlations between structural parameters and the various properties of the investigated molecules and improving the conception of new therapeutic drugs.

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QUALITATIVE STRUCTURE-PROPERTIES STUDY AND QSAR MODELING OF ANTITRYPANOSOMAL ACTIVITIES OF ALKYLDIAMINE CRYPTOLEPINE DERIVATIVES

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Cryptolepine is a natural indoloquinoline alkaloid found in the West African climbing shrub Cryptolepis sanguinolenta that possess a moderate antitrypanosomal activity [1].

Sleeping sickness "human African trypanosomiasis" and Chagas disease "South American trypanosomiasis" are widespread potentially life-threatening diseases. Caused by protozoan parasites, Trypanosoma brucei [2] and Trypanosoma cruzi [3] respectively.

Trypanosoma infections are not different from those available 20 years ago and are far from ideal, limited by toxicity and the emergence of drug-resistant parasites, thus, the development of new drugs is an important priority to treat these vector-borne diseases [4, 5].

Quantitative structure-activity relationship (QSAR) is among the most practical tool in computational chemistry. The fundamental idea of QSAR consists of the possibility of relationships between a set of descriptors, which are derived from molecular structures, and a particular kind of biological activity. QSAR can be regarded as a computer-derived rule that quantitatively describes the biological activity in terms of chemical descriptors; it has been frequently used to predict biological activities of new compounds [6].

In the present work, Qualitative approximations of the structure-properties relationships [7] were applied to twenty-two molecules of alkyldiamine cryptolepine derivatives to determine the role of several physicochemical properties which are used in QSAR modeling as independent variables; the compounds used are potent inhibitors of the trypanosome papain-like cysteine proteases, which could, at least in part, explain their antitrypanosomal activities [8].

A multiple linear regression (MLR) method was used to design the relationships between molecular descriptors and Antitrypanosomal activities of the studied series of cryptolepine derivatives.

The correlation between the inhibitory activities against Cruzain and Rhodesain with physicochemical descriptors expressed by the following relations (1) and (2) respectively:

$$\log(1/ICCruz) = -1.775 + 0.013SAG - 0.015V + 0.099HE - 0.230\log P + 0.027MW \quad (1)$$

n =22; r= 0.904; s= 0.235; F= 14.300; Q= 3.85

$$\log(1/ICRhod) = -2.030 + 0.010SAG - 0.013V + 0.100HE - 0.285\log P + 0.027MW \quad (2)$$

n =22; r= 0.869; s= 0.309; F= 9.864; Q= 2.81

In order to test the validity of the predictive power of selected QSAR models, the leave-one-out technique (LOO technique) was used. High agreement between experimental and predicted inhibitory values obtained in the validation procedure, indicating the validation and the good quality of the derived QSAR models which show that hydrophilic derivatives of cryptolepine give a good antitrypanosomal activity against Cruzain and Rhodesain.

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THE APPLICATION OF EXTENDED HÜCKEL THEORY FOR PHARMACOPHORE MODELING

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Pharmacophore models play an essential role in drug discovery. Generating pharmacophore models which encode accurate molecular recognition features are highly dependent on properly defined annotation points. Simplistic or ill-defined pharmacophore annotations which do not capture subtle electronic or geometric effects lead to many inaccuracies. “Rule” based methods which typically employ SMARTS patterns to specify annotation "rules" are subject to such inaccuracies. Here we have developed a new approach for pharmacophore modeling which is based on a semi-empirical method using Extended Hückel Theory (EHT). In contrast to “rule” based approaches, the EHT method uses a model to assign annotation points and generate features. The pharmacophore features generated through the EHT annotation scheme take into account ligand resonance and electron withdrawing effects and are sensitive to non-standard interactions, such as C-H and halogen bond interactions, during pharmacophore screening.

SKIN SENSITIZATION STUDY FROM ONLY ANIMAL DATA BY QUALITATIVE STRUCTURE-TOXICITY RELATIONSHIPS (QSTR) APPROACH

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Objectives

In silico assessment of skin sensitization is increasingly needed owing to the problems concerning animal welfare, as well as excessive time consumed and cost involved in the development and testing of new chemicals.

Materials and methods

We previously made skin sensitization model from human and animal data and reported. Its accuracy was 61.2% (sensitivity 60.7%, specificity 62.8%). This time we made skin sensitization QSTR model from only animal data (LLNA, 471 chemicals, ICCVAM Test Method Evaluation Method (NIH Publication Number 09-6439) by using K-step Yard sampling (KY) methods (U.S. Patent No. 7725413, 2010).

Results

A total of 320 compounds (212 positive sensitizers and 108 negative sensitizers) were used in this study. 288 compounds were used to make a QSTR model and external validation study were performed by 32 compounds. The concordance of QSTR prediction for LLNA data were 71.9% (sensitivity 54.5%, specificity 81%) and better than previous report..

Dicscussion

The concordance was better than previous time and indicate that the data of human and animal study were gualitatively different from each other.

Acknowledgment

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GALANTAMINE DERIVATIVES - ACETYLCHOLINESTERASE INTERACTIONS: MOLECULAR DOCKING SIMULATIONS

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Two training sets of 22 synthetic galantamine derivatives binding to acetylcholinesterase were docked by GOLD. The docking protocol was optimized in terms of scoring function, rigidity/flexibility of the binding site, presence/absence of a water molecule inside and radius of the binding site. Good correlations were found between the affinities of compounds expressed as pIC_{50} values and their docking scores. The optimized docking protocol was validated by an external test set of 11 natural galantamine derivatives and the correlation coefficient between the docking scores and the pIC_{50} values was 0.800. The derived relationship was used to analyze the interactions between galantamine derivatives and AChE.

VIRTUAL SCREENING USING CRYSTALIZED AND MODELED STRUCTURES OF THE CHEMOKINE RECEPTOR CCR5

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The G protein-coupled receptors of the chemokine receptor subfamily have gained the attention of pharmaceutical research in the recent years, since several of their members represent potential drug targets. As example, the CXC receptor CXCR3 is involved in inflammatory processes and the CXCR4 in certain types of cancer. Furthermore, CXCR4 and CCR5 can act as co-receptors in the cell invasion process of different HIV strains (1,2). Despite the open challenges in crystalizing GPCRs, the X-ray structure of the CCR5 has been solved (3), which allows the application of structure-based drug design tools.

Using molecular docking, we screened more than 5 M compounds for their binding to the CCR5 crystal structure, in order to predict binders with new chemistry. As it has been shown that docking works well using not only crystal strutures but also computer-generated models (4), we built such a homology model of the CCR5 using the structure of the CXCR4 and applied the same docking setup as above to assess whether we can predict chemical compounds with scaffolds different to the ones found in docking to the crystal structure. Finally, we also re-shaped the binding site around a set of experimental binders and docked for a third time. For all setups, candidate compounds were selected and tested, and results will be presented at the meeting.

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HEAT SHOCK PROTEIN 90 INHIBITORS FOR ELUCIDATION OF STRUCTURE - KINETICS RELATIONSHIP

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Introduction

The kinetic aspect of the interaction of small molecules with their protein targets is receiving increasing attention. However, the molecular basis of slow-kinetic behaviour is still not understood. In an attempt to provide deeper insights into structure-kinetics relationship, HSP90, the heat shock protein, has been selected for detailed studies. The 90kDa protein is a chaperone, which stabilizes proteins against heat and assists them to fold. HSP90 is up regulated by heat and other stressors to protect cells against these damaging effects. [1]

Aim of the study

Investigating how molecular features trigger the interaction kinetics of small molecules at the HSP90 protein, Surface Plasmon Resonance (SPR) is the method used to derive kinetic data. This, in combination with X-ray structures of the protein, should lead to ligand- and structure-based models for prediction of on- and off-kinetics.

Methods

In a first attempt, we applied statistical modeling techniques in order to elucidate general trends in a data set of 180 HSP90 inhibitors. Methods include calculation of ligand-based descriptors, histogram analysis, principal component analysis, decision trees, as well as self organizing maps. QSAR studies and CoMFA have been carried out to find kinetics contributing features.

Results and Conclusion

With respect to physico-chemical properties, certain trends are observed, which point at an influence of the molecular weight and the number of rotatable bonds. This has also been observed for other targets. [2] Building supervised models using a set of ADME related descriptors, lead to a set of predictive models, which allow separating fast- from slow-dissociating compounds. Main descriptors contributing to the final model- which shows accuracy of 0.72, sensitivity of 0.72, specificity of 0.70 and an area under the ROC curve of 0.72 in 10-fold CV- comprise molecular weight, number of aliphatic cycles and number of hydrogen bond acceptor atoms in the molecules.

Acknowledgement

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THE ENERGETICS AND CONFORMATIONAL PROPERTIES OF BIOACTIVE CONFORMTIONS: A MOLECULAR MECHANICS AND QUANTUM MECHNICS STUDY

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The identification of bioactive conformations, namely, those conformations adopted by ligands upon binding to their biological targets is critical for both target-based and ligand-based computer aided drug design. Bioactive conformations can be obtained computationally from within conformational ensembles generated by conformational search tools. However, such an approach inevitably generates many other non-relevant conformations and thus requires a focusing mechanism. Criteria for focusing the conformational ensemble of a (unbound) ligand on its bioactive conformation can be based on structural or energy characteristics. Structural criteria assume that structures of bound ligands are different from those of unbound ligands in some consistent way. This assumption is based on the idea that ligands tend to unfold within binding sites to maximize interactions with binding site residues. Energy criteria assume that bioactive conformations are found within a reasonably low energy window from the energy of the unbound ligand. Such a window can be estimated from the ligand free energy of binding, which results in part from the ligand strain energy that is the energy difference between the bound and unbound states of the ligand.

This work focuses on the energetics and conformational properties of bioactive conformations and on how they compare with those of the unbound state. The ligands studied in this work are all FDA approved drugs whose complexes are available in the PDB. Unbound conformational ensembles were obtained by first subjecting each ligand to multiple conformational search procedures and then by merging and clustering the resulting ensembles. The resulting cluster centers were re-minimized using three force fields and four QM methods. These steps are collectively referred to as the workflow. The bound (bioactive) state for each ligand was represented by its crystal structure or approximated by a conformation generated from it through constrained or unconstrained energy minimization. The structural properties of bound and unbound ligands were compared in order to identity systematic differences between them. The strain energy was evaluated using energy differences between the global minimum of the unbound state or the Boltzmann averaged energy of the unbound ensemble and the approximated bioactive conformations.

The above described workflow is able to generate ligand conformations which closely resemble the X-ray conformation (RMSD<1.0 Å) in 98% of the cases. This workflow is also able to produce bioactive conformations similar in energy to the global minima somewhat more often than standard conformational search methods, yet not unexpectedly, in cannot generate bioactive conformations as global minima. The energy window within which the different methods compared in the workflow generate the bioactive conformation (approximated by its closest local energy minimum) was calculated. This window is found to be 4-6 kcal/mol with respect to the global minimum and marginally lower with respect to a Boltzmann averaged energy of the unbound ligand.

