IBMC
Institute of Biomedical Chemistry

XXXI Symposium on Bioinformatics and Computer-Aided Drug Discovery

PROCEEDINGS BOOK

Institute of Biomedical Chemistry

Moscow, Russia (Virtual), October 20-22 2025

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Russian Academy of Sciences
Ministry of Science and Higher Education of Russian Federation
Institute of Biomedical Chemistry
Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry
of the Russian Academy of Sciences

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PROCEEDINGS BOOK OF THE XXXI
SYMPOSIUM “BIOINFORMATICS AND
COMPUTER-AIDED DRUG DISCOVERY” –
Moscow: Institute of Biomedical Chemistry, 2025

The materials of the XXXI International Symposium “Bioinformatics and Computer-Aided Drug Discovery” (Virtual, October 20–22, 2025) are presented. The Symposium is dedicated to addressing the emerging challenges and opportunities in *in silico* drug discovery. It covers contemporary areas of biomedical science focused on analyzing normal and pathological states of the organism and elucidating pathological processes at the cellular and molecular levels.

The main topics include the development and practical application of computational methods for identifying and validating new pharmacological targets, in silico design of potent and safe pharmaceutical agents, optimization of the structure and properties of drug-like compounds, and rational approaches to the use of pharmacotherapeutic agents in medical practice.

This information will be valuable to researchers developing computational methods and applying them to drug research and development using bioinformatics and chemoinformatics approaches based on post-genomic technologies. It may also be of interest to undergraduate, graduate, and postgraduate students specializing in related fields.

Responsible editors: Member of Rus. Acad. Sci. V.V. Poroikov, Prof. R.G. Efremov

Dear Colleagues,

On behalf of the Organizing Committee and the Administration of the Institute of Biomedical Chemistry, it is my great pleasure to welcome you to the XXXI Symposium on Bioinformatics and Computer-Aided Drug Discovery (BCADD-2025).

The Symposium was first initiated in 1995 by my teacher, Alexander Archakov, Member of the Russian Academy of Sciences (Member of the RAS), as part of the "Man and Drugs" Congress. Since then, it has been held annually under the leadership of Vladimir Poroikov (Member of the RAS), a leading Russian scientist in digital pharmacology and computer-aided drug discovery. The event has been co-organized by Nikolay Zefirov (Member of the RAS), and since 2018 jointly with Professor Roman Efremov.

BCADD 2025 highlights the enduring importance and dynamic progress of biomedical science in the discovering of new medicines. The analysis of large-scale biomedical data, advances in artificial intelligence and machine learning, and the development of modern bio and chemoinformatics methods are creating essential prerequisites for a deeper understanding of pathological processes and the identification of promising biomarkers and pharmacological targets. The widespread adoption of in silico approaches not only saves time and resources in the search for safer, more effective drugs but also provides a solid foundation for integrating and generating knowledge in this multidisciplinary field.

Last year, the XXX Symposium brought together more than 400 participants. We were honored to host 44 speakers from 17 countries, including Armenia, Australia, Brazil, Germany, India, Israel, Sweden, and the United States. Nearly forty young researchers took part in the Young Scientists' Contest, with the best presentations receiving special diplomas.

This year, we have over 400 researchers registered from 50 countries. To foster better communication and overcome time zone challenges, the Organizing Committee has introduced an extended online E Poster Session, which will run for 22 days instead of the traditional 2–3 hours. This format offers greater flexibility for our international participants.

The Symposium provides a valuable platform for researchers from around the world to exchange innovative ideas, discuss key challenges in bioinformatics, chemoinformatics, medicinal chemistry, and pharmacology, and establish new collaborations for future projects.

By upholding and advancing the traditions of this Symposium, we are building a better scientific future together. I would like to sincerely thank all participants and wish you inspiring lectures, fruitful discussions, and new partnerships that will lead to mutually beneficial collaborations.

Director of the Institute of Biomedical Chemistry,
Corresponding Member of the Russian Academy of Sciences

Elena Ponomarenko

Dear Colleagues!

We are pleased to welcome you as participants of the XXXI Symposium "Bioinformatics and Computer-Aided Drug Discovery" (BCADD-2025).

Our Symposia are dedicated to the emerging challenges and opportunities in drug development using modern in silico technologies. This series of annual Symposia started in 1995 in the framework of the Second Russian National Congress "Man and Drugs". Originally, it was initiated by the Academician Alexander Archakov and co-chaired by Professor Vladimir Poroikov. An essential contribution to the organization of the first Symposia was made by Professor Alexis Ivanov. In 1996-2017 the Symposia were co-chaired by the Academician Nikolay Zefirov and Professor Vladimir Poroikov. Significant impact on the next Symposia have been provided by Professor Oleg Raevsky, who has initiated the organization of the Russian Section of the International QSAR Society.

Since 2018, the mutual efforts to organize and perform the Symposia are applied by Professors Vladimir Poroikov and Roman Efremov.

Many world-wide famous researchers presented their lectures at the past symposia including Per Artursson (Uppsala University, Sweden), Igor Baskin (Lomonosov Moscow State University, Russia), Artem Cherkasov (University of British Columbia, Canada), Alexey Egorov (Lomonosov Moscow State University, Russia), Frank Eisenhaber (A*STAR Bioinformatics Institute, Singapore), Alexey Finkelstein (Institute of Protein Research, Russia), Viktor Finn (VINITI, Russia), Alexander Gabibov (Institute of Bioorganic Chemistry, Russia), Mikhail Gelfand (Institute for Information Transmission Problems, Russia), Jerome Golebiowski (CNRS GDR "Odorant Odor Olfaction", France), Viktor Kuzmin (Bogatsky Physico-Chemical Institute, Ukraine), José Medina-Franco (National Autonomous University of Mexico, Mexico), Alexander Nemukhin (Lomonosov Moscow State University, Russia), Kyoung Tai No (Yonsei Univeristy, Republic of Korea), Oleg Raevsky (Institute of Physiologically Active Compounds, Russia), Narahari G. Sastry (CSIR-North East Institute of Science and Technology, India), Hanoch Senderowitz (Bar-Ilan University, Israel), Alexander Sobolevsky (Columbia University, New York, USA), Oliver Steck and Andreas Vitte (Tripos, Germany), Igor Tetko (Institute of Structural Biology, Helmholtz Zentrum München, Germany), Vladimir Tumanyan (Institute of Molecular Biology, Russia), Alexandre Varnek (University of Strasbourg, France), Gennady Verkhivker (Chapman University, Irvine, USA), Erik Weber (Environmental Protection Agency, USA), Robert Woods (University of Georgia, Athens, USA), and others.

At the upcoming, XXXI Symposium, plenary/keynote lectures and oral talks will be presented by the experienced as well as younger scientists from many countries including Argentina, Bangladesh, Brazil, Chile, Costa Rica, Germany, Greece, France, India, Indonesia, Israel, Italy, Mexico, Nigeria, Russia, Serbia, Sweden, United Kingdom and United States. Their lectures cover the wide topics dedicated to the development and application of in silico methods for drug discovery & development.

