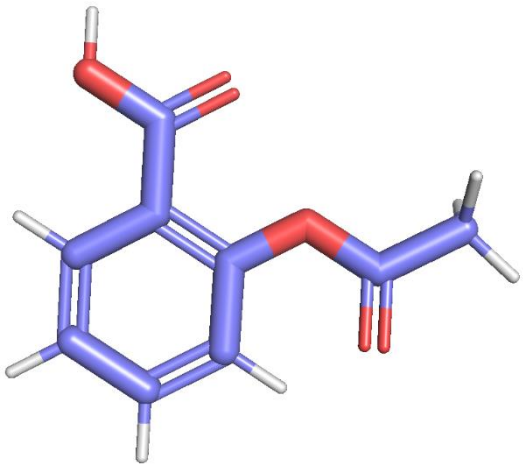
KATEDRA FYZIKÁLNÍ CHEMIE
UNIVERZITY PALACKÉHO V OLOMOUCI

6th Advanced in Silico Drug Design workshop/challenge 2023

Olomouc

30st January – 3rd February 2023



Book of Abstracts

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INSTITUTE OF MOLECULAR AND TRANSLATIONAL MEDICINE

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6th Advanced in Silico Drug Design workshop/challenge 2023 (6ADD) is focused on usage of several *in silico* tools and approaches in drug design. We will cover both structure-based drug design (molecular docking, molecular dynamics, structural bioinformatics tools) and ligand-based drug design (QSAR, pharmacophores, deep learning) with lectures and hands-on tutorials. Last day you can try your skills on the ligand selection challenge.

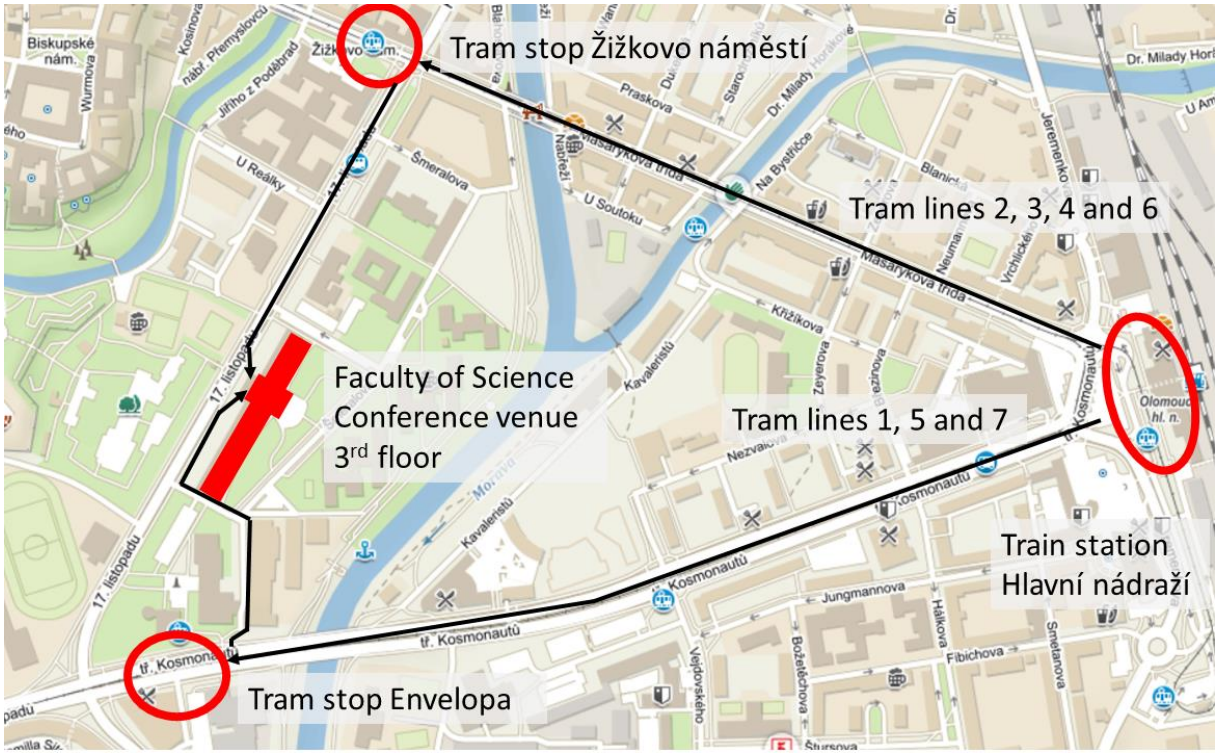
See you in Olomouc!