The energy cost of obtaining the bioactive conformation (i.e., strain energy) was further studied and since it is impossible to calculate the energy of the bioactive conformation directly from X-ray coordinates, approximations to the bioactive conformation were introduced. Unconstrained minimization performed both in previous studies and for comparison purposes in this research as well is insufficient since the resulting local minima are often structurally remote from the X-ray structure (0.42-0.47 Å). Other methods aimed at identifying conformations which are structurally close to the X-ray conformations, yet energetically relaxed were considered. Better approximations for the bioactive conformation presented in this work include T/B constraints which are based on the atomic B-factors and a newly developed Knee Point Detection (KPD) method. The overall energy cost obtained by both methods was found to be in the range of 5-7 kcal/mol (to be compared with an energy cost of 4-6 kcal/mol obtained by approximating the bioactive conformation by its closest energy minimum).

The structural and energy criteria were tested for their ability to focus conformational ensembles on bioactive conformations. None of the 3D descriptors considered in this work showed statistically significant differences between bound and unbound conformations. In contrast, energies calculated by several QM methods and by the CHARMm force field were shown able to somewhat focus conformational ensembles on bioactive conformations. For example, when using energy cutoffs which corresponded to retaining 50% and 70% of the ensembles, QM methods and CHARMm offer 60-65% and 80-84% probability of obtaining the bioactive conformation, respectively.

HALOGEN BONDING IN MEDICINAL CHEMISTRY: PROSPECTS AND QUANTITATIVE DESCRIPTION

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Halogen bonding (XB), defined as a weak non-covalent attractive interaction of heavy halogens (Cl, Br and I) and Lewis donors, has emerged during the last decade as a promising avenue for optimizing intermolecular interactions in drug design [1,2,3]. Lewis donors can be N, O atoms in molecules as well as aromatic π-systems [2]. Most mentions of XB however come from retrospective analysis of X-ray crystallographic data, as well as results of high throughput screening in hit finding and lead optimization activities [3]. For now only a few examples exist, which demonstrate the use of XB in completely prospective design and development. To guide the rational use of XB, first, its origin and traits should be well understood, and, second, a set of appropriate tools should be available at the disposal of a researcher to model it.

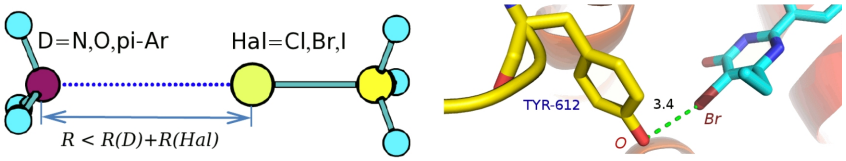

Figure 1. Halogen bonding (left) and close O--Br contact in PDE5A1 - 5BO complex of PDB:3SIE (right)

We consider the prospects of XB in medicinal chemistry from several perspectives. First, its origin is analyzed in terms of intermolecular forces, with the electrostatic one being pivotal [4]. Second, a unique XB's combination of significant hydrophobic undirected and directed electrostatic interactions with possible target is highlighted. Next, we consider the current status of quantitative description of XB at different levels of tools used in modern drug design and development. We overview different approaches to halogen bonding modeling, their accomplishments and relative prospects. We also describe a set of methods developed in our group for description of XB [5], including the use of multipole expansion up to quadrupole around heavy halogens and its proper substitute, approximated by point off-atom charges, for application in classical force field modeling packages. The areas of future development are outlined.

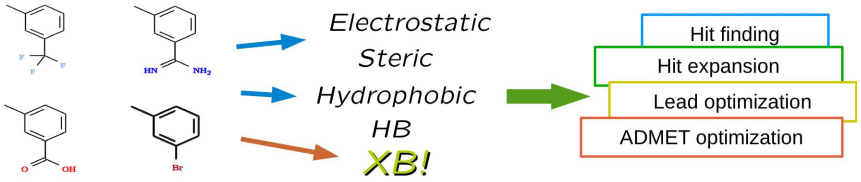

Figure 2. Future use of halogen bonding in pharmaceutical design and develoment pipeline

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HOMOLOGY MODELS OF PROSTAGLANDIN EP1, EP2, EP3 AND EP4 RECEPTORS FOR DEVELOPMENT OF GASTROPROTECTIVE MEDICINES

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Gastroprotection and adaptive gastroprotection medicines are welcome since by estimation about 10% of EU and US people suffer from dysfunction of gastrointestinal tract, especially caused by administration of non-steroidal anti-inflammatory drugs (NSAID). Despite the protective effect of prostaglandin E_2 (PGE_2) was shown in early 1980s [1], no consistent and widely accepted model of gastroprotection has appeared in the literature since that time. PGE_2 is known to exert its activity through the four subtypes of PGE_2 receptors – EP1, EP2, EP3 and EP4, which are GPCR-receptors, whose activation results in different and sometime opposite cellular response. There is certain controversy about the relative importance of the four subtypes in gastroprotective activity, however perhaps the most convincing study implies EP1 receptor is the most relevant target for rational drug design [2].

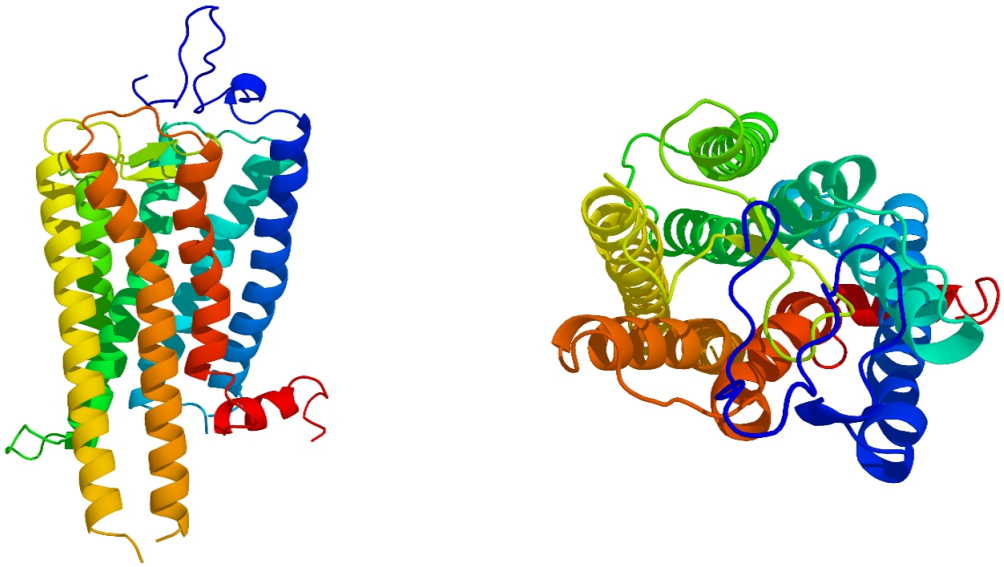

Figure 1. Homology model of EP1 subtype of human PGE2 GPCR receptor

To guide structure based drug design of gastroprotective medicines with desired activity and selectivity profile, high quality models of all subtypes of PGE_2 receptors are necessary.

Homology models for all four subtypes of human PGE_2 receptors were constructed with different approaches to assure diversity and increase success rate. First, automatic construction by means of GPCR-ModSim [3] web-service was conducted. Second, manual construction was also undertaken, in which amino-acid sequences were obtained from Uniprot, followed by their multiple sequence alignment by means of ClustalO, and finally model building with MODELLER software.

All models for human EP1, EP2, EP3 and EP4 receptors were checked for presence and proper orientation of crucial amino-acids and structural elements. The most consistent of them are prepared to virtual screening studies aimed at checking the models' ability to discern active and inactive compounds.

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INTERACTIVE WEB REPOSITORY FOR PREDICTIVE MODELS.

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The constant evolution of web technology has made web browsers capable for advanced interactions and visualisations of scientific data. Currently it is the quickest and most efficient way to get the data to the intended audience. The users do not need to install any standalone software and can start immediately to explore and use the data. The web technology has already found wide use for making available large datasets with chemical and biological data (e.g. PubChem, ChEMBL). Currently efforts are ongoing for providing web resources that are derivatives of such data, i.e. a new knowledge in the form of silico predictive models.

QsarDB repository (http://qsardb.org/) is a web based solution for archiving and interactively accessing QSAR and QSPR models in modern web browsers. The repository stores models in an open QsarDB data format that is designed for the electronic organization and archiving of QSAR/QSPR model information. It can be used for the representation of compounds, experimentally measured activities/properties, descriptors, models, and predictions. The format is highly flexible and extensible, and is based on open standards.

The web environment of the repository is based on DSpace, which is an open source platform for building digital repository applications. The DSpace provides a core repository functionality, such as storage of data and metadata, permanent identifiers for content, browsing and searching of content, management of user communities, etc. This system has been extended to provide interactive visualization of QSAR/QSPR models, including data sets, structures, plots, models statistics and applicability domain. The prediction functionality is also available. However, the automatic calculation of descriptors is only possible with open source software. Currently the repository includes 72 models (e.g. multilinear regression models, random forests), including predictive toxicology and physicochemical endpoints.

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PREDICTION OF STABILITY CONSTANTS OF THE METAL ION – ORGANIC LIGAND COMPLEXATION BY CONSENSUS QSPR MODELING

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Here we reports predictive QSPR models for the stability constants log*K* of the 1:1 (M:L) complexes of metal ions (M) with different classes of organic ligands (L) in aqueous solution at 298 K and an ionic strength 0.1 M. The complexation was studied for 42 metal ions: Li^{+}, Be^{2+}, Na^{+}, Mg^{2+}, Al^{3+}, K^{+}, Ca^{2+}, VO^{2+}, Mn^{2+}, Fe^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Ga^{3+}, Sr^{2+}, Y^{3+}, Ag^{+}, Cd^{2+}, In^{3+}, Ba^{2+}, La^{3+}, Hg^{2+}, Pb^{2+}, Ce^{3+}, Pr^{3+}, Nd^{3+}, Sm^{3+}, Eu^{3+}, Gd^{3+}, Tb^{3+}, Dy^{3+}, Ho^{3+}, Er^{3+}, Tm^{3+}, Yb^{3+}, Lu^{3+}, Th^{4+}, UO_2^{2+}, NpO_2^{+}, and Am^{3+}. Studied ligands are molecules of various organic classes. As a rule, acyclic or cyclic organic ligand has several functional groups, such as carboxylic, amine, phosphoryl, carboxy, sulfonic, ether, amide, phenolic groups in different combinations. The QSPR models have been built using ensemble multiple linear regression analysis and Substructural Molecular Fragment descriptors on data sets including from 883 (Cu^{2+}) to 28 (Am^{3+}) organic ligands. The models have reasonable prediction performance: root-mean squared error varies from 0.49 (Li^{+}) to 2.30 (In^{3+}) (the log*K* units) which is close to observed experimental systematic errors. The log*K* values were predicted by consensus models as arithmetic means of several hundreds of individual models taking into account their combined applicability domains. The Substructural Molecular Fragments enable detection of ligand moieties with important contributions into stability constants and they can be used as building blocks of new ligands. Developed models were applied for screening of selective ligands to every metal ion among some groups of metals using the 2962 organic ligands from the IUPAC Stability Constants Database. For technique aims, the obtained models allow one to assess the ligand selectivity of one metal with respect to another metal measured by the logarithm of a ratio of their stability constants.