It is necessary to emphasize that the traditional Young Scientists Contest (YSC) aroused great interest: 51 abstracts by undergraduates and graduates, as well as researchers without scientific degrees under the age of 30 were submitted for participation in the competition. The YSC abstracts were evaluated by seventeen Members of the International Scientific Committee (ISC) including distinguished scientists from Brazil, China, Germany, Greece, India, Israel, Mexico, Russia. Based on the voting of the ISC members and taking into account the geographical diversity of the participants, 17 abstracts have been selected for flash presentations. The best presentations will be awarded by the Diploma of the First, Second and Third Degrees.

To extend the communication between the participants, the Organizing Committee arranged a distributed in time E-Poster Session that is going during not traditional two-three hours but for 22 days, which helps to overcome the limitations of stirring life of the most people working in science and the time difference for the participants from different continents. The best posters will be awarded by special Diploma.

The Symposia on Bioinformatics and Computer-Aided Drug Discovery are arranged by scientists for scientists; neither commercial entity is involved in preparing the meeting nor registration fee is requested.

Let us use the Symposium's discussion platform to share original scientific ideas, innovative methodological solutions, and breakthrough multidisciplinary technologies. This is especially important in the current global context, which complicates international scientific and educational collaboration and hinders the efficient exchange of information and data. These elements have always been central to scientific creativity, particularly in biomedical research.

We believe that holding our Symposium under these conditions - with participation from scientists across many countries - will strengthen scientific diplomacy, sustain and expand professional and personal ties among colleagues, and foster new creative collaborations. In turn, this will advance the discovery of new medicines through the effective use of computational technologies. We also hope that our Symposium will help ease global tensions. The online format offers unique opportunities for this, including talks by distinguished colleagues from around the world.

Welcome to the XXXI Symposium on Bioinformatics and Computer-Aided Drug Discovery. We wish you engaging lectures, fruitful exchanges, and valuable discussions!

Vladimir Poroikov

Member of the Russian Academy of Sciences,

Prof. Dr.

Roman Efremov

Prof. Dr.

Scientific Program

XXXI Symposium on Bioinformatics and Computer-Aided Drug Discovery (BCADD-2025)

Scheduled time - Moscow (UTC+3)

Monday October 20, 2025

Chairpersons: Vladimir Poroikov and Roman Efremov

08:30	*Opening of the Symposium*

Plenary lecture	
09:00	AI-ASSISTANT, AI-ANALYST AND AI-RESEARCHER: THREE LEVELS OF DIGITAL TECHNOLOGIES IN CHEMISTRY **Valentine Ananikov** Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, Russia

Oral presentations	
10:00	TRANSCRIPTOMIC PROFILING OF T CELLS IN 4T1 TNBC TUMORS **Md. Iftehimul** Institute of Biotechnology, Bangladesh Agricultural University, Mymensingh, Bangladesh
10:20	TRANSCRIPTOMICS-BASED DRUG REPURPOSING OF SP600125 TO TARGET PRONEURAL-MESENCHYMAL TRANSITION IN GLIOBLASTOMA **Kirill Odarenko** Institute of Chemical Biology and Fundamental Medicine, Novosibirsk, Russia
10:40	DO-NO-HARM MOLECULAR GENERATION 12-MODEL BENCHMARK AND KRAS G12D CASE STUDY **Daria Ryabchenko** Skolkovo Institute of Science and Technology, Moscow, Russia

Keynote lectures	
11:00	ON OUR UNDERSTANDING OF AGING, PERSONALIZED MEDICINE AND GERIATRIC CARE **G. Narahari Sastry** Department of Biotechnology, Indian Institute of Technology Hyderabad, Kandi, Telangana, India
11:30	FRAGMENT-BASED NMR SCREENING FOR INHIBITORS OF BACTERIAL ENZYMES **Vladimir Polshakov** Chemical Department, Lomonosov Moscow State University, Russia

Oral presentations	
12:00	HARNESSING BIOINFORMATICS FOR HPV THERAPEUTICS ENHANCED DRUG REPURPOSING, PROTEIN HOMOLOGY, AND COMPREHENSIVE DATA MINING FOR TARGETED TREATMENT DEVELOPMENT **Arli Aditya Parikesit** Department of Biotechnology, School of Life Sciences, Indonesia International Institute for Life Sciences, Jakarta, Indonesia
12:20	SEARCH FOR MONKEYPOX VIRUS 2-O-METHYLTRANSFERASE INHIBITORS BY MOLECULAR MODELING **Ekaterina Mandrygina** Research Computing Center, Lomonosov Moscow State University, Moscow, Russia
12:40	STRUCTURE-BASED DISCOVERY OF INHIBITORS TARGETING NIPAH VIRUS RNA-DEPENDENT RNA POLYMERASE THROUGH VIRTUAL SCREENING AND MOLECULAR DYNAMICS SIMULATIONS **Manos Vlasiou** University of Nicosia, School of Veterinary Medicine, Nicosia, Cyprus

lunch break 13:00-15:00

Chairpersons: Jose Medina-Franco and Vladimir Palyulin

Keynote lectures	
15:00	COMBINING COMPUTATIONAL METHODS AND EPR SPECTROSCOPY FOR PROTEIN–LIGAND BINDING SITE ANALYSIS **Olesya Krumkacheva** International Tomography Center SB RAS, Novosibirsk, Russia
15:30	NEXT-GENERATION COMPUTATIONAL MODELS OF THE BLOOD-BRAIN BARRIER **Christian Jorgensen** University of Portsmouth, Portsmouth, United Kingdom

Oral presentations	
16:00	DEVELOPMENT OF A VIRTUAL SCREENING PIPELINE FOR THE DISCOVERY OF NOVEL SARS-COV-2 MPRO INHIBITORS **Daniel Malikin** Lomonosov Moscow State University, Moscow, Russia
16:20	ROLE OF INTERACTION FINGERPRINTS IN MACHINE LEARNING MODELS FOR SARS-COV-2 MPRO INHIBITORS **Anastasiia Fomina** Chumakov FSC R&D IBP RAS (Institute of Poliomyelitis), Moscow, Russia
16:40	IN SILICO SCREENING OF PROBIOTIC-DERIVED METABOLITES AS LUXS QUORUM SENSING INHIBITORS IN OTITIS MEDIA PATHOGENS **Samir Zergat** University of Pisa, Pisa, Italy
17:00	AN INTEGRATED COMPUTATIONAL STRATEGY FOR PROFILING TERPENOID FOR DUAL-TARGET LEADS AGAINST KLEBSIELLA PNEUMONIAE PENICILLIN-BINDING PROTEIN 3 AND BETA-LACTAMASE **Gideon Gyebi** Department of Biotechnology and Food Science, Faculty of Applied Sciences, Durban