Karel Berka and Pavlo Polishchuk

Local Organizers and Invited Lecturers

doc. Karel Berka	prof. Thierry Langer (UniVie)
dr. Pavlo Polishchuk	assoc. prof. Johannes Kirchmair (UniVie)
Alina Kutlushina	dr. Melissa F. Adasme (EMBL-EBI)
Aleksandra Ivanova	dr. James Blackshaw (EMBL-EBI)
dr. Václav Bazgier	dr. Wim Dehaen (UCT)
Kateřina Storchmannová	dr. Maria Matveieva (UCT)
Dominik Martinát	dr. Olena Mokshyna (IOCB)
Anna Špačková	dr. Semen Yesylevskyy (IOCB)

Venue



Faculty of Science, Palacky University Olomouc, Czech Republic
tř. 17. listopadu 12, Olomouc
GPS: 49.5924922,17.2632337
3rd floor PC room 3.002

Faculty building in Google Street View

List of On Site Participants

1. Anita Ament – Palacky University Olomouc, CZ
2. Jan Beránek – University of Chemistry and Technology, Prague, CZ
3. Krishnendu Bera – Masaryk University Brno, CZ
4. Valerio Brando – Università degli studi di Napoli Federico II, IT
5. Adam Bubík – Masaryk University Brno, CZ
6. Lucia Iľkovičová – Masaryk University Brno, CZ
7. Indu – Institute of Biophysics, Masaryk University, Brno, CZ
8. Tomas Jelinek – Czech Technical University, Prague, CZ
9. Jakub Juračka – Palacky University Olomouc, CZ
10. Nina Kadášová – Palacky University Olomouc, CZ
11. Leonid Kikot – Selvita S.A., PL
12. Mikuláš Klenor – Institute of Organic Chemistry and Biochemistry, Prague, CAS, CZ
13. Artem Kokorin – University of Luxembourg, LU
14. David Kopečný – Palacky University Olomouc, CZ
15. Katarzyna M. Krupka – University of Wroclaw, PL
16. Natalia Kulik – Institute of Microbiology, CAS, CZ
17. Laura Landolfi – Università degli studi di Napoli Federico II, IT
18. Martin Lepšík – Institute of Organic Chemistry and Biochemistry, Prague, CAS, CZ
19. Jan Macháň – Palacky University Olomouc, CZ
20. Simona Martikánová – Palacky University Olomouc, CZ
21. Dominik Martinát – Palacky University Olomouc, CZ
22. Miriama Mateášová – Masaryk University Brno, CZ
23. Guzel Minibaeva – Palacky University Olomouc, CZ
24. Dominik Prager – Palacky University Olomouc, CZ
25. Bensadok Raoula – University Of Science And Technology Houari Boumediene, DZ
26. Hanna Severina – National University of Pharmacy, Kharkiv, UA
27. Jan Stehlík – Palacky University Olomouc, CZ
28. Katerina Storchmannova – Palacky University Olomouc, CZ
29. Anna Špačková – Palacky University Olomouc, CZ
30. Guglielmo Tedeschi – University of Chemistry and Technology, Prague, CZ
31. Vojtěch Vařečka – Masaryk University Brno, CZ
32. Náth Vozábal – Masaryk University Brno, CZ