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STRUCTURE-GUIDED DESIGN AND DISCOVERY OF NOVEL SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs): STRUCTURAL BIOLOGY OF THE PROTEIN-LIGAND INTERACTIONS AND THE DUAL REGULATION MECHANISM STUDY

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Estrogen receptors (ER) are ligand-activated transcription factors that belong to the nuclear hormone receptor superfamily, acting through their two receptors, ERα and ERβ, regulate a wide range of physiological and pathological processes. Because various ER ligands can demonstrate marked tissue selectivity, for example, estrogen receptor-α (ERα) ligands have different effects on the liver, bone, the cardiovascular system, and reproductive tissues.[1] Thus, understanding the molecular and structural basis of tissue-selective signaling by small molecules remains the largest barrier to improving therapeutics that target the estrogen receptors.

In this regard, we will report our latest efforts to develop series of novel small molecules for ERs based on the *structural* and *chemical*, as well as *elemental diversity* oriented syntheses. Novel ligands for the estrogen receptor, based on a three-dimensional structural motif, heterocycles of fused bicyclic core, as well as the isoelectronic and isostructural replacement of a C=C bond with a B-N or C=N bond have been designed and synthesized. [2-6] These bifunctional ligands proved either possess both anti-proliferative and anti-inflammatory activities, or anti-proliferative activity for both ER positive (ER^+) and ER negative (ER^-) resistance breast cancer cell, or served as selective estrogen receptor downregulators (SERDs) for Tamoxifen resistance cancer cell. The structure-activity relationship (SAR) and the dual mechanism of the interaction of these ligands with ER, as well as the potential use of these new ligands as bifunctional drugs for breast cancer therapy will also be discussed. The generation of these compounds provides important insight into the diversity of the ligands for these important pharmaceutical targets.

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NEW LIGANDS FOR DETECTING DRUG RESISTANT BACTERIA

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The ongoing emergence of bacterial strains resistant to even third- and fourth-generation β-lactam antibiotics is one of the most pressing and challenging issues in clinical therapy. Therefore, new drugs and new approaches for fighting multidrug-resistant Gram-negative bacteria are categorically necessary.

The OPTObacteria EU FP7 project is aimed at the development of a multianalyte automatic system for the detection of drug resistant bacteria. In order to allow a faster and more effective treatment and control of the infections, the detection system will use an optoelectronic device coupled with ligands, able to selectively bind a series of pharmacologically relevant ESBLs [1]. In particular, CTX-M-15 and KPC-2 for class A, NDM-1, IMP and VIM-2 and Amp-C for class C have been considered.

This research, aimed at the identification of new ESBLs ligands, has been mainly carried out with computational methodologies performing virtual screening simulations with the FLAPdock software developed by Molecular Discovery Ltd [2].

FLAP uses Molecular Interaction Fields produced by the GRID algorithm to derive Fingerprints for Ligands and Proteins, which characterize the protein active site and can be used to find complementary ligands in a docking-like approach. A specific version of the algorithm has been developed *ad hoc* to better simulate the interaction with both serine- (classes A and C) and metallo-b-lactamases (class B).

In order to identify new scaffolds able to bind the selected ESBLs, the Specs database was chosen and screened against all the proteins. The original library of about 200.000 compounds was filtered according with the molecules' LogP, then tautomers and protomers were enumerated using the Moka software. The most interesting molecules, according to the FLAP S-Score, the pose, the number of hydrogen bonds formed with the surrounding residues and the chemical diversity, were purchased and subsequently tested in experimental assays. The analyses confirmed a 30% and a 50% prediction success rate for KPC-2 and NDM-1, respectively. These results overcome the standard virtual screening success rate which, for random screens, typically range from 0.1 to 0.5%. In particular, one compound demonstrated for KPC-2 an IC_{50} value of 69 mM, comparable to the IC_{50} shown by the control 3-amino-phenylboronic acid, i.e. 64 mM. Similarly, different molecules selected for targeting NDM-1 demonstrated a percentage of inhibition ranging from 20% to 60%, comparable to that provided by known inhibitors.

The relevance of these results is also highlighted by the non-covalent inhibition character of the analyzed molecules, while standard antibiotics and known boronic acid ligands are known to form covalent complexes with b-lactamases.

Studies for improving the affinity, ameliorating the chemical synthesis and allowing the anchoring onto the optical fiber are ongoing.

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DEVELOPMENT AND STRUCTURE-ACTIVITY RELATIONSHIP OF NOVEL ANTI-ANGIOGENIC AGENTS AS HSP90 INHIBITOR

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Hypoxia is a special feature occurring during acute and chronic vascular diseases and induces the transcriptional genes that are involved in glycolysis, haematopoiesis, invasion and angiogenesis. Especially, angiogenesis, which is the process forming new blood vessels, is essential for adaptation of tumor cells to hypoxic environment. Hypoxia-inducible factor-1α (HIF-1α), a key mediator of angiogenesis, is overexpressed under hypoxic condition and transcripts various gene that concerned with survival and proliferation of tumor cells. HIF-1α can be also induced by growth factor stimuli and oncogenic activations, which are common features of human cancer including prostate, breast, colon, and lung cancers. Deguelin, a rotenoid isolated from the African plant *mundulea sericea* (Leguminosae), exhibits potent apoptotic and antiangiogenic activities in a variety of transformed cells and cancer cells. Deguelin also exhibits potent tumor suppressive effects in several human xenograft tumor models. Our initial studies confirmed that deguelin disrupts ATP binding to HSP90 and consequently induces destabilization of its client proteins such as HIF-1α. Interestingly, a fluorescence probe assay revealed that deguelin and its analogues do not compete with ATP binding to the *N*-terminus of HSP90, unlike most HSP90 inhibitors. We recently established the structure-activity relationship (SAR) to delineate the structural features required for activity and tried to find novel HSP90 inhibitors consisting of new scaffold with an improved antiangiogenic activity. We have identified new potent deguelin analogues through the SAR studies. Moreover, the ring-truncated compounds designed based on the SAR studies exhibited excellent HIF-1α suppression and potent cell growth inhibition. In particular, two analogues of the ring-truncated compounds, exhibited excellent anti-proliferative activities with IC_{50} of 140 and 490 nM in the H1299 cell line, respectively, and antiangiogenic activities in zebrafish embryos in a dose dependent manner. Moreover, we prepared a *C* -terminal HSP90 homology model with biological evidence of the representative analogues binding with the ATP binding site of HSP90 *C*-terminus. We will report SAR, biological activities and molecular binding mode of the novel HSP90 inhibitors.

IMPROVING VIRTUAL SCREENING USING DATA FUSION

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Data fusion, combining data from several sources, can be a valuable tool in virtual screening (VS). Recent studies show that data fusion not only improves the average recovery of active compounds but also has the ability to improve the results beyond the best single method.[1,2] However, which fusion scheme should be applied and how many VS methods should be used is still not thoroughly understood. By using simulated data large number of virtual data sets can quickly be generated and fused, shedding light on the mechanisms regulating the performance of data fusion in VS.

Previously simulated data have been used to create simple data fusion scenarios.[3] In our study we generate more complex data sets with a varying degree of correlation. In this way it is possible to simulate both the fusion of several related sources, like different scoring schemes, and the fusion of different VS techniques.

Preliminary results indicate that data fusion indeed in most cases improve the results compared to the average result of the single methods. However, the results show that data fusion is most successful when combining several methods with similar performance. What data fusion scheme has the best performance also varies depending on the performance of the single methods and their correlation.

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ATOMIC CHARGE BASED DESCRIPTORS AND THEIR APPLICATIONS IN QSAR

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Partial atomic charges are real numbers describing the distribution of electron density in a molecule. The partial atomic charges cannot be determined experimentally, and they are also not quantum mechanical observables. For this reason, the rules for determining partial atomic charges depend on their application (e.g. molecular mechanics energy, pKa etc.), and many different methods have been developed for their calculation. Charge calculation methods can be divided into two main groups, namely quantum mechanical (QM) approaches and empirical approaches [1,2]. QM approaches provide accurate charges, but they are very slow and therefore not feasible for large sets of molecules. Empirical charges can be calculated quickly and their accuracy is similar to QM, but they use empirical parameters based on QM charges.

Partial atomic charges provide clues regarding the chemical behaviour of molecules and are therefore frequently used in molecular modelling applications such as molecular dynamics, docking, conformational searches, binding site prediction, etc.. Recently, partial atomic charges have also become popular chemoinformatics descriptors and inputs for QSAR and QSPR models [3].

We will present an overview of QM and empirical charge calculation methods. Afterwards, we will provide a summary of the properties which can be predicted via QSAR/QSPR methods employing charge descriptors. Then, we will show a case study demonstrating the applicability of QM and empirical charges for the prediction of acid dissociation constants [4,5]. This case study also includes an investigation regarding how the selection of a specific charge calculation approach influences the quality of the charge based QSPR models. Last but not least, we will show a web application for the calculation of empirical charges using EEM (Electronegativity Equalization Method) [6,7] – one of the most popular and useful empirical charge calculation approaches.

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QSAR-ANALYSIS OF TETRAHYDRO-2H-ISOINDOL CYCLOOXYGENASE-2 INHIBITORS BY GUSAR SOFTWARE

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A quantitative analysis of "structure-activity" relationships for twenty-six 4,5,6,7 - tetrahydro -2H - isoindole and benzothiophene derivatives studied on cyclooxygenase 2 catalytic activity inhibition (IC_{50} values) in the range of concentration 0.6 ÷ 700 nmol/L [1] with GUSAR software was carried out [1-6]. Six statistically significant consensus QSAR models (M1-M6) for prediction of IC_{50} values were built based on both separate MNA- and QNA- descriptors and their combinations. The characteristics of created models are shown in Table 1. M1, M3 and M5 models were based on the training set TrS1 which contains all studied structure. M2, M4 and M6 models were obtained based on the training set TrS2. A test set (TS) was used for external evaluation of the accuracy of prediction of the models M2, M4 and M6. Training set TrS2 and test set TS included 20 and 6 structures of COX - 2, respectively. They were obtained by dividing the pre- sorted in ascending order of IC_{50} values in ratio 3:1, i.e. excluded from TrS1 every fourth compound to TS.