	University of Technology, Durban, South Africa
17:20	CONSENSUS METHODOLOGY FOR DIRECTED SEARCH OF COMPOUNDS WITH ANTIMICROBIAL ACTIVITY AGAINST S. AUREUS **Arina Golubeva** Volgograd State Medical University, Volgograd, Russia
17:40	A CHEMINFORMATICS APPROACHES FOR THE IDENTIFICATION OF INHIBITORS AGAINST MACROLIDE 2'-PHOSPHOTRANSFERASE TYPE I **Carlos Alberto Lobato-Tapia** Universidad Politécnica Metropolitana de Puebla, Puebla, Mexico

Keynote lectures	
18:00	MACHINE LEARNING METHODOLOGIES AND THE FUTURE OF DRUG DISCOVERY **Rachelle Bienstock** RJB Computational Modeling LLC, Chapel Hill, NC, USA
18:30	COMBINING MACHINE LEARNING AND STRUCTURE-BASED APPROACHES FOR THE EFFICIENT IDENTIFICATION OF NOVEL BIOACTIVE SCAFFOLDS **Alan Talevi** National University of La Plata (UNLP), La Plata; Argentinean National Council of Scientific and Technical Research, La Plata; Boolzi SA, Buenos Aires, Argentina

Tuesday October 21, 2025

Chairpersons: Kunal Roy and Dmitry Shulga

Keynote lectures	
09:00	A NOVEL DRUG DESIGN APPROACH: QUANTITATIVE STRUCTURE-INTERACTION ACTIVITY RELATIONSHIP (QSIAR) IN ANTI-TUBERCULAR AGENTS **Anil Saxena** Global Institute of Pharmaceutical Education and Research, Kashipur, Uttarakhand, India
09:30	MULTI-AGENT DRUG DISCOVERY ORCHESTRA **Andrei Dmitrenko** ITMO University, St. Petersburg, Russia; D ONE AG, Zurich, Switzerland

Oral presentations	
10:00	TOXAI ASSISTANT - AN IN SILICO ALTERNATIVE TO RATS TESTING FOR ACUTE TOXICITY **Oleg Tinkov** Pridnestrovian State University , Tiraspol, Moldova
10:20	REVOLUTIONIZING DRUG SAFETY ASSESSMENT VIA QSAR AND Q-RASAR BASED TOXICITY PREDICTION TO PROTECT HUMAN HEALTH **Shubha Das** Drug Discovery and Development Laboratory, Department of Pharmaceutical Technology, Jadavpur University, Kolkata, India
10:40	ADVERSE REACTIONS OF WORLD-WIDE APPROVED DRUGS **Polina Savosina**

	Institute of Biomedical Chemistry, Moscow, Russia
11:00	CONSENSUS QSAR APPROACHES FOR PREDICTING PLACENTAL BARRIER PERMEABILITY IN REPRODUCTIVE TOXICOLOGY **Pabitra Samanta** Drug Discovery and Development Laboratory, Department of Pharmaceutical Technology, Jadavpur University, Kolkata, India
11:20	FULLY-CONNECTED CONVOLUTIONAL NEURAL NETWORKS BASED ON MULTIPLE DOCKING A NEW MACHINE LEARNING METHOD FOR SEARCHING BIOLOGICAL ACTIVE COMPOUNDS **Pavel Vassiliev** Volgograd State Medical University, Volgograd, Russia
11:40	DEEP LEARNING CONVOLUTIONAL CORRELATION NEURAL NETWORK BASED ON MULTIPLE DOCKING FOR IDENTIFYING PHARMACOLOGICALLY ACTIVE COMPOUNDS **Maksim Perfilev** Volgograd State Medical University, Volgograd, Russia

Keynote lectures

12:00	STRUCTURE AND FUNCTIONING OF TRPV CHANNELS: INSIGHTS FROM MOLECULAR MODELING **Yuri Trofimov** Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences; Research Institute for Systems Biology and Medicine, Moscow, Russia
12:30	MOLECULAR DYNAMICS AND PHARMACOPHORE MODELING OF THE INACTIVE MINERALOCORTICOID RECEPTOR FOR ANTAGONIST DISCOVERY **Carlos Lagos** Universidad San Sebastián, Centro Basal Ciencia & Vida, Santiago, Chile

lunch break 13:00-15:10

Chairpersons: Athina Geronikaki and Alexey Lagunin

Young Scientists flash presentations

15:10	IN SILICO–GUIDED IDENTIFICATION AND BIOLOGICAL EVALUATION OF TRITERPENOID-TYPE P-GLYCOPROTEIN INHIBITORS **Arsenii Moralev** Institute of Chemical Biology and Fundamental Medicine, Novosibirsk, Russia
15:20	COMPUTATIONAL MODELING OF BIOACCUMULATION POTENTIAL OF PER- & POLY-FLUOROALKYL SUBSTANCES: MACHINE LEARNING BASED QUANTITATIVE READ-ACROSS STRUCTURE-PROPERTY RELATIONSHIP APPROACH **Akash Chandra** Drug Theoretics and Cheminformatics Laboratory, Jadavpur University, Kolkata, India
15:30	MAGNESIUM BINDING TO TRPV6 ION CHANNEL: INSIGHTS FROM MOLECULAR MODELING **Irina Veretenenko** Shemyakin–Ovchinnikov Institute of bioorganic chemistry RAS, Moscow, Russia
15:40	COMPUTATIONAL WORKFLOW FOR PREDICTING DRUG METABOLISM BY GUT MICROBIOTA

	Anton Kolodnitsky Institute of Biomedical Chemistry, Moscow, Russia
15:50	TIP: WEB APPLICATION FOR PREDICTING DRUG–TRANSPORTER INTERACTIONS **George Khodos** Pirogov Russian National Research Medical University, Moscow, Russia
16:00	DENR+POL: THEORETICALLY CONSISTENT POLARIZABLE EMPIRICAL CHARGES FOR DRUG-LIKE AND BIOLOGICAL MOLECULES **Vitaly Frolov** Department of Chemistry, Lomonosov Moscow State University, Moscow, Russia
16:10	X-RAY CRYSTALLOGRAPHIC ANALYSIS OF 17-PYRIDIN-2-YL ESTRANE DERIVATIVES: LEAD-LIKE COMPOUNDS AGAINST BREAST AND CERVICAL CANCER **Nikola Radnović** University of Novi Sad, Faculty of Sciences, Department of Chemistry, Biochemistry and Environmental Protection, Novi Sad, Serbia
16:20	IMPLEMENTATION OF HIGH-THROUGHPUT SCREENING DATA FOR DRUG SYNERGY PREDICTION IN ONCOLOGY **Vladislav Sukhachev** Institute of Biomedical Chemistry, Moscow, Russia
16:30	COMPARATIVE EVALUATION OF LSTM AND GRAPH NEURAL NETWORKS FOR ADVERSE DRUG REACTION PREDICTION **Nsikan Udo** Moscow Institute of Physics and Technology, Dolgoprudny, Russia
16:40	FROM IN SILICO DESIGN TO EXPERIMENTAL IMPLEMENTATION: DEVELOPMENT OF A NOVEL GLUCOKINASE ACTIVATOR **Kira Inzhevatkina** National Research Mordovia State University, Saransk, Russia
16:50	DEVELOPMENT OF A PROBABILITY FACTOR BASED ON BLIND AND TARGET-SITE DOCKING ANALYSIS FOR IMPROVED IC_{50} PREDICTION OF CANDIDATE COMPETITIVE ENZYME INHIBITORS **Dionysia Amanatidou** Department of Biomedical Sciences, School of Health, International Hellenic University, Thessaloniki, Greece
17:00	COMPARATIVE EFFICIENCY OF STRUCTURE ACTIVITY RELATIONSHIP AND PROTEOCHEMOMETRIC MODELLING **Georgii Malakhov** Department of Bioinformatics, Institute of Biomedical Chemistry, Moscow, Russia
17:10	A LARGE-SCALE DATASET OF QUANTUM CHEMICAL PROPERTIES OF DRUG-LIKE MOLECULES FOR Δ-LEARNING MODELS **Dmitry Frolov** Sirius University of Science and Technology, Sirius, Russia
17:20	THE POLAR PATCH IN THE HYDROPHOBIC GATE OF THE TRPV1 CHANNEL AND ITS FUNCTIONAL ROLE **Ivan Lazarev** Shemyakin–Ovchinnikov Institute of Bioorganic chemistry RAS, Moscow, Russia
17:30	AMIACTIVE (AIA): A LARGE-SCALE QSAR BASED TARGET FISHING AND POLYPHARMACOLOGY PREDICTIVE WEB TOOL **Luis Felipe Melo**