Poster Abstracts

Protein-Ligand Scoring Conundrum Solved for Diverse Crystallographic Complexes

Adam Pecina, Jindřich Fanfrlík, **Martin Lepšík**, Pavel Hobza, Jan Řezáč

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Computer-aided drug design aims to streamline the costly and time-demanding drug discovery process. Accurate prediction of protein-ligand binding affinities (scoring) is the cornerstone of several steps, from native pose prediction, via hit finding, to lead optimization. A standard approach is to use ultrafast scoring functions (seconds) which, however, lack accuracy and reliability. The state-of-the-art molecular dynamics-based free-energy methods yield better predictions but still rely on the variable accuracy of molecular mechanics force fields and are much slower (days). The recent outbreak of the use of machine-learning potentials in scoring function development is hampered by the lack of high-quality training datasets. Here, we demonstrate our solution of the protein-ligand scoring conundrum using our universal, fast and accurate quantum mechanics-based scoring function dubbed SQM2.20. To be able to develop it, we compiled a unique benchmark dataset comprising consistent high-quality experimental data (crystal structures and affinities) of 10 diverse protein targets and hundreds of their respective ligands and we offer this dataset to the general public. The SQM2.20 attained average accuracy comparable to the state-of-the-art methods but much faster (minutes) and with consistency across all the targets. As a physics-based approach, SQM2.20 can handle any systems for which a structure is available, including diverse ligand chemistries and, unlike more empirical approaches and machine learning methods, does not depend on any system-specific data or prior knowledge. Our scoring function can be readily integrated into computer-aided drug design workflows used in the pharmaceutical industry.

MolMeDB - database of interactions of small molecules with membranes

Jakub Juračka, **Kateřina Storchmannová, Dominik Martinát, Václav Bazgier, Karel Berka**

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Biological membranes are natural barriers of cells. The membranes play a key role in cell life and also in the pharmacokinetics of drug-like small molecules. There are several ways how a small molecule can get through the membranes. Passive diffusion, active or passive transport via membrane transporters are the most relevant ways how the small molecules can get through the membranes. There is an available huge amount of data about interactions among the small molecules and the membranes also about interaction among the small molecules and the transporters. MolMeDB (https://molmedb.upol.cz) is a comprehensive and interactive database. In the past, we have collected interactions of small molecules with the membranes such as partitioning, penetration, and free energy profiles of the small molecules, especially drugs crossing the membranes. Recently, we have expanded our area of interest about the interactions of small molecules with transporters. Nowadays, data is available from 52 various methods for 40 biological or artificial membranes and for 184 transporters in MolMeDB. The data within the MolMeDB is collected from scientific papers, our in-house calculations (COSMOmic and PerMM) and obtained by data mining from several databases. Data in the MolMeDB are fully searchable and browsable by means of name, SMILES, membrane, method, transporter or dataset and we offer collected data openly for further reuse.

In silico tuning of API for liposomal drug delivery

Kateřina Storchmannová[1], Martin Balouch[2], František Štěpánek[2], **Karel Berka**[1]

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2. Dep. of Chemical Engineering, University of Chemistry and Technology, Prague, Czech Republic

Liposomes are intensively studied as carriers of various types of active pharmaceutical ingredients (APIs). Unfortunately, some APIs are not appropriate for formulation in the liposome because of their physicochemical properties, particularly permeability and partitioning. This problem has three solutions: (I) a change of liposome, (II) the addition of a permeability enhancer, and (III) a small modification of the structure of API.

We decided to go the third way. The MolMeDB [1] (https://molmedb.upol.cz) is a comprehensive and interactive database about interactions of (small) molecules with membranes, including permeability data. Because of the non-existence of a large amount of data about the behaviour of APIs in the liposomes, we analyzed data in the MolMeDB database.

Based on the data analysis from the MolMeDB database and by using the Liposome Biochemical Classification System (LBCS) [2], we tried to determine the influence of functional groups on the permeability and partitioning of small molecules and the possibility of controlling the usability of the molecules for liposomal formulation.

References

[1] Juracka J, et al. Database, baz078 (2019).

[2] Balouch M. et al. MSDE, 6 (5), 368-380 (2021).

Pharmacophore Modelling of SARS-CoV-2 Mpro and Human CDK2 active site

Mikuláš Klenor, Martin Lepšík

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SARS-CoV-2 causing the Covid-19 disease remains a global threat for the human health. Due to a frequent appearance of new variants of the virus, there is a strong need for a wide variety of potent antiviral drugs. One of the most prominent SARS-CoV-2 drug targets is the main protease (Mpro). Tens of its active site as well as allosteric inhibitors have been synthesized and crystallized in complex with the enzyme. We leverage this ample structural information to build pharmacophore models to aid in database screening.