Atoms and structural fragments of the studied structures influencing on increase and decrease of COX-2 inhibition were identified by GUSAR visualization of quantitative "structure-activity" relationships in the created models. This information may be relevant to the molecular design of new COX-2 inhibitors. It has been shown that in most cases the detected structural fragments related with inhibitory activity of the studied compounds coincided with the results of expert evaluation of their effects on the basis of experimental data that can be used for optimization of structures to change the value of their biological activity.

Table 1. Characteristics and prediction accuracy of IC_{50} values for consensus models M1 - M6. pIC_{50} activity in TrS1 and TrS2 lies in the range 6.15-9.22.

Training set	Models number	N	R^2_{TrS}	Q^2	R^2_{TS}	F	SD	V
QSAR model based on MNA-descriptors								
TrS1	M1	26	0,865	0,818	-	19,626	0,320	5
TrS2	M2	20	0,885	0,833	0,421	16,90	0,290	4
QSAR model based on QNA-descriptors								
TrS1	M3	26	0,826	0,731	-	14,996	0,357	5
TrS2	M4	20	0,779	0,654	0,824	11,293	0,390	4
QSAR model based on MNA- and QNA-descriptors								
TrS1	M5	26	0,889	0,837	-	15,301	0,316	5
TrS2	M6	20	0,874	0,802	0,706	11,022	0,334	4

N – number of structures in the training set; R^2_{TrS} - a multiple coefficient of determination calculated for compounds from the training set; R^2_{TS} - a multiple coefficient of determination calculated for compounds from the test set; Q^2 – a cross-validated R^2 calculated during leave-one-out cross-validation procedure on data of the training set; F – Fisher's coefficient; SD – standard deviation; V- the number of variables in the final regression equation.

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VIRTUAL SCREENING FOR HIV PROTEASE INHIBITORS USING A NOVEL DATABASE FILTERING PROCEDURE

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New prospective ligands were found for HIV protease using the ZINC [1] database as a starting point, through filtering using a novel feature matrix matching procedure and ending with Schrödinger's virtual screening workflow [2] using Glide [3,4]. The docking algorithm used was able to find several known ligands including ureas, and the cognate ligand of the PDB structure used was docked in the same pose as in X-ray structure with a RMSD of 0.51 angstrom, demonstrating the validity of the algorithm used.
To reduce the set of ~14M compounds found in the database, a filtering procedure was developed, where the 3D structure of the active site of the protease was analysed with SiteMap [5], and then described as a distance matrix where hydrogen bond donor, hydrogen bond acceptor and hydrophobic subsites represented graph nodes. Similar treatment was then applied to database molecules: they were converted to distance matrices where the vertices were not single atoms but rather hydrogen bond donor, -acceptor and hydrophobic groups. Finding a potentially suitable ligand was then a simple matter of comparing each molecule's distance matrix with the one derived from the protein's binding site. A certain degree of overlap was required between matrices to select a compound for further processing. In the present case, the molecule was forced to fill at least 4 hydrophobic subsites and interact with at least 6 donor or acceptor subsites. To discard overly large molecules that would not fit into the protease's binding site, the matching hydrophobic, acceptor and donor groups were required to form at least 80% of the molecule. The parameter values were tuned by testing the procedure on known active and inactive ligands from the Directory of Active Decoys (DUD) [6] and the ChEMBL [7] database. The optimal parameters selected about 0.1% of the entire database, quickly and effectively decreasing the initial number of millions of compounds to more manageable numbers. Since this procedure requires only 2D information of the molecules and is therefore reasonably quick, it shows potential to be developed into a fully fledged virtual screening method for rapid database filtering before more computationally demanding methods.

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SEARCH OF NOVEL COVALENT INHIBITORS OF FMDV Lbpro

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Foot-and-mouth disease virus (FMDV) causes a highly contagious disease that infects cloven-hoofed animals [1][2]. Viral proteases are crucial to the life cycle of many viruses and were recognized as valid target in drug design [3]. The FMDV leader protease (Lb^{pro}) inhibits the host protein synthesis by the cleavage of the homologous eukaryotic initiation factors (eIF4GI and eIFG4II)[1, 2]. FMDV Lb^{pro} is a papain-like cysteine protease [1]. Although four 3D-structures of FMDV Lb^{pro} were elucidated, only few inhibitors were known[4]. To search for FMD virus Lb^{pro} inhibitors and to get some insights into the active site interactions, here, a set of 52 structural diverse *in house* compounds (previously selected, by virtual screening (VS), as potential covalent cruzain inhibitors) was submitted to a docking procedure, analyzed by visual inspection into the active site and the hits submitted to inhibition assays for experimental validation. FMDV Lb^{pro} 3D-structure (2JQF) is only available as a mutant (C51A). Through the importance of the catalytic Cys51 for the activity, Ala51 was replaced by Cys51 with Sybyl 8.0[5] followed by a local minimization using Sybyl Tripos force field. 3D-structures of the compounds were obtained by Corina 3.20[6] and the most abundant tautomer, in water, was generated by Moka 2.5.2[7]. The generated tautomers were docked, 50 runs, with Gold 5.2.2[8], applying the default automatic setting, maximum of search efficiency and ChemPLP score function. For each compound all the generated poses were visually inspected. Considering that these compounds were previously selected by VS as potential covalent cruzain inhibitors, only those in which the docking-poses exhibit their electrophilic moiety close to the Cys51 were further submitted to enzymatic assays. Using this criteria 6 compounds (11%) were selected as potential FMDV Lb^{pro} covalent inhibitors and submitted to inhibition assays, that were done at least in duplicate following literature protocol[4]. Two of them showed FMDV Lb^{pro} inhibition activity (IC_{50} values in the range of 300μM to 500 μM). They will be further examined to verify the proposed covalent inhibition mechanism. And, their best docking poses were used to get some insights into the interactions in the active site (e.g. hydrogen bond interactions with Glu147 and His148, hydrophobic interactions with Ala149 as well as aromatic interaction with Trp52). All these information will be used to generate pharmacophore models of FMDV Lb^{pro} inhibitors. In this study, from the original set, visual inspection of the docking-poses selected six potential covalent FMD virus Lb^{pro}inhibitors (11%). From which 2 (33%) showed FMDV Lb^{pro} inhibition activity (IC_{50} values in the range of 300 to 500 μM). These two inhibitors will be further examined to verify the proposed covalent inhibition mechanism. The visual inspection of these two inhibitors into the FMDV Lb^{pro} active site gives some insights about the interactions that could be important to generate pharmacophore models of FMDV Lb^{pro} inhibitors. *Financial Support*: FAPESP (2012/06633-2), INCT/NAP e CEPID de Processos Redox em Biomedicina. OpenEye Scientific Software, Inc Santa Fe.

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IN SILICO IDENTIFICATION OF NOVEL POTENTIAL INHIBITORS OF HUMAN ECTO-5'-NUCLEOTIDASE (E5NT/CD73)

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Ecto-5'-nucleotidase (e5NT, CD73) is a Zn^{2+}-binding glycosylphosphatidilinositol-anchored homodimeric protein found in most human tissues.[1] E5NT is found in both open and closed conformations and catalyzes the hydrolysis of AMP to adenosine, acting as a major control point for the extracellular provision of this signal molecule.[1,2] Recent studies have shown that e5NT is upregulated in various human cancerous cells, suggesting that tumor-derived adenosine constitutes an important mechanism of tumor immune escape.[3] In addition, higher expression levels of e5NT have been associated with tumor neovascularization, invasiveness and metastasis.[3,4] All these findings suggest that targeting tumor-derived e5NT is an effective strategy in controlling tumor progression, alone or in combination with other strategies.[2,3] Recently, crystal structures of human e5NT in complex with various ligands (including inhibitors) have been determined and are available in PDB.[2] In spite of its potential relevance as a target for anticancer therapy, so far only few e5NT inhibitors have been reported, and the the majority of them are not suitable as drug candidates.[5] In this study, in order to search for novel potential e5NT inhibitors, crystal structures of human e5NT in complex with PSB11552 (open conformation) and AMPCP (closed conformation) were used to generate four VS models: Models O1/O2 and C1/C2, respectively. In these VS models, a sequence of five filters (pharmacophore, drug-like, structural similarity, docking and visual inspection) was applied to the ZINC database. In the first step, hydrogen-bond acceptor (HBA), hydrogen-bond donor (HBD), hydrophobic, aromatic ring and zinc-binding features were recognized in the e5NT catalytic site by *LigandScout* program v.3.1 and selected to construct pharmacophore models. For the construction of Pharmacophore Models O2 and C2, the minimum energy regions, obtained by *GRID* program v.22C were also considered. All generated pharmacophore models were applied to the ZINC database (release 12, 2011; ~$23x10^6$ structures; conformers generated by *Omega* program[6]), selecting 58, 1388, 191 and 1138 compounds (Models O1, O2, C1 and C2, respectively), which were further submitted to a drug-like filter[7]. This filter reduced the initial number of compounds in 0%, 0.03%, 9.9% and 7.1% (Models O1, O2, C1 and C2, respectively). To reduce the number of similar compounds keeping, however, structural diversity, the remaining compounds (except those from Model C1) were reduced to a new sub set, considering a Tanimoto coefficient (obtained using *Babel* program v.2.3.1) of maximally 0.85. This step reduced the number of compounds in 34.4%, 36.1% and 29.1% (Models O1, O2 and C2, respectively). The resulting compounds were docked into the e5NT catalytic site, using *Gold* program v.5.2.2. In these calculations, *Asp* and *Goldscore* scoring functions were used, and *Gold* default parameters were applied. The docking filter reduced the number of compounds in 55.2%, 96.5%, 81.4% and 93.1% (Models O1, O2, C1 and C2, respectively). Finally, the compounds that best fitted into e5NT catalytic site were subjected to visual inspection. In this final step, compounds that displayed a complete or nearly complete fit into the features of the pharmacophore models were prioritized, leading to the selection of 4, 27, 18 and 22 potential inhibitors of e5NT (Models O1, O2, C1 and C2, respectively). All the generated VS models are being tested as e5NT inhibitors for their experimental validation. These initial studies are expected to contribute for further anticancer drug design targeting e5NT. *Financial support*: FAPESP (2014/07248-0), INCT/NAP e CEPID de Processos Redox em Biomedicina. OpenEye Scientific Software, Inc Santa Fe.