	Federal University of Paraiba, João Pessoa, Brazil
17:40	CHEMECAL PROFILE EVALUATION AND ACTIVITY OF TAMARINDUS INDICA L. SEEDS ON HELICOBACTER PYLORI AND UREASE **Ester Tonini** Department of Pharmaceutical Sciences, Health Center Sciences, Federal University of Espírito Santo, Vitória, Brazil
17:50	DESIGN AND SYNTHESIS OF PEPTIDE INHIBITORS TARGETING HER2 AS A THERAPEUTIC STRATEGY IN BREAST CANCER **Luis Angel Gil Ruiz** Laboratory for the Design and Development of New Drugs and Biotechnological Innovation, Escuela Superior de Medicina, Instituto Politécnico Nacional, Mexico

Keynote lectures	
18:00	ULTRA-LARGE LIBRARIES AND CHEMICAL SPACES OF VIRTUAL SCREENING SAMPLES WITH PROPOSED SYNTHETIC ROUTES **Marc C. Nicklaus** Actyon Discovery, Inc., San Diego/Catonsville, United States
18:30	COMPUTER-AIDED ANTIMICROBIAL DISCOVERY: STRUCTURE–ANTIMICROBIAL ACTIVITY RELATIONSHIPS OF RECOMBINANT HOST DEFENSE PEPTIDES AGAINST DRUG-RESISTANT BACTERIA **William J. Zamora** University of Costa Rica, San Pedro, San José, Costa Rica; 4National Advanced Computing Collaboratory (CNCA), National High Technology Center (CeNAT), Costa Rica

Wednesday October 22, 2025

Chairpersons: Rajesh Goel and Dmitry Osolodkin

Keynote lectures	
09:00	AN IMPROVED Q-RASAR MODELING FRAMEWORK FOR ENVIRONMENTAL TOXICITY ENDPOINTS **Kunal Roy** Jadavpur University, Kolkata, India
09:30	PROTEIN ENGINEERING METHODS FOR CHALLENGING MEMBRANE-BOUND DRUG TARGETS **Ivan Gushchin** Moscow Institute of Physics and Technology (National Research University), Dolgoprudny, Russia

Oral presentations	
10:00	THE NATURE OF ENTROPY-ENTHALPY COMPENSATION, EXOTIC ARRHENIUS PARAMETER AND KINETIC ISOTOPE EFFECT IN THE DENATURATION KINETICS OF PROTEINS **Alexey Baklanov** Institute of Chemical Kinetics and Combustion SB RAS, Novosibirsk, Russia
10:20	COMPUTER MODELING OF SUPRAMOLECULAR CHEMICAL SYSTEMS PROPERTIES AND REACTIVITY AND ITS POTENTIAL IMPACT IN

	COMPUTER-AIDED DRUG DISCOVERY **Alexander Novikov** Saint Petersburg State University, Saint Petersburg, Russia
10:40	HOW FLAVONOID PARAMETERIZATION DETERMINES DRUG-INDECED MEMBRANE BIOPHYSICAL OUTCOMES **Anna Malykhina** Laboratory of Membrane and Ion Channel Modeling, Institute of Cytology of Russian Academy of Sciences, Saint Petersburg, Russian Federation

Keynote lectures	
11:00	A LONG, HARD ROAD TO PHYSICALLY CORRECT CALCULATION OF PROTEIN–PROTEIN BINDING FREE ENERGIES **Anton Chugunov** Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences; Research Institute for Systems Biology and Medicine, Moscow, Russia
11:30	STATE-OF-THE-ART COVALENT VIRTUAL SCREENING WITH ALPHAFOLD3 **Nir London** The Weizmann Institute of Science, Rehovot, Israel

Oral presentations	
12:00	TOOL FOR DIVERSITY VISUALIZATION ON THE LEVEL OF MOLECULAR SCAFFOLDS, TDV CHEMICAL DATA AT GLANCE **Pavel Pogodin** Institute of Biomedical Chemistry, Moscow, Russia
12:20	STUDYING THE ALLOSTERIC COMMUNICATION IN BIOMOLECULES USING INFORMATION THEORY **Ruslan Mallaev** M.M. Shemyakin and Yu.A. Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, Moscow, Russia
12:40	IN SILICO REVERSE FRAGMENT BASED DRUG DISCOVERY APPROACH (R-FBDD) CORE IDEAS, CURRENT STATUS AND FUTURE DIRECTIONS **Dmitry Shulga** Department of Chemistry at Moscow State University, Moscow, Russia

lunch break 13:00-16:00

Chairpersons: Alexander Kel and Olga Tarasova

Oral presentations	
16:00	A NOVEL STRATEGY TO OVERCOME PARPI RESISTANCE TARGETING UBE2N WITH NON-COVALENT INHIBITORS **Shafi Ullah Khan** Université de Caen Normandie, INSERM U1086 ANTICIPE (Interdisciplinary Research Unit for Cancers Prevention and Treatment), BioTICLA laboratory (Precision medicine for ovarian cancers), Caen, France
16:20	STEROIDAL PREGNANES AS NOVEL 11-HSD1 INHIBITORS INSIGHTS FROM MACHINE LEARNINGBASED QSAR AND MOLECULAR MODELING **Oludare Ogunyemi** Structural and Computational Biology Group, Nutritional and Industrial Biochemistry

	Research Unit, Department of Biochemistry, College of Medicine, University of Ibadan, Ibadan, Nigeria
16:40	IRACEMA, A DATABASE MANAGEMENT SYSTEM FOR BIOACTIVE COMPOUNDS ISOLATED AND CHARACTERIZED BY BRAZILIAN RESEARCHERS **Thais Lourenco** University of São Paulo, São Paulo, Brazil