To further validate the methodology, we used pharmacophore modelling to describe the interaction patterns of a series of inhibitors of Cyclin-Dependent Kinase 2 (CDK2) based on a recent X-ray crystal structure of an enzyme-inhibitor complex [1]. CDK2 is an important drug target for cell cycle disorder and thus this work aims to contribute to the development of new anti-cancer medicines.

Taken together, the pharmacophore modelling in both of these projects serves as a filtering step before molecular docking of large compound libraries within high-throughput screening will take place.

References:

1. Jansa J, Jorda R, Škerlová J, Pachl P, Peřina M, Řezníčková E, Heger T, Gucký T, Řezáčová P, Lyčka A, Kryštof V. Imidazo[1,2-c]pyrimidin-5(6H)-one inhibitors of CDK2: Synthesis, kinase inhibition and co-crystal structure. Eur J Med Chem. 2021, 216, 113309.

MOLEonline & ChannelsDB

Anna Špačková[1], **Karel Berka**[1], **Václav Bazgier**[1], Lukáš Pravda[2], David Sehnal[2], Radka Svobodová[2]

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Proteins play a significant role in organisms, especially their structure which is determined by the amino acids sequence. On the surface of protein molecule are active sites, that can react only with some molecules, there are also buried active sites connected with outer space by tunnels. This structure can affect which molecule can react with protein buried active site on the principle of enzyme substrate. Selection of molecules that can pass through tunnel is based on physicochemical properties and size of tunnels as well as molecules. Knowledge of which molecules can pass through and react with buried active site is important in drug design. Available online tool MOLEonline (https://mole.upol.cz/) can detect and visualize channels in uploaded protein structure. MOLEonline together with database ChannelsDB (https://channelsdb.ncbr.muni.cz/), where protein channels information is stored, is important in discovery of potential drugs. As our research says, the amount of searches in MOLEonline as well as in ChannelsDB has been increasing every single year, which is the reason why it is important to keep improving the tools for the users. We did research of molecules stored in ChannelsDB database together with their physical-chemical properties and shape. Prediction of uploaded tunnel name based on ChannelsDB statistical data has been done. Fitting molecules, that can pass through the selected tunnel based on their molecular shape have been predicted. We also add tunnels which were been calculated by Caver (https://www.caver.cz/) to ChannelsDB database. This progress can help determine the molecules suitable for potential drugs and thus for the further research.

Computational modeling of glycomimetics-inhibitors of neurodegenerative diseases

Natalia Kulik[1], Patrick Weber[2], Zuzana Mészáros[1,3], Pavla Bojarová[1], Kristýna Slámová[1], Arnold E. Stütz[2], Vladimír Křen[1]

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2. Graz University of Technology, Austria
3. University of Chemistry and Technology, Czech Republic

Neurodegenerative diseases include hundreds of different disorders, of which Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) are the best known and best studied. All of these diseases are associated with progressive brain damage and neurodegeneration, followed by loss of cognitive abilities such as memory and decision making.

Alzheimer's disease is characterized by the appearance of tiny protein aggregations called 'plaques' and 'tangles'' that damage different parts of the brain, leading to apoptosis of neurons and loss of connections. To date, there is no known treatment for AD, and all therapeutic methods focus on slowing the progression of the disease. Neurofibrillary tangles (NFTs) are formed by hyperphosphorylated tau protein, causing tau to detach from microtubules and form insoluble inclusions. O-GlcNAcylation of the protein competes with its phosphorylation sites, and selective inhibition of human O-β-D-N-acetylglucosaminidase (hOGA) would increase O-GlcNAc-modified tau, leading to a reduction in tau aggregates.

The aminocyclopentane mimetics with potential hOGA inhibitory activity were synthesized and experimentally tested. The observed binding poses were structurally investigated using computational methods. The crystal structure of hOGA was completed by loop modeling with Yasara and used for docking. MD simulation allowed selection from the alternative docking poses. Computational methods were used to model the binding poses of potential hOGA inhibitors and to explain the observed differences in inhibitory activity. A combination of docking results and experimental data could lead to the construction of an effective pharmacophore model.

Acknowledgement:

We kindly acknowledge support from the bilateral Czech-Austrian project co-funded by the Czech Science Foundation (No. GA21-01948L) and the Austrian Science Fund (No. I5236).