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SEARCH FOR NEW DUAL INHIBITORS OF THE 5-LIPOXYGENASE-ACTIVATING PROTEIN AND SOLUBLE EPOXIDE HYDROLASE WITH PHARMACOPHORE MODELING

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Leukotrienes are inflammatory lipid mediators with key roles in several inflammatory conditions, such as asthma and allergic rhinitis[1]. Leukotrienes are derived from arachidonic acid, which is liberated from the membrane phospholipids by cytosolic phospholipase A_2($cPLA_2$), transferred by the 5-lipoxygenase-activating protein (FLAP) to 5-lipoxygenase (5-LO), which catalyzes leukotriene synthesis. Since 5-LO is not functional in the cell without FLAP, inhibition of this helper protein has an anti-inflammatory effect[2].

Soluble epoxide hydrolase (sEH) metabolizes the anti-inflammatory epoxyeicosatrienoic acids (EETs) to 5S,6S-dihydroxy-7E,9E,11Z,14Z-eicosatetraenoic acids (di-HETEs). Its inhibition consequently prevents inflammation[3]. Targeting both leukotriene synthesis *via* inhibition of FLAP and the metabolism of EETs by suppressing sEH with a dual inhibitor may lead to novel, powerful anti-inflammatory compounds[4].

We created two ligand-based pharmacophore models for FLAP inhibitors in LigandScout[5] based on known active compounds from the literature. The two models were refined with exclusion volumes and validated in a prospective virtual screening of the commercial SPECS virtual library (www.specs.net). Ten hit compounds for each model were selected and biologically tested in specific assays for FLAP-mediated inhibition of leukotriene synthesis and FLAP-independent 5-LO activity in a cell-free model, confirming FLAP as the target. By these means, three FLAP active compounds out of 10 tested substances were identified per model, achieving a hit rate of 30%, respectively.

The total 20 hit-compounds were also screened with a previously developed model collection for sEH. Out of 7 compounds that were predicted to be sEH active, four displayed a strong inhibitory effect on purified sEH in a cell-free assay. Together, in the course of this work two new dual inhibitors for sEH and FLAP could be among only 20 tested compounds, prominently emphasizing how much time and resources in the identification of new drug leads can be saved through computational methods.

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PERSPECTIVES OF HALOGEN BONDING DESCRIPTION IN SCORING FUNCTIONS: SUBSTITUENT EFFECT IN AROMATIC CORE

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Halogen bonding (XB) is a non-covalent attractive interaction between heavy halogen atoms (Cl, Br, I) and donors of electron density such as carbonyl oxygen or unsaturated bonds. It complements traditional interaction patterns allowing construction of directional bonds in hydrophobic environment and thus provides new prospective approaches in drug design [1]. However broad application of XB in drug design is now hampered due to the lack of fast and reliable schemes of its description.

It is natural to base such schemes on the nature of the interaction: high anisotropy of molecular electrostatic potential (MEP) (Fig. 1a), known as σ-hole [2]. We propose to describe such anisotropy by using atomic multipoles[3]. The question then is how to predict XB strength in a diverse set of drug-like molecules.

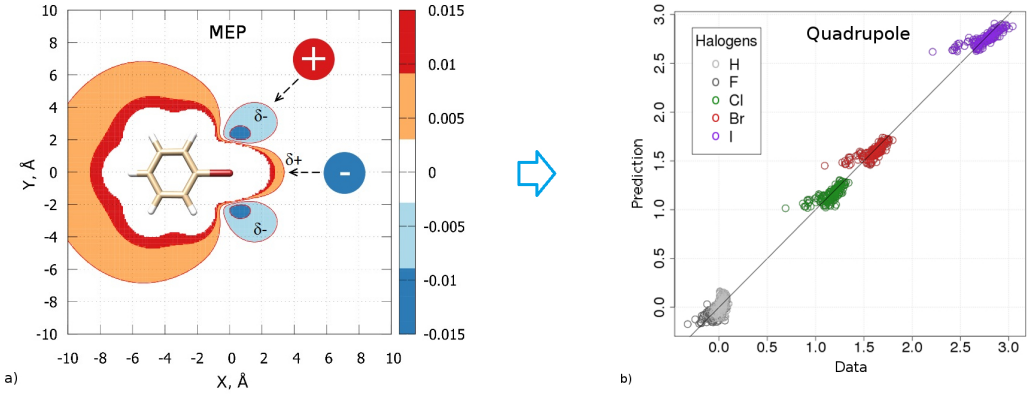

Fig1. MEP anisotropy of halogen atoms: a) σ-hole of pheniliodide MEP (MP2/aug-cc-pVTZ-PP, a. u.) and b) quadrupoles (a. u.) predicted by Hansch model on a set of aromatic structures.

Here we studied the factors governing the variation of multipoles according to chemical surroundings in QSPR approach. We investigated the relative importance of local and non-local aromatic effects. Also we tested the relative parameter significance and additivity of substituent effects.

To address the issues stated above a focused set of drug-like aromatic fragments with different halogens and substituents was compiled. Several multipole models were fitted to RHF/6-31G* reference MEP. Atomic charges and atomic quadrupole moment on halogen atom as well as electrostatic potential in σ-hole area were studied. Free-Wilson analysis was carried out for additivity tests, and Hansch QSPR models with Hammett constants as descriptors were built (Fig. 1b).

We showed that both inductive and resonance effects are essential for quantitative description of atomic charges. In contrast to charges, atomic quadrupoles are not influenced by resonance interaction. We showed that atomic dipole moment has negligible contribution to XB anisotropy description.

We performed the first step to construct an empirical scheme for XB description, which makes possible further rational development aimed at using in scoring functions for virtual screening and QSAR studies.

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THE DNA MINOR GROOVE AS A NEW TARGET FOR ANTITUMOR NON-PHOSPHOROUS GLYCEROLIPIDS: BIOPHYSICAL AND MOLECULAR MODELING INSIGHTS

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The anticancer lipids emerged as a perspective class of therapeutic candidates due to their preferential potency for transformed vs normal cells. The alkyl cationic non-phosphorous glycerolipids (ACNPG) are the structurally close chemotype whose synthesis is environmentally safer. The original ACNPG (synthesized by N. Plyavnik at Moscow State Academy of Fine Chemical Technologies) demonstrated a cytoplasmic accumulation, inhibition of a few tyrosine kinases and a high cytotoxicity against human tumor cell lines whereas normal counterparts were spared. In search for other targets valuable for antitumor characteristics we hypothesized that the positive charge and hydrophobicity would allow ACNPG to interact with negatively charged biomacromolecules, in particular, with nucleic acids. Indeed, in a cell free system ACNPG formed stable complexes with double stranded DNA as revealed by differential scanning calorimetry. Both charges and hydrophobicity of individual ACNPG were found to be critical prerequisites of binding to DNA. Molecular docking of single lipid molecules on DNA surface was performed using AutoDock 4.2 and ICM-Pro version 3.7-2b (the Lamarckian genetic algorithm and the Monte-Carlo method, respectively). The target DNA was rigid whereas lipids were flexible. Partial charges on atoms were calculated using the topological (Gesteiger-Hückel method) and quantum mechanistic (semi-empirical AM1, PM3, PM6 and DFT) approaches. The B3LYP hybrid functional potential with basic 6-31G (d), 6-31G (d, p) andcc-pvdz were used to calculate the distribution of electron density. The obtained electron density distributions were further used for calculation of partial atomic charges, applying Mulliken's population analysis, Natural population analysis, and CHELPG (Charges from Electrostatic Potentials using a Grid based method)). The calculations with DFT/ B3LYP with the level 6-31G (d,p) in combination with CHELPG showed the most probable charge distribution across the imidazole ring. Thus, the docking procedure was performed with this methodology. We found that, irrespectively to the docking algorithm, all studied ACNPG bound to the DNA minor groove. The contribution of hydrophobic interactions was predominant. The charges influenced the geometry of lipid positioning in the groove, so that positively charged moieties were located closely to negatively charged O atoms in the DNA backbone. The triazol aromatic rings and hydrophobic 'tails' laid in the minor groove whereas the 6-member ring with positively charged N atom tended to localize in the hollow formed by phosphate groups. This site was identified in a backbone-forming crest that limits the groove. The H bonds between the acceptor O atoms in the glycerol moiety and the donor DNA base groups can strengthen the ACNPG-DNA complex. Finally, the docking to topoisomerase I (topo I) placed all ACNPG in the enzyme's cavity normally responsible for DNA chain traverse after the catalytic attack. The amino acid residues Lys374 and Arg362 involved in binding of known topo I inhibitors formed an H bond with the lipid molecule. Still, the energy of lipid-topo I binding was smaller than the respective values for lipid-DNA complexes. Thus, we for the first time demonstrated that ACNPG can form stable complexes with the DNA minor groove, thereby broadening the therapeutic potential of this novel chemotype. To deliver ACNPG to the nuclei, the synthetic work is under way linking the nuclear localization signal peptide to the lipid with preferred DNA binding characteristics.

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DOCKING INSIGHT OF OLIVOMYCIN A-MG2+ DIMER BINDING TO SP1/NFAT PROMOTER SITE OF C-MYC ONCOGENE

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Olivomycin A belongs to the class of aureolic acid antitumor antibiotics. Its cytotoxicity is associated with the ability to bind to DNA minor groove in GC-rich regions in the presence of Mg^{2+} as a bidentate ligand. Other authors and we have reported that the aureolic acid derivatives down-regulate a wide number of genes coding for transcription factors, heat shock and DNA repair proteins. Among the targets of olivomycin A the c-*Myc* promoter contains GC-rich sequences bearing binding sites for transcriptional factors SMAD, Sp1, E2F and NFAT, potential olivomycin A targets. In order to shed light into the mechanism of transcriptional deregulation of c-*Myc* by olivomycin A, we explored the interaction of this compound with the regulatory region $d(TGGCGGGAAAAAG)_2$that carries the binding sites for transcriptional factors Sp1 and NFAT (Sp1/NFAT) with application of docking by using soft ICM-Pro version 3.7-2b. Partial charges on ligand atoms were calculated using DFT approaches. The B3LYP hybrid functional potential with cc-pvqz basic was used to calculate the distribution of electron density. The obtained electron density distributions were further used for calculation of partial atomic charges, applying CHELPG method. Molecular docking revealed that olivomycin A has a strong preference to the wild type Sp1/NFAT binding site compared to double stranded DNA. The tricyclic moiety of olivomycin A as well as antibiotic sugars were anchored in the minor and major grooves of Sp1/NFAT oligonucleotide. Moreover, the sugar residues ‘embraced’ the DNA backbone, thereby facilitating the interactions of olivomycin A chromophore with base pairs. The substitution of GC bases to AT in Sp1/NFAT-m significantly changed the geometry and energy parameters of drug-DNA complexes. Dramatic conformational perturbations of tricyclic chromophores resulted in that sugar residues was no longer available to form H-bonds with nucleobases in minor and major grooves so that the complex showed a weak DNA binding. Importantly, the data generated in in silico experiments corroborated the results of biophysical measurements (a good agreement in means). Thus, we for the first time generated a model that shows the mode of olivomycin A binding to the GC-rich DNA stretch. The model demonstrated how the drug can affect local environment in the transcription factor binding sites, thereby providing evidence for the mechanism of the genome wide transcriptional deregulation by this anticancer drug candidate.