Keynote lectures	
17:00	A COMPUTATIONAL PIPELINE FOR ACCELERATING THE DESIGN OF GLYCOMIMETICS **Robert J. Woods** Complex Carbohydrate Research Center, University of Georgia, Athens, GA, USA
17:30	IN SILICO SMALL MOLECULE DRUG DISCOVERY FROM THE PHARMA COMPANY POINT OF VIEW **Germes Chilov** JSC "Valenta Pharm", Shchelkovo, Moscow Region, Russia

Plenary lectures

18:00	ON THE USE OF MACHINE LEARNING MODELS FOR NEW APPROACH METHODOLOGIES **Tudor I. Oprea** Expert Systems Inc., San Diego, California, USA
19:00	*Closure of the XXXI Symposium on Bioinformatics and Computer-Aided Drug Discovery*

PLENARY LECTURES

AI-ASSISTANT, AI-ANALYST AND AI-RESEARCHER: THREE LEVELS OF DIGITAL TECHNOLOGIES IN CHEMISTRY

V.P. Ananikov

Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, Russia

Artificial intelligence (AI) is rapidly reshaping chemical sciences, with direct implications for bioinformatics and drug discovery. The accelerating growth of experimental and computational data requires systematic approaches to integrate AI into research practice. In this work, a three-level classification of AI applications in chemistry is introduced — AI-Assistant, AI-Analyst, and AI-Researcher — reflecting the increasing sophistication of digital tools and their role in the scientific process.

At the first level, AI-Assistant, large language models and automation platforms facilitate routine but critical tasks: literature mining, preparation of scientific texts, patent searches, annotation of chemical databases, and laboratory documentation. These tools significantly reduce entry barriers for young scientists and accelerate the collection of knowledge indispensable for drug discovery campaigns. In bioinformatics, AI-assistants enable rapid preprocessing of genomic, proteomic, and chemical datasets, transforming manual data handling into scalable workflows.

The second level, AI-Analyst, involves custom algorithm development and advanced data engineering. Here, chemists and data scientists employ machine learning and deep learning frameworks to interpret spectra, images, reaction kinetics, and structural libraries. In pharmaceutical research, this translates into accurate modeling of compound activity, toxicity prediction, ligand–target interaction mapping, and automated screening of large chemical libraries. By bridging raw experimental data with actionable insights, AI-Analyst systems reduce timelines in lead optimization and enhance reproducibility in preclinical pipelines.

The third and most transformative level, AI-Researcher, envisions intelligent systems capable of hypothesis generation, autonomous experimental design, and strategic exploration of chemical space. Early prototypes demonstrate the ability to suggest novel synthetic routes, identify hidden patterns and generate hypotheses without direct human input.

Together, these three levels establish a roadmap for integrating AI into chemistry and life sciences. The progression from automation to digital scientific thinking highlights the emergence of "technology-as-participant", where AI acts not merely as a tool but as a collaborator in knowledge creation.

Supported by the Russian Science Foundation (grant 23-43-00086).

1. Ananikov, V.P. (2024). Top 20 Influential AI-Based Technologies in Chemistry. *Artificial Intelligence Chemistry*, 2(2), 100075. DOI: 0.1016/j.aichem.2024.100075
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ON THE USE OF MACHINE LEARNING MODELS FOR NEW APPROACH METHODOLOGIES

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Expert Systems (ExSys) has a state-of-the-art platform for small-molecule-based drug discovery prediction that combines public and proprietary cheminformatic tools and machine learning (ML) algorithms. Our platform supports a wide variety of ML models that evaluate target-based bioactivity, several physicochemical properties, ADME properties, and cell- and target-based toxicity. Experts in ML model development have designed the ExSys platform based on decades of expertise in data biocuration and aggregation, data generation, and advanced ML model evaluation and deployment.

These ML models are proactively developed in response to the FDA Modernization 2.0 initiative, as well as the European Union 3R policy, regarding New Approach Methodologies (NAMs). Our efforts focus on validated ML models to help reduce or replace animal studies while benefiting early drug discovery. At present, NAMs are subject to rapidly evolving regulatory expectations as the demand for integrated, predictive, human-centered methods is increasing.

Here, we report the evaluation of current ExSys models that estimate $K_{p,uu,brain}$, the unbound brain-to-plasma partition coefficient, a key pharmacokinetic parameter in central nervous system (CNS) drug discovery that measures the free drug concentration in the brain versus in the plasma at steady-state [1]. Tyically, $K_{p,uu,brain}$ is estimated by adjusting $K_{p,brain}$ (the brain-to-plasma concentration ratio) according to the $F_{u,b}$ (fraction unbound, brain) vs. $F_{u,p}$ (fraction unbound, plasma) ratio, which is expressed as $K_{p,uu,brain} = K_{p,brain} * (F_{u,b}/F_{u,p})$ [1]. A recent in silico model to predict $K_{p,uu,brain}$ started with $K_{p,brain}$ data for 36 marketed drugs and 256 (undisclosed) in-house compounds.[2] The model estimated $F_{u,b}$ and $F_{u,p}$. as well as $K_{p,uu,brain}$ starting from ionization (e.g., acidic/basic), hydrophobicity (e.g., ClogP), and hydrogen bonding capacity (e.g., donor/acceptor counts). The authors acknowledge the difficulty in developing such models, since multiple pharmacokinetic parameters are involved [2].

The ExSys ML models summarized below use the ChemProp descriptors and algorithm [3]. Our models use a 70:10:20 split (training set/validation/test set), with ten concurrent models that output uncertainty quantification (UQ) values.[4] Combined with training set size (compounds), UQ enables model quality evaluation. The external set predicted below is a CNS brain-permeable set of 23,406 pre-plated compounds from ChemDiv (www.chemdiv.com).

ExSys Model	Training Set Size	External Set UQ <0.15	Mean UQ
$LogF_{u,brain}$	216,292	23,341	0.041
$LogF_{u,plasma}$	216,292	23,384	0.038
$LogK_{p,brain}$	2,380	2,035	0.299

This summary highlights a critical but often overlooked factor in the development and application of ML-based NAMs: the interplay between training set size and uncertainty quantification. The observed discrepancies, spanning one to two orders of magnitude, illustrate how model robustness and predictive accuracy can be significantly compromised when training data are unevenly distributed across properties. There is an urgent need for harmonized, large-scale datasets where multiple pharmacokinetic and toxicological parameters are measured on the same compounds. Addressing this gap will be essential to ensure that ML-driven NAMs deliver reliable, reproducible, and regulatory-relevant predictions. Until such discrepancies are properly factored in, adoption of ML-based NAMs in drug discovery may be at risk.