Hydrogen Bonding in Focus: salen analogues case study

Katarzyna M. Krupka, Michał Pocheć, Jarosław J. Panek, Aneta Jezierska

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Schiff bases [1] find a number of applications in modern biochemistry, medicine and drug design, due to their extensive antifungal, antiviral, anticancer and antibacterial activity. Moreover, salen analogues [2] act as excellent ligands for the p-, d- and f-block metal ions. Their coordination compounds with d-block metals are being used as biosensors and also play a key role in advanced drug delivery systems in cancer therapy. The most significant molecular interactions responsible for the structure and properties of Schiff bases are intramolecular hydrogen bonds, which can be modulated by substitution. This modulation can have different aspects of practical impact – from molecule properties modifications to additional functionalities or reaction paths.

A unified description of the substituent effect on the intramolecular hydrogen bridge was developed on the basis of over 500 tri-ring salen analogues with different substitution patterns. The sheer scale of this project allowed for the insight into the effects contributing to the proton transfer phenomenon. Both proximal and distal effects were investigated using Density Functional Theory (DFT). [3,4] The generalized composite substituent effect was divided into the increments describing the different interactions of the hydrogen bridge and the substituent.

Acknowledgements

The Authors thank the Wrocław Centre for Networking and Supercomputing (WCSS) and Poznań Supercomputing and Networking Center (PSNC) for generous CPU time resources and use of file storage facilities.

References:

[1] Schiff, H. Ann. Chem. Pharm. 140 (1866) 92-137.
[2] Pfeiffer, P.; Breith, E.; Lübbe, E.; Tsumaki, T. Liebigs Ann. 503 (1933) 84–130.
[3] Hohenberg, P.; Kohn, W. Phys. Rev. 136 (1964) B864-B871.
[4] Kohn, W.; Sham, L.J. Phys. Rev. 1965, 140 (1965) A1133-A1138.

Simulation of oligosaccharide binding to HEV32 domain

Jan Beránek, Vojtěch Spiwok

University of Chemistry and Technology, Prague

HEV32 is a 32-residue domain of a protein hevein, known for its ability to form complexes with chitin-based polysaccharides. It is a suitable model system for studying protein-saccharide interactions. We studied interaction of HEV32 domain with mono-, di- and trisaccharide derived from chitin using well-tempered funnel metadynamics. For each saccharide, four different combinations of collective variables were used. There were always two collective variables per a system, the first one describing the distance between the saccharide and the binding site, and the second one describing conformational changes in the HEV32 domain. For all systems, 2 μs long simulations were carried out and the free energy surface was obtained. Because of slow convergence in the cases of some combinations of the CVs, the affected simulations were prolonged to 3 μs. Standard binding free energy of all saccharide molecules to HEV32 were predicted from the free energy surfaces. For systems with trisaccharides, we observed in two cases that binding energies were in agreement with the experimentally determined value ≈ −22 kJ/mol [1]. In the other cases, the predicted binding energy was different, and this difference is discussed. Conformational changes taking place in HEV32 during binding of the saccharides was also characterized.

References:

[1] N. Aboitiz, M. Vila-Perelló, P. Groves, J. Asensio, D. Andreu, F. Cañada, J. Jiménez-Barbero, ChemBioChem, 5, 1245-1255 (2004)

Assisting isoform–selective ligand design with molecular docking

Vojtěch Vařečka

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Human carbonic anhydrase IX (CA IX) is a zinc-coordinating metalloenzyme that catalyses reversible hydration of carbon dioxide to bicarbonate and proton. Unlike other CA isoforms, which are indispensable for cellular and tissue homeostasis, CA IX features predominantly in cancer. It has been directly connected with tumor survival, metastasis and overall poor patient prognosis. Combined with physiological presence limited to gallbladder, duodenum and small intestine, CA IX represents an enticing drug target. While a vast array of carbonic anhydrase inhibitors is commercially available, selective inhibition of individual isoforms remains challenging due to conservation of catalytic domain across the isoforms. Here, an attempt is made to create a protocol that combines rational design and molecular docking to provide quick, general insight into potentially selective ligands.