PREDICTION OF FE3+ AND CU2+ IONS IN PROTEIN STRUCTURES

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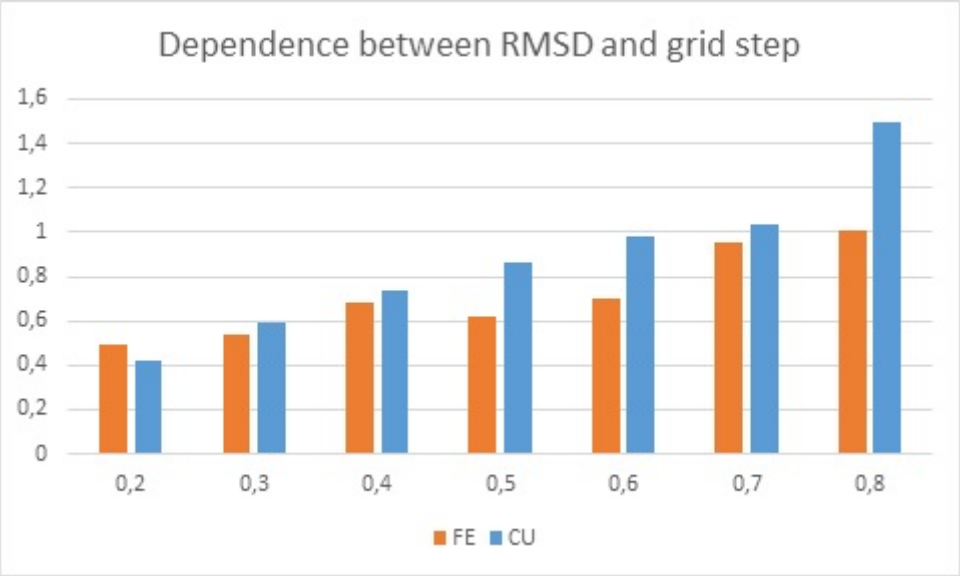
In current time, prediction of secondary structures and cofactor for new protein structures is very important. Especially for different amyloid protein structures, which ion's cofactor is very important for understanding the mechanisms of Parkinson and Alzheimer disease. By this reason an instrument for predicting copper and iron ions in user protein structure is needed. By these reasons algorithms for prediction ions is very important.

Earlier, our group has developed empirical potential-based algorithm for ion prediction. But, our algorithm work only for ions with large statistics (Zinc, Calcium and Magnesium). Now we have extended algorithm on sets with less statistics (Iron and Copper). For regularization of obtained empirical potentials we use exponential smoothing with different alpha-coefficient for different ion.

For testing our algorithm, we select set from 10 structure of X-ray and NMR structure from PDB. Each structure binds only one type of ion. For each structure we predict position and type of ions. (most probable type of ion is the type for which pseudoenergy of binding is maximal). For test set we obtain RMSD between real and predicted ion position equal approximately 0,5 A for iron and 0,4 A for copper ion. In test for detection of ion type we obtain approximately, 78% correct type prediction for iron and 66% for copper.



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PREDICTING MOLECULAR MECHANISMS OF ACTION ASSOCIATED WITH BINARY ENDPOINTS

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The *in silico* identification of mechanisms of action related to drug candidates can help elucidate therapeutic targets and discover off-target activity that could be linked to adverse effects, providing information to better understand the underlying pathways involved in the efficacy and adverse effects of drugs. Additionally, predicting the mechanism of action of chemicals is of utmost importance to determine their environmental fate, and to predict the effects of long term exposure.

To address these needs, we have used Prous Institute's software solution Symmetry [1, 2] to train a model that predicts nearly 500 mechanism of action based on a training set extracted from literature, congresses and patent analysis. The training set contains approximately 1,500,000 Structure-Activity Relationships (SAR) with a ratio of ~1.5 SAR per training set structure, and it is continuously updated. Symmetry features classification and multi-label learning algorithms that allow the construction of *in silico* models based on molecular descriptors. The prediction quality of the Mechanism of Action (MoA) model has been assessed in internal cross-validation, and in external validations. In both cases results were satisfactory, with an internal validation that yielded a high recall of 88%.

One interesting application of Symmetry's MoA model is predicting the mechanisms of action associated with a binary data set and using that information to find differentially expressed mechanisms, i.e. mechanisms associated with positives but unrelated to negatives for a given endpoint. A methodology is proposed to find the relevant mechanisms of action associated with a binary training set, and avoid spurious MoA relationships.

As a case study, a binary data set of drug induced phospholipidosis (PLD) has been analyzed and MoAs related to this endpoint have been highlighted. The resulting MoAs associated with PLD are compared with those described in the literature [3].

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COMPUTATIONAL PREDICTION OF SYNERGISTIC PHARMACOLOGICAL EFFECTS FOR COMPLEX MOLECULAR SYSTEMS

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The authors discuss the results of *in silico* prediction of pharmacological activity of complex molecular systems, with account of the mutual effect of the constituent components and of their synergism. In this study, the complex molecular systems are salts of organic compounds with organic acids and bases, supramolecular complexes formed by noncovalent intermolecular interactions between some compounds and mixtures containing several individual substances.

Calculations were made using IT Microcosm, author's QSAR software package.

The following studies were performed and the following results were obtained.

1. Prediction of the level of antioxidant, hemorheologic and 5-HT_3 antagonistic activities of salts and bases of 303 condensed azole derivatives. It was shown that taking the acid residue in consideration increased the accuracy of predicting the level of the pharmacological activity: by 12.5% as a maximum, and by 6.5% on the average.

2. Computational optimization of the composition of supramolecular clathrate complexes of glycyrrhizinic acid with antioxidant, antiarrhythmic and antidiabetic pharmacons (three condensed azole derivatives) with the purpose of achieving the maximal pharmacologic effect.

It was found that:

- the optimal composition of the clathrate with the highest level of antioxidant activity was pharmacon : glycyrrhizinic acid 1 : 4;

- the antiarrhythmic activity of the clathrates of pharmacon with glycyrrhizinic acid equaled the activity of the pure pharmacon;

- the hypoglycemic activity of the clathrates of pharmacon with glycyrrhizinic acid is more low than the activity of the pure pharmacon.

The calculated results were confirmed in experiments on rats.

3. Prediction of the spectrum of 13 pharmacological activities of *Juglans regia* extract for mixture of 23 main active substances. It was calculated that the pharmacologic effects of the extract become manifest as a result of the complex effect of all 23 components; they are due to its combined immunostimulatory and metabolic action, which is predominantly peripheral. The calculated results were confirmed in experiments on calves and dogs.

4. Prediction of the synergism for seven active compounds in *Gymnema sylvestre* extract. It was predicted that a complex of active substances in extract should show a more powerful, a more stable and prolonged hypoglycemic effect than any component of the extract, either individually or in limited combinations, due to a mutual potentiating synergistic effect of all of the components. The calculated results were confirmed in experiments on rats.

5. Prediction of the synergism for pairwise combinations of five antidiabetic drugs with metformin. Calculations were performed for synergistic-effect values obtained in clinic. It was shown that there is a statistically highly significant dependence between the synergistic effect of antidiabetic drug combinations and the metric of membership of these compounds in the hypoglycemic compound class calculated by IT Microcosm. Spearman's rank correlation coefficient $R_S = 0.8169$, statistical significance $p = 7.192 \cdot 10^{-3}$.

Thus, IT Microcosm permits to predict exactly the presence and levels of various pharmacological activities of complex molecular systems: complex organic salts, supramolecular complexes and organic compound mixtures with inclusion of the component synergism. This allows an optimisation of the qualitative and quantitative composition of the complex molecular systems, which can lead to the design of novel, powerful drugs based on several gently acting, nontoxic compounds and several synergistic admixtures potentiating their effects.

LIGAND-BASED PHARMACOPHORE MODELING AND VIRTUAL SCREENING FOR NOVEL 17β-HSD2 INHIBITORS

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17β-Hydroxysteroid dehydrogenase 2 (17β-HSD2) catalyzes the inactivation of estradiol into estrone.[1] This enzyme is expressed only in few tissues and therefore its inhibition is considered as treatment option for osteoporosis to ameliorate estrogen deficiency.[2, 3] Currently, only few inhibitors are known (e.g thiopene amides and hydroxyphenylmethanones [4, 5]) and none of them has reached clinical trials. To support the search for novel inhibitors, a collection of three ligand-based pharmacophore models for 17β-HSD2 inhibitors were constructed. These models were employed for virtual screening of commercial database. The screening resulted in 1,300 unique hits, from which 29 were evaluated *in vitro* for 17β-HSD2 inhibition. Seven of these hits inhibited 17β-HSD2 with low micromolar IC_{50}-values, the most potent hit having an IC_{50} of 240 nM. Four of the hits represented phenyl-benzenesulfonate- or sulfoxy-scaffold. In order to derive SAR-rules for this novel scaffold, further 35 derivatives were purchased and evaluated for 17β-HSD2 inhibition. These results were then successfully used for the development of a predictive SAR model for this scaffold.

In this study, we discovered 13 novel 17β-HSD2 inhibitors; most were selective over 17β-HSD1 and other related HSDs. These results also validated the pharmacophore model collection: the overall success rate of the model collection was 24%, and one of the three models had an individual success rate of 50%. Finally, this model was refined for better specificity and it can now be applied for further virtual screening campaigns.

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BIOMACROMOLECULAR 3D-QSAR TO PREDICT AND DECIPHER DRUG RESISTANCE AND DRUG SELECTIVITY

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Being able to quantitatively predict the risk of drug resistance and drug selectivity at molecular level will greatly benefit the drug development. Many efforts have been dedicated towards these issues.[1-9] Recently, a new method, called MB-QSAR (Mutation-dependent Biomacromolecular Quantitative Structure-Activity Relationship) was established in our group[10-12], which followed and extended Comparative Molecular Field Analysis (CoMFA)[13] and Comparative Molecular Similarity Indices Analysis (CoMSIA).[14]

Considering that the drug resistance mutants or a set of target proteins from various species could be regarded as a series of "analogue" being targeted by the same ligand (drug) and sharing mechanism of action, following the principle of CoMFA/CoMSIA, a suitable sampling of the molecular field values in the interesting regions of a series of mutated or homological proteins should correlate with the observed biological properties. Thus, a MB-QSAR model could be constructed, the model can then be used for the prediction of biological properties of new mutants, and the molecular interaction diagram of MB-QSAR model also can provid detailed information for designing the high potency and resistance-evading/selective inhibitors.