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KEYNOTE LECTURES

MACHINE LEARNING METHODOLOGIES AND THE FUTURE OF DRUG DISCOVERY

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There is currently a great deal of "hype" and promise surrounding the application of machine learning techniques in the drug discovery space. The key question is whether these methodologies will actually deliver on their promise and be successful in designing the next generation of new chemical entities. One of the most significant questions is whether machine learning methods can improve chemical diversity and identify novel chemistries, compounds and scaffolds. Often compounds identified by these methods seem to be only slightly modified versions of already known ligands, sharing the scaffolds and shapes of the representatives in the training set. How does the performance of machine learning models based on statistical methods (i.e. QSAR techniques) compare with generative deep learning neural network models in the drug design space? Another issue is whether machine learning predictive methods, such as AlphaFold3, and Boltz, can outperform traditional physics based docking methods in predicting target-ligand interactions. This presentation will present specific examples and results comparing traditional virtual screening, lead discovery and physics based docking methods with machine learning and deep learning method results.

We will discuss applications of machine learning methods to some new modalities and novel areas of drug discovery space. In particular, success in the application of machine learning methods and deep learning methods in targeting noncoding RNA for small ligand drug discovery.

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IN SILICO SMALL MOLECULE DRUG DISCOVERY FROM THE PHARMA COMPANY POINT OF VIEW

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In silico stage of a small molecule drug discovery process is one of the first (once the choice of drug target and the desired mechanism of action are made) and risk bearing stages of discovering and developing an innovative drug. Mistakes at this initial stage could advance an improper molecule for further development and waste of resources, as well as they may lead to a premature closing of the project. With the advancement of computational techniques more criteria are set for the successful completion of this *in silico* discovery part. From the practical perspective, robust model of on-target and off-target interactions must be developed with 3D structural interpretation of the predictions. Only molecules that fit the desired affinity and selectivity profile together with a clear structural visualization should be considered. Second, the designed molecules must fit numerous filters in order to have the desired ADMET depending on the use of the drug (route of administration, site of action, duration of effect etc.). Of crucial importance for pharma companies are such properties as novelty and patentability of the structure as well as anticipated cost of the manufacturing of the corresponding active pharmaceutical ingredient (API). These properties must be screened early at beginning. Successful evaluation of all of these properties is mandatory for the overall project success.

A LONG, HARD ROAD TO PHYSICALLY CORRECT CALCULATION OF PROTEIN–PROTEIN BINDING FREE ENERGIES

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Nowadays, predicting the 3D structure of proteins is generally solved using comparative modeling and more recently, artificial intelligence (AI) algorithms; and their conformational flexibility is routinely assessed using molecular dynamics (MD) simulations. However, the most important quantity in biochemistry and pharmacology — the free energy of protein–protein interactions ($\Delta G_{\text{binding}}$) — remains incredibly difficult to calculate. Although algorithms for *in silico* characterization of intermolecular interactions — protein–ligand and protein–protein docking — have been introduced decades ago, they do not accurately capture the most important characteristic — $\Delta G_{\text{binding}}$ — at any acceptable level of accuracy, making docking resemble fortune telling on coffee grounds. The reason for this disappointing situation is that docking is based on a single-point force field terms summation, which has almost nothing to do with *real* $\Delta G_{\text{binding}}$, a truly thermodynamic quantity that arises from the integration of molecular events probabilities over vast conformational ensembles. At the same time, there are more physically accurate methods for calculating $\Delta G_{\text{binding}}$, which are based on the intensive MD computations in order to obtain the correct probabilities for various states in the molecular ensembles, which, by definition, determine the free energy (e.g., $\Delta G = -RT\ln K_{\text{eq}}$). These methods are supported by a variety of techniques behind the "vanilla" MD, including enhanced conformational sampling through the selection of certain collective variables, biasing energy functions, parallelizing calculations, and more.

In this talk, we will share our personal experience in calculating $\Delta G_{\text{binding}}$ for small peptides that bind to voltage-gated potassium channels and block ion current. Over the course of more than a year, we have tried virtually all existing methods: "vanilla" MD, ensemble protein–protein docking, umbrella sampling, advanced weight histogram, alchemical modeling of point mutations to estimate $\Delta\Delta G$, and several types of well-tempered metadynamics (WTMD). Although this long hard road was mostly a record of failures, we still hope that there is a light at the end of the tunnel that will illuminate the true nature of free energy of protein–protein binding and a way to calculate it. At the end, we were able to assess correct absolute and relative binding energies for several blocker–channel pairs, although at cost of several months of WTMD production runs.

MULTI-AGENT DRUG DISCOVERY ORCHESTRA

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Hit identification is a central challenge in early drug discovery, traditionally requiring substantial experimental resources. Recent advances in artificial intelligence, particularly large language models (LLMs), have enabled virtual screening methods that reduce costs and improve efficiency. However, the growing complexity of these tools has limited their accessibility to wet-lab researchers. Multi-agent systems offer a promising solution by combining the interpretability of LLMs with the precision of specialized models and tools. In this work, we present MADD, a multi-agent system that builds and executes customized hit identification pipelines from natural language queries. MADD employs four coordinated agents to handle key subtasks in de novo compound generation and screening. We evaluate MADD across seven drug discovery cases and demonstrate its superior performance compared to existing LLM-based solutions. Using MADD, we pioneer application of AI-first drug design to five biological targets and release the identified hit molecules. Finally, we introduce a new benchmark of query-molecule pairs and docking scores for over three million compounds to contribute to the agentic future of drug design.

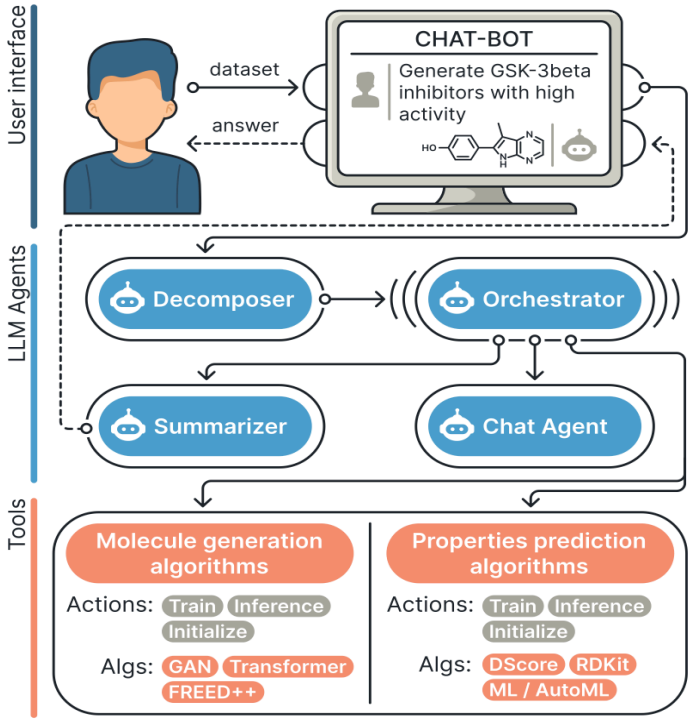

Figure 1. Overview of MADD architecture

PROTEIN ENGINEERING METHODS FOR CHALLENGING MEMBRANE-BOUND DRUG TARGETS

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Knowledge of the atomic structure of a drug target greatly facilitates the process of drug discovery by allowing rational structure-based and physics-based approaches. Accordingly, development of structure determination and structure prediction methods has been a top priority for structural biologists, and high-resolution models were obtained for many important macromolecules involved in diseases. Yet, some proteins are naturally resistant to experimental structure determination efforts due to low stability, conformational heterogeneity, and/or hydrophobicity, especially in the case of peripheral and integral membrane proteins, while computational methods still have important limitations [1]. Here, we argue that the recent transformative advances in protein engineering provide unique opportunities for addressing these challenging drug targets.