Interaction of selected drugs at dimer interface of human 14-3-3ζ protein

Krishnendu Bera[1, 2, 3] and Jozef Hritz[2, 3]

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3. NCBR, Masaryk University, Kamenice 5, 62500 Brno, Czech Republic

The 14-3-3 proteins bind with thousands of binding partners and they are considered as promising drug targets in cancer and neuropsychiatry (1). It is family of adaptor proteins and there is no defined binding site for small organic molecules. 14-3-3 proteins function depends on their oligomeric form which may alter between the monomeric, homodimeric and heterodimeric states (2). In this project we have considered small FDA approved drugs (molecular weight ≤ 2000) and docked at the dimer interface of 14-3-3ζ dimer protein using autodock vina in triplicate. 18 consistent drugs selected based on cut-off ≤ -9 kcal/mol. Further, 10 ns all-atom molecular dynamics (MD) simulations have been performed for each of the 18 protein drug complexes and compare with apo form of the protein. The MM/GBSA (3) based binding energy have be calculated from MD simulations of protein-drug complexes using 1000 snapshots. Based on binding energy four drugs selected for further analysis such as hydrogen bond, RMSD, RMSF, Rg etc.The computational predictions will be validated experimentally by NMR, ITC and fluorescence titration experiments.

Keywords:

14-3-3, Molecular docking, MD simulation, MM/GBSA

Acknowledgement:
KB and JH acknowledges funding from grant agency Masaryk University, Grant numbers: MUNI/G/1002/2021 and Czech Science Foundation [GF20-05789 L]. The computational resources were supplied by (Metacentrum and IT4Innovations National Supercomputing Centre (open-17-7)) the project “e-Infrastruktura CZ” (e-INFRA LM2018140 and ID:90140) provided within the program Projects of Large Research, Development and Innovations Infrastructures. KB is also supported by Brno PhD Talent Scholarship – funded by the Brno City Municipality, Brno, Czech Republic.

References:

1. Waløen, K et al. (2021) Mol Pharmacol. 100:155–169.
2. Trošanová, Z. et al. (2022) Journal of Molecular Biology. 434:167479.
3. Valdés-Tresanco, M.S. et al. J. Chem. Theory Comput. 17:6281–6291.

Designing of Insecticides Against *Bemisia tabaci* targeting ecdysone receptor

Indu[1,2], Jozef Hritz[3,6], Vaclav Brazda[1,4], Rajesh Kumar[5], **Krishnendu Bera**[3,6]

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6 CEITEC Masaryk University, Brno, Czech Republic

Bemisia tabaci is a major destructive pest that destroys more than 600 crop species worldwide. It is also responsible for transferring more than 100 viruses in plants which interferes with plant growth by becoming a limiting growth factor. This project aims to find novel lead molecules using computational approaches. The ecdysone receptor of B tabaci is involved in metamorphosis, cell differentiation and reproduction processes. No similar protein is present in mammals which makes it an ideal target. The unavailability of a full-length structure in PDB lead us to model the full-length protein using Alphafold 2.2.0 1. The disordered regions of the protein were predicted by using IDP predictor software, i.e. DEPICTER 2. Further, 32,552 bacterial and fungal secondary metabolites were retrieved from the npatlas 2.0 database 3 and docked each metabolite with the simulation obtained last conformation of EcR protein using idock 2.2.3 software 4. I have chosen a cut-off -10 kcal/mol binding energy and found 14 metabolites. I have redock these 14 metabolites again with Autodock vina 1.1.2 5 to validate idock 2.2.3 results and found an almost similar result with minor deviations. These dockings were compared with 20E, a natural hormone binding with EcR protein. Lastly, one compound K6323 with the most suitable scoring function were selected for 30 ns MD simulations of the protein complex with E20 and K6323 and compared with apo form of the protein. Further, QMMM/GBSA-based binding energy was calculated from 100 snapshots from MD simulation. The binding energy of K6323 was found to be better than the natural inhibitor 20E. These computational predictions can be analysed further experimentally.

References:

1. Berendsen, H. J. C., van der Spoel, D., & van Drunen, R. (1995). Computer Physics Communications,
2. Carmichael, J. A., et al. (2005). J. of Biological Chem., 280(23), 22258–22269.
3. Barro D. et al. (2011). Annual Review of Entomology, 56(1), 1–19.