In previous work, we have shown MB-QSAR can be successfully employed to predict resistances of acetohydroxyacid synthase (AHAS) mutants against a series of inhibitors and to decipher the structure-resistance relationship for ASAH mutants[10-12]. In this work, the MB-QSAR method was employed to predict the drug resistance of HIV-1 protease mutants against six approved drugs (saquinavir, indinavir, ritonavir, nelfinavir, amprenavir and lopinavir), the drug selectivity of protein kinases for some kinase inhibitors, such as sunitinib, dasatinib, gefitinib, bosutinib and erlotinib, and to decipher the structure resistance/selectivity relationships in HIV-1 protease mutants and protein kinases. The MB-QSAR models provided key information for designing inhibitors with high affinity, species selectivity and resistance-evading.

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MOLECULAR MODELING STUDIES ON SOME BENZAZOLE DERIVATIVES AS TOPOISOMERASE I POISON

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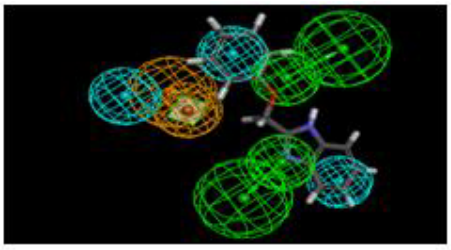
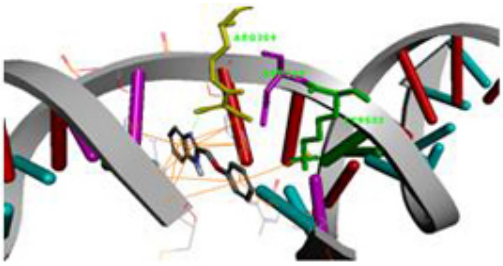
DNA topoisomerases, which catalyze the interconversion of various topological states of DNA, were originally discovered to change the superhelical structure of closed circular DNAs. Depending on the nature of the reactants and reaction conditions, topoisomerases can catalyze DNA relaxation/supercoiling, catenation/decatenation and knotting/unknotting reactions [1,2]. Based on their functional mechanisms, DNA topoisomerases have been classified into two types. Type I DNA topoisomerase breaks and rejoins only one of the two strands during catalysis, while type II DNA topoisomerase acts on both strands for each DNA strand-passing reaction and it requires ATP for full activity [3]. The mechanisms of intereference with Topoisomerase activity are quite different and can be divided into two classes; Topoisomerase poisons and Topoisomerase catalytic inhibitors. Investigation of the inhibitory activity of eukaryotic Topoisomerases is widely used in anticancer drug development.

Recently, a new series of benzazoles, has been investigated for their inhibitory activity on eukaryotic DNA topoisomerase I poison in cell free system [4]. Among the tested compounds, 2-(phenoxymethyl)-1H-benzimidazole showed very significant the topoisomerase I posion activity with IC_{50} value 14,1 μM. Its activity was found to be more effective than the standart drug Camptothecin (IC_{50} value 526 μM).

In this study, for the lead optimisation and generation of DNA Topoisomerase I poison active heterocyclic compounds, molecular modeling studies such as Three-Dimensional Common-Feature Hypotheses and molecular docking were done by using software Discovery Studio 3.5 [5] and the results were discussed.





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DRUG SAFETY ASSESSMENT THROUGH AUTOMATIC EXTRACTION OF STRUCTURE-ACTIVITY RELATIONSHIPS

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An improved workflow for automatic building of 3D-QSAR models from chemical biology databases such as ChEMBL[1] will be presented. Starting with a chemical structure of choice a 3D-smilarity search identifies neighborhood compounds in chemical biology space. These compounds form the basis for an iterative procedure to produce significant and robust 3D-QSAR models[2]. The resulting models provide indication of potential drug safety threats but also enable a mechanistic understanding of potential toxicity effects by relating the model back to the structure and highlighting those parts of the structure that renders it toxic. Such a drug safety assessment goes beyond similarity and physicochemical property-based computational models and can help the medicinal chemist to make better compounds.

On the basis of prospective[3] and retrospective examples the presentation will showcase simple and straightforward visual analysis of structure-activity relationships that yield insights that would not be revealed on the basis of chemical similarity alone.

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COMPUTATIONAL ANALYSIS PIPELINE IN HIGH-THROUGHPUT ANTIBODY SCREENING

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No matter whether hybridoma or phage display is used, antibody screening is a long and resource consuming process. It involves several rearrangement cycles, each reducing the pool of candidates. Among these, an important step is sequencing, applied to remove duplicates and to maximize diversity in the sample. To perform in silico rearrangement, we have developed an integrated processing pipeline. Starting with raw reads, it operates in several stages. First is the quality control and the assembly of contigs. This is succeeded with extraction of immunoglobulin sequences, which follow common leaders in plasmid. Then, duplicate sequences are coalesced and further processed as one. There is a classification of immunoglobulins in seven canonical structure families, defined by conservative regions in the chain. The subject of natural selection, and location of all variability, are variable regions. Knowledge of their sequences, together with the type of structural frame, is enough to distinguish antibodies by function. Using our IgCAT annotation tool [1], we automatically locate the region bounds, determine germline genes, their similarity score and canonical structure family. Further, we cluster candidates by variable region sequence, so that a human investigator might select only a few representatives for further evaluation, to save redundant work with very close results. Finally, DNA sequences are annotated for undesired codon usage and amino acid sequences for potential post-translational modifications (PTMs) sites. This is important, because their presence may decrease antibody production rates in recombinant expression systems or may completely alter the antibody function in vivo, correspondingly. Our pipeline typically reduces initial sample size by a factor of four. Roughly half of candidates are found to be duplicates, and half of unique sequences fall in large clusters.

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DESCRIPTION OF THE BINDING SITE AND GSH CONJUGATION FEATURES OF THE NEW HUMAN GST P1-1 INHIBITORS

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Glutathione S-Transferases (GSTs) are enzymes involved in cellular detoxification by catalysing the nucleophilic attack of glutathione (GSH) on the electrophilic centre of numerous of toxic compounds and xenobiotics, including chemotherapeutic drugs. Human GST P1-1, which is known as the most prevalent isoform of the mammalian cytosolic GSTs, is overexpressed in many cancers and contributes to multidrug resistance by directly conjugating to chemotherapeutics. It is suggested that this resistance is related to high expression of hGST P1-1 in cancers, thereby contributing to resistance to chemotherapy [1, 2].

In the recent years, we reported the design and synthesis of some novel benzoxazoles, which are able to inhibit the hGST P1-1. Among the tested compounds, 2-(4-chlorobenzyl)-5-(4-nitrophenylsulfonamido)benzoxazole is found as the most active hGST P1-1 inhibitor compound, possessing 10.2 μM IC_{50} value and showing similar inhibitor potency with the reference agent ethacrynic acid [3].

In this present work, molecular docking studies performed by using CDocker method [4] in order to describe the binding site features of the tested benzoxazoles on the hGST P1-1 enzyme. As shown in Figure 1, the molecular docking study is revealed that the new synthesized benzoxazoles are acting as inhibitors of hGST P1-1 by binding to the H-site to perform conjugates with GSH.

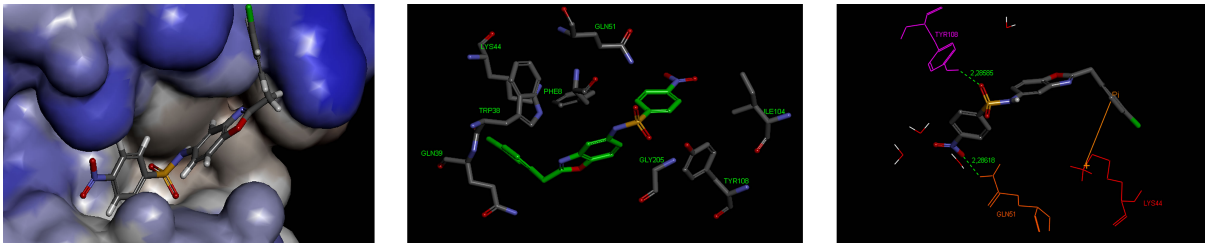

Figure 1. Superposition in the vicinity of the nonpolar H-site pocket, stereo images of the stacked position with the H-site residues and the binding site interactions of the new synthesized inhibitor in hGSTP1-1.

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PREDICTION OF METABOLITES BASED ON KNOWLEDGE AND POTENTIAL ENERGY SURFACE OF REACTIONS

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Metabolism is the set of life-sustaining chemical transformations within the cells of living organisms[1]. For a drug, it metabolizes only in cells of human. For a pesticide, it metabolizes not only in cells of living organisms, i.e. plants, animals, insects and etc., but also in the environment (outside of living organisms). Indeed, metabolism is combined by a set of chemical reactions whether it is drugs or pesticides. In a metabolism, there are many types of chemical reactions, such as deacetylation, dehydrohalogenation, dehalogenation, reduction, aliphatic hydroxylation, epoxidation, aromatic hydroxylation, O-Sulfation, N-Formylation, ring closure, rearrangement, ring contraction and etc. In general, there are several metabolites by the end of the metabolism of a drug or a pesticide. And, the metabolites have a close relationship with metabolic environment.

In traditional, metabolites are detected and identified by technology of analytical chemistry which cannot be employed in design stage of drug or pesticide. Herein, we will talk about “prediction of metabolites”. Two approaches will be used in prediction of metabolites: 1) proposition of metabolism paths based on reaction knowledge [2] and 2) validation of the paths by Potential Energy Surface (PES) [3] of reactions, which calculated by B3LYP (Becke, 3-parameter, Lee-Yang-Parr.) [4] / 6-31++G(d, p) [5], one of approaches in density functional theory (DFT). Prediction of metabolites of 2,4-Dichlorophenoxy acetic acid (2,4-D), CAS number: 94-75-7, a herbicide and plant growth regulator widely applied in agriculture, also will be presented.

ACKNOWLEDGMENTS

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SCREENING OF ACTIVE ENZYME INHIBITORS FROM CHINESE MEDICINES BY CAPILLARY ELECTROPHORETICALLY MEDIATED MICROANALYTICAL TECHNIQUE AND ONLINE MICRO-ENZYME REACTOR

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In this presentation we introduce some new approaches on the development of new methods for drug screening of active components from Chinese medicine in our research group [1-3]. We have sucessfully developed a capillary electrophoretically mediated microanalytical technique for screening aromatase inhibitors from Chinese medicines [2] and an neuraminidase-immobilized enzyme microreactor for screening of neuraminidase inhibitors for anti-avain influenza virus from Chinese medicines by capillary electrophoresis [3]. In addition, these novel methods can also be well used for studing the molecular interaction between drug and target enzyme and measuring the enzyme dynamic paramters such as Michaelis constant. Injection procedure of EMMA and electropherograms for screening the aromatase inhibitors are shown in Figure A and B.