The first avenue where the protein engineering methods may be helpful is protein stabilization. Recent AI-based methods significantly increase the rate of identification of stabilizing substitutions, in some cases reaching 50-100%, as opposed to 0-10% for previously used methods. We show that stable analogs may be identified both in the cases where a high-resolution structure has already been determined [2] ProteinMPNN, predicts an amino acid sequence that would fold and match user-defined backbone structure. Its performance was previously tested for proteins composed of standard amino acids, as well as for peptide- and protein-binding proteins. In this short report, we test whether ProteinMPNN can be used to reengineer a non-proteinaceous ligand-binding protein, flavin-based fluorescent protein CagFbFP. We fixed the native backbone conformation and the identity of 20 amino acids interacting with the chromophore (flavin mononucleotide, FMN as well as where only an approximate model is available [3] a number of message passing neural network (MPNN. Importantly, development of so-called “inverse folding” methods allows stabilization of fine-tuned conformations, thus making possible engineering of protein variants that mimic a particular functional state.

The second exciting opportunity is what can be called “computational solubilization” of membrane-bound proteins. Natural membrane proteins require solubilization with detergents or other membrane mimics for most studies, which is often laborious and complicates assessment of protein-ligand interactions. On the other hand, modern methods allow generation of membrane protein analogs, where the hydrophobic amino acids facing the membrane are replaced with polar ones in such a way that the overall protein structure is maintained [4]. We describe successful engineering of soluble analogs of a model seven transmembrane (7TM) protein bacteriorhodopsin: designed variants retain ligand binding ability and functionality, and X-ray structure reveals almost perfect match to that of the native protein [5] clear examples are currently missing. Here, we report successful engineering of proteins dubbed NeuroBRs that mimic the active site (retinal-binding pocket. Soluble membrane protein analogs are stable, can be inexpensively produced in large quantities, and thus are promising alternatives for high-throughput *in vitro* screening campaigns.

We conclude that protein engineering holds great potential for drug discovery efforts aimed at challenging drug targets, and combination of AI-based, physics-based, and bio-/cheminformatics-based computations will undoubtedly further speed up the pace of drug discovery and development.

The study was supported by the Ministry of Science and Higher Education of the Russian Federation (agreement 075-03-2025-662, project FSMG-2025-0003).

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NEXT-GENERATION COMPUTATIONAL MODELS OF THE BLOOD-BRAIN BARRIER

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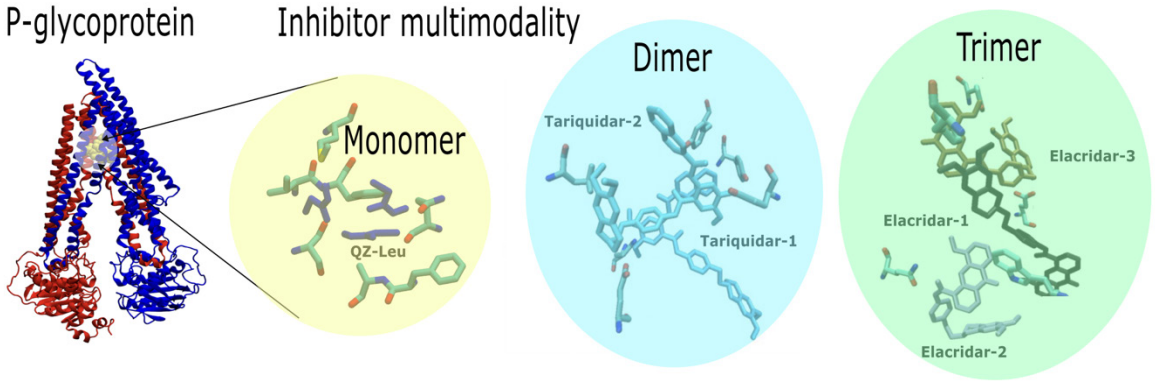
The use of computational models powered by Molecular Dynamics (MD) simulations has allowed for the construction of atomic-detail models of biophysical systems of interest. Here we demonstrate the use of MD simulations to construct a model of the blood-brain barrier endothelial cell membrane. We show permeability simulations across these systems and elucidate the thermodynamics of transport for libraries of compounds. We then proceed to explore various recent approaches for high-accuracy permeability estimation.

Secondly, we demonstrate recent results for modelling the P-glycoprotein receptor embedded in the blood-brain barrier, including our new multimodal model of P-glycoprotein inhibition, based on cryo-EM, machine learning estimations and coarse-grain modelling.



COMBINING COMPUTATIONAL METHODS AND EPR SPECTROSCOPY FOR PROTEIN–LIGAND BINDING SITE ANALYSIS

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Understanding protein-ligand interactions is of paramount importance for therapeutic development, but experimental methods often face limitations, leading researchers to rely on computational approaches like blind docking. While appealing for its ability to predict binding sites in silico, blind docking is hindered by incomplete conformational exploration and imperfect scoring algorithms. These challenges underscore the need for complementary methodologies.

At the same time, dipolar EPR spectroscopy has become a widely used technique in biological chemistry and structural biology for measuring distance distributions — typically ranging from 1.5 to 8 nm —between paramagnetic species attached to biomolecules. This method allows for the detection of multiple coexisting conformations within a biological system, including all possible binding configurations in protein-drug complexes. However, as dipolar EPR data are inherently one-dimensional, resolving complete structural information often requires additional experimental or computational insights.

In our study [1], we integrate the strengths of blind docking and EPR spectroscopy to overcome their respective limitations. By incorporating EPR-derived distance restraints into GPU-accelerated blind docking predictions, we present a hybrid approach that refines binding site identification in protein-ligand complexes. This methodology not only provides experimentally validated and computationally advanced maps of binding sites but also resolves ambiguities associated with traditional methods, such as fluorescence spectroscopy.

To validate our approach, we investigated interactions between the transport protein human serum albumin and porphyrin-based photosensitizers, compounds critical in photodynamic therapy. Using our combined approach, we identified binding sites for seven potential photosensitizers whose structural information was previously uncertain. Remarkably, some photosensitizers were found to bind at non-standard albumin sites, that may be undetectable by other methods. By comparing our results with previous literature, we demonstrated that our method provides more comprehensive information on binding sites than the commonly used combination of blind docking and fluorescence techniques.

This work was supported by the Ministry of Science and Higher Education of the Russian Federation (No. 075-15-2021-580).

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MOLECULAR DYNAMICS AND PHARMACOPHORE MODELING OF THE INACTIVE MINERALOCORTICOID RECEPTOR FOR ANTAGONIST DISCOVERY

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The mineralocorticoid receptor (MR) is a critical therapeutic target in cardiovascular and renal diseases. However, structural data on its inactive conformation remain limited. In this study, we employed molecular modeling to complete the recently published, yet incomplete, crystallographic structure of the MR-Esaxerenone complex, enabling the exploration of MR in its inactive state.

To characterize binding patterns and derive a pharmacophore model of pure MR antagonists, molecular dynamics simulations were conducted. Clustering strategies were applied to identify prevalent binding modes and pinpoint key residues in the protein-ligand interactions. This analysis revealed critical anchoring points that determine antagonist affinity and specificity for MR.

We conducted a virtual screening campaign of approximately 100 million compounds using the most representative binding mode. This effort led to the identification of several novel chemotypes with potential selective antagonist activity for MR. These compounds represent promising candidates for MR-targeted therapies, providing new opportunities in modulating this receptor for potential clinical applications.

Through molecular modeling and dynamics, we generated a detailed model of MR's inactive state, identifying novel chemotypes for MR antagonists. This work underscores the potential of virtual screening and computational modeling in drug discovery for diseases modulated by MR.

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STATE-OF-THE-ART COVALENT VIRTUAL SCREENING WITH ALPHAFOLD3

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Recent years have seen an explosion in the prominence of covalent inhibitors as research and therapeutic tools. However, a lag in application of computational methods for covalent docking slows progress in this field. AI models such as AlphaFold3 have shown accuracy in ligand pose prediction but were never assessed for virtual screening. We show that AlphaFold3 reaches near-perfect classification (average AUC=98.3%) of covalent active binders over property-matched decoys, dramatically outperforming classical covalent docking tools. We identify a predicted metric that allows to reliably assign a probability of binding and demonstrate it also improves non-covalent virtual screening. Furthermore we validated AF3 in what is, to our knowledge, the first prospective virtual screening campaign based on a co-folding method. By screening 900K virtual compounds, we identified potent covalent inhibitors of BTK with novel scaffolds. Experimental characterization of these inhibitors is still ongoing, but they already make the case for using AF3 for virtual screening.

This research was generously supported by the Institute for Artificial Intelligence, the Honey and Dr. Barry Sherman Lab, the Dr. Barry Sherman Institute for Medicinal Chemistry, the Abisch- Frenkel RNA Therapeutics Center, the Moross Integrated Cancer Center, the Goldhirsh-Yellin Foundation and Celia Zwillenberg-Fridman.

ULTRA-LARGE LIBRARIES AND CHEMICAL SPACES OF VIRTUAL SCREENING SAMPLES WITH PROPOSED SYNTHETIC ROUTES

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Ultra-large libraries and chemical spaces of commercially available screening samples (such as Enamine REAL Database/Space, WuXi GalaXi, eMolecules eXplore, OTAVA CHEMriya) have changed the whole landscape of R&D in drug development. Likewise, proprietary ultra-large libraries and spaces at large pharmaceutical companies have emerged during the past 15 years or so (such as PLC (Eli Lilly), BI-CLAIM (Boehringer-Ingelheim), PVGL (Pfizer), MASSIV (Merck), GSK XXL (GSK)). The chemical spaces among these collections are typically defined by relatively straightforward combination rules for fragments ("synthons"), often described in a Lego-like fashion. The smaller enumerated libraries ($<10^8$ molecules) among the commercial structure sets are based on in-house reaction types, which may or may not have been publicly disclosed.

A third category of libraries/spaces are fully public of sets of virtual screening compounds with associated data sets. The Synthetically Accessible Virtual Inventory (SAVI) project is one of these efforts. It was initially conceived by the Computer-Aided Drug Design (CADD) Group at the U.S. National Cancer Institute together with several collaborators world-wide as a response to the challenges experienced in the synthesis of *de novo* designed molecules for the CADD Group. One of its hallmarks, which distinguishes it from most other ultra-large library/space projects is its use of sophisticated rules describing the chemical logic permitting – of forbidding (via so-called KILL statements) – the synthesis of a proposed molecule from commercially available building blocks (Enamine). These rules ("transforms") are derived from the expert-system type LHASA project [1], using the language pair CHMTRN/PATRAN [2]. In its 2020 version, a SAVI library of 1.75 billion molecules associated with a proposed (single-step) synthetic route as well as a score for the predicted reliability of this route was made publicly available [3]. About 1 billion of these molecules and their proposed reactions had the highest positive score.

Based on this SAVI approach, a collaboration of the SAVI team with a group of scientists in the Rarey group at the University of Hamburg, Germany, converted the LHASA type transforms, including their KILL statements where possible, into a synthon-based approach. Utilizing the same building blocks as had been used for SAVI-2020, the this generated SAVI Space [4] showed a good reproduction of the SAVI-2020 product sets for most transforms, although with a somewhat lower KILL rate. With a newer, 2024, version of the Enamine off-the-shelf building block set, a SAVI Space of 7.5 billion molecules was generated. As is typical for chemical spaces compared to enumerated libraries, the SAVI Spaces require only a few gigabytes of disc space vs. terabytes for SAVI-2020.

Equally starting conceptually from the SAVI project, the SAVI team has developed a more modern way of generating large libraries, called SLICE (SMARTS and Logic In ChEmistry) [5]. The task the SLICE team gave itself was to make it (a) faster than SAVI in its execution, (b) its transforms easier to write than in CHMTRN. SLICE consists of: (1) SLICE Designer, a GUI to define SMARTS patterns, configure atom and bond properties, and establish chemical constraints and logic; (2) SLICE Engine, which uses Designer-generated transform files to generate virtual libraries from specified building blocks. The observed speedup of SLICE vs. SAVI is between 40- and more than 100-fold.

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FRAGMENT-BASED NMR SCREENING FOR INHIBITORS OF BACTERIAL ENZYMES

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A major priority in modern biomedical research is the target-oriented discovery of new drugs. Among the biophysical methods applied to this challenge, nuclear magnetic resonance (NMR) spectroscopy holds a leading position. NMR provides detailed insights into molecular structure, dynamics, and intermolecular interactions – factors essential for elucidating drug mechanisms of action and for identifying novel bioactive compounds.

NMR methods are widely used both for the structural characterization of natural products with biological activity and for analyzing the highly specific binding of small molecules to biomolecular targets. These capabilities have driven the development of fragment-based and NMR-guided screening strategies [1]. This presentation will review current approaches to NMR screening and strategies for the rational design of bioactive compounds using fragment-based methods. Both target-observed techniques (SAR-by-NMR) and ligand-observed experiments (STD, WaterLOGSY, FAXS, INPHARMA) will be discussed.

The concepts will be illustrated by examples of clinically approved drugs identified through NMR-based approaches, as well as by results from our own studies on potential inhibitors