Enzymatically-dead Nicotinamide Phosphoribosyltransferase

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University of Chemistry and Technology, Prague, CZ

Nicotinamide phosphoribosyltransferase (NAMPT) catalyzes reaction between nicotinamide (NM) and 5-phosphoribosyl-1-pyrophosphate (PRPP) in the mammalian NAD salvage pathway. In cancer cells, NAMPT is important for its participation in the synthesis of NAD, subsequently cancer cells use NAD primarily to produce energy through glycolysis. For this reason, inhibitors of NAMPT could by use as a drugs in cancer treatment. Both NAMPT-monomers host a specular Catalytic Site (CS) able to perform on reaction, but there is the lack information about specific mechanism of action. It is possible two reaction mechanism, nucleophillic substitution SN1 or SN2. Our goal was to find out which substitution of amino acids involved in CS, could lead to an enzymatically-dead NAMPT. We focused on four of them: D219, H247, R311, D313. We are going to show how each of those substitution affect NAMPT activity. Taking into account experimental results, we will perform validation-confirmation-refutation of our data analyzing and visually investigating in silico computational tools as docking tools. Advances in computational approaches allow us to predict the best binding pose, scored by binding free energy (Kcal/mol) of ligands (NM and PRPP) on our target (NAMPT-CS). Docking results demonstrate how binding of ligands is influenced by substitutions representing a probable view of the process going on. To confirm in silico results, we transfected cells with plasmids carring gene Nampt with one of mutation. By measuring cellular NAD amounts, we determined that NAMPT-A219 had dubled amounts of NAD, NAMPT-A247 had a 1.5-folds higher amount and unchanged NAMPT-A311,A313; NAMPT-A219,A311,A313 in compare with non-transfected control. We may also observe in docking results how D219 seems to ensure NM selectivity, H247 seems not to be directly involved in reaction, otherwise seems to be a key to define SN1 or SN2, and R311, D313 are primary interested in correct PRPP binding pose.

Accommodation, Restaurants and Sights

workshop dinner venue

Notes

Program

Monday, January 30

11:30am	**DAK**	Registration
12:30pm	**Karel Berka**	Drug design intro
1:30pm	**Adasme, Blackshaw**	ChEMBL (Zoom)
2:45pm		Coffee
3:15pm	**Karel Berka**	Structural bioinformatics tools 4 DD
4:00pm	**Karel Berka**	Alphafoldology
5:00pm	**DAK**	Posters

Tuesday, January 31

9:00am	**Wim Dehaen**	Molecular similarity and optimization
9:45am	**Olena Mokshyna**	Fantastic natural products and where to find them
10:30am		Coffee
11:00am	**Johannes Kirchmair**	Metabolism prediction
12:00pm		Lunchtime
1:00pm	**Thierry Langer**	Pharmacophores
2:00pm	**DAK**	Photo
2:15pm		Coffee
2:30pm	**Thierry Langer**	Tutorial Pharmacophores
5:30pm	**Karel Berka**	Tour through Olomouc
6:30pm		Workshop dinner

Wednesday, February 1

9:00am	**Mariia Matveieva**	QSAR modelling
9:45am	**Pavel Polishchuk**	Multi-instance learning
10:30am		Coffee
11:00am	**Pavel Polishchuk**	De novo design
12:00pm		Lunchtime
1:00pm	**Alina Kutlushina**	QSAR tutorial
3:15pm		Coffee
3:30pm	**Pavel Polishchuk**	De novo tutorial
5:00pm	**DAK**	Posters

Thursday, February 2

9:00am	**Karel Berka**	Molecular Docking
9:45am	**Karel Berka**	Molecular Dynamics basics
10:30am		Coffee
11:00am	**Semen Yesylevskyy**	Is the lipid membrane druggable? Insights from MD
12:00pm		Lunchtime
1:00pm	**Karel Berka**	Docking tutorial
2:45pm		Coffee
3:00pm	**Aleksandra Ivanova**	High-throughput MD tutorial
5:30pm		Excursion to IMTM

Friday, February 3

9:00am	**Pavel Polishchuk**	Challenge