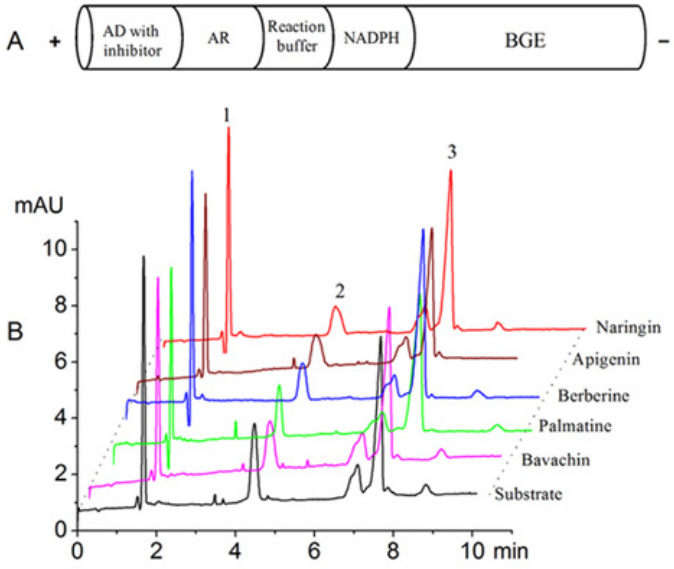

Figure 1: Injection procedure of EMMA (A) and Electropherograms for screening the aromatase inhibitors (B). Peak identifications: 1, AD; 2, NADP+ ; 3, NADPH.

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4-SUBSTITUTED QUINAZOLINE DERIVATIVES AS novel EphA2 RECEPTOR TYROSINE KINASE INHIBITORS

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Erythropoietin-producing hepatocellular receptor tyrosine kinase subtype A2 (EphA2) is an attractive therapeutic target for suppressing tumor progression. In our efforts to discover novel small molecules to inhibit EphA2, a class of compound based on 4-substituted quinazoline containing 7-(morpholin-2-ylmethoxy) group was identified as a novel hit by high throughput screening campaign. Structural modification of parent quinazoline scaffolds by introducing substituents on aniline displayed potent inhibitory activities toward EphA2.

STUDIES ON THE SYNTHESIS OF SOME NEW PIPERAZINYL FLAVONE COMPOUNDS AS ANTICANCER AGENT

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Flavonoids are a vast group of heterogeneous polyphenols with various health benefits. They are ubiquitously found in fruits, vegetables, tea, and wine (1-3). They have been shown to possess a variety of biological activities at nontoxic concentrations in organisms. Therefore, flavonoids are important components of the human diet. The role of dietary flavonoids in cancer prevention is widely discussed. Compelling data from laboratory studies, epidemiological investigations, and human clinical trials indicate that flavonoids have important effects on cancer chemoprevention and chemotherapy (3,4). Many mechanisms of action have been identified, including carcinogen inactivation, antiproliferation, cell cycle arrest, induction of apoptosis and differentiation, inhibition of angiogenesis, antioxidation and reversal of multidrug resistance or a combination of these mechanisms (2,5);

Due to their structural and therapeutic diversity, along with their commercial availability, piperazine derivatives have drawn considerable attention from organic and medicinal chemists. Piperazine molecular templates have been associated with a broad spectrum of biological activity such as antibacterial, antidepressant and antitumor (6). Additionally, it was reported that the existence of piperazine on moiety of the compounds are important for the antitumor activity (7).

In this study, as part of an ongoing research, in view of the anticancer property of the flavone pharmacophore, in order to increase the activity of flavones, a new series of benzyl / benzoyl substituted piperazine containing flavone derivatives have been synthesized. The synthesized compounds are going to be investigated for their anticancer activities by using cell cultures.

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GENOMICS AND TRANSCRIPTOMICS FOR PERSONALIZED BREAST CANCER TREATMENT

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Women who are carriers of mutations in the genes BRCA1 and BRCA2 have a high risk of developing breast cancer and ovarian cancer. Therefore, healthy women who have a family history of breast cancer or ovarian cancer should be tested for mutations in these genes to identify predisposition to these diseases. In case of detection of mutations in the BRCA1 or BRCA2 genes woman should be supervised [1].

Classical approaches in clinical practice allow us to estimate with a certain probability the risk of recurrence of breast cancer for physical characteristics, such as the size of the tumor, its histological grade, and the number of metastatic axillary lymph nodes. Using immunohistochemical methods allows to evaluate estrogen receptors ER and progesterone receptor PR genes expression levels. These data allow to conclude the desirability or undesirability of hormone therapy. Targeted therapy applied to patients whose tumor cells there is increased expression of the HER2 gene, encoding a member of the epidermal growth factor (EGF) receptor family of receptor tyrosine kinases. HER2-positive and HER2-negative breast cancer subtypes are distinguished using immunohistochemical techniques or hybridization in situ [2]. For targeted therapy trastuzumab use - preparation of monoclonal antibodies blocking the activity of the HER2 gene in breast tumor cells, slowing the growth of this tumor.Trastusumab (Herclone, Herceptin) is a monoclonal antibody that interferes with the HER2/neu receptor and blocks the activity of the HER2 gene in breast tumor cells, slowing the growth of this tumor.This drug is used for the targeted therapy of certain breast cancers. Usually it is used either in combination with chemotherapy, or as adjuvant therapy after surgical treatment of breast cancer.

New markers to define the breast cancer subtypes, stage and to predict the risk of recurrence and response to therapy were obtained by means of genomics, transcriptomics and systems biology. Changes in transcription levels of certain genes associated with a particular type of tumor indicate a "biological aggressiveness" of transformed cells and to assess their metastatic potential [3]. Currently known subtypes of breast cancer response to chemotherapy differ.

Thus, genomic information is of paramount importance for the diagnostics of disease and selection of treatment strategies. Personalized medicine is one of the basic concepts of health. The individual selection of medicines is made possible due to advances in molecular diagnostics.

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THE KINETICS OF FORMATION OF POLYNITROGENMOLECULAR COMPLEXES IN ALKALY MEDIA

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The ability of2,4,7-trinitrofluoren (I) and2,4,7-trinitrofluorenon (II) to form s-complexes with solvent molecules (ethanol, acetone, acetonitrile, DMF) in alkaline medium were studied. Formation of s-complexes (complexes Yanovsky-Meyzengeymer) fixed by the appearance of the electronic absorption spectra of the TNF and TNFon new absorption bands in the 24000 - 2000 cm^{-1}, and by PMR spectra.

A spectrophotometric study of the interaction of the compounds I and II with solvents under various conditions were carried out. Varied : a) metal cations (s-, p-, d-) in the same solvent; b) in various solvents ; c) the presence or absence of ammonium hydroxide ; g) temperature . According these investigation the experimental curves were constructed, the reaction order and activation energy of s- complexes were calculated. For the calculation of the reaction order was used acetone as solvent, and ratio TNF : NaOH 1: 0.5 ; 1: 1; 1:2 ; 1 and 4 were taken .

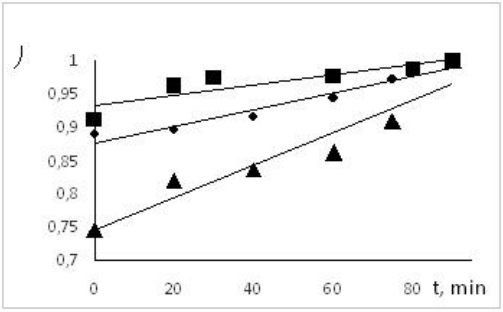

Fig.1 Time dependence (t, min.) At various ratios TNF: NaOH: 1 - 1:0.5 ; 2-1:2 ; 3-1:4

According to calculations, the dependence (where A – absorbance) of the solution time for all experiments are linear (Fig. 1). formation of s- complex is a reaction pseudo-first order for all the ratio of components (for example, a large excess of alkali). The dependence of the degree of conversion a of time for a ratio of 1:2 ; and 1:4 is almost identical and can be described by equation $(0{,}012 \pm 0{,}002)t \pm 0{,}02 =$.

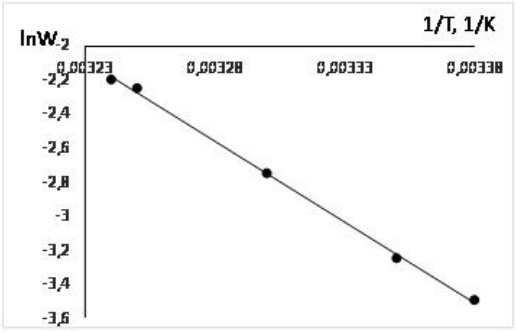

Fig. 2The dependence of logarithm of the rate constant (lnWi) of the inverse temperature(1/ T).

Changing the intensity of the absorption bands in the electronic spectra recorded at various temperatures, giving calculated activation energy of this reaction which is 30±5kJ/ mol. Thus, it can be argued that the reaction occurs only joining one nucleophilic group of the solvent and the limiting stage of this reaction lies in the diffusion area.

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HOW THE METHODOLOGY OF 3D STRUCTURE PREPARATION INFLUENCES THE QUALITY OF pKa PREDICTION?

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The acid dissociation constant pK_a is an important molecular property and its values are of interest in chemical, biological, environmental and pharmaceutical research. Therefore, there is a strong interest in the development of reliable and fast methods for pK_a prediction. A very successful approach for pK_a prediction is the usage of QSPR (Quantitative Structure Property Relationship) models [1]. These QSPR models can employ various descriptors, which are mainly based on molecular 3D structure (i.e., 3D descriptors). A very important question is, how the methodology of 3D structure preparation influences the quality of QSPR models. Can we use any source of 3D structure? Or only some methodologies for 3D structure preparation provide acceptable QSPR models? And is an optimization of 3D structures necessary?

In our work, we would like to answer these questions. For our study, we selected QSPR models based on atomic charges, because charge descriptors are frequently used for pK_a prediction and provide very accurate results [2, 3, 4]. Specifically, we focus on two types of atomic charges – quantum mechanical (QM) charges and empirical charges. QM are calculated using four different QM charge calculation approaches and empirical charges using EEM (Electronegativity Equalization Method) [5, 6] parameterized for the same approaches. We analyzed 3D structures generated by seven tools (Balloon, CORINA, Frog, Omega, Open Babel and RDKit) and optimized using three approaches (no optimization, MMFF94 optimization and B3LYP/6-31G* optimization). The study was performed on three groups of molecules – phenols, anilines and carboxylic acids. We created, parameterized and evaluated more than 450 QSPR models.

We found, a source of 3D structure is very important for accuracy of QSPR models. For appropriate 3D structure generators, the pK_a prediction is accurate and optimization is not necessary. Even when we have weaker 3D structures, the pK_a prediction can provide acceptable results. In a case of low quality 3D structures, the pK_a prediction is not precise and an optimization is necessary.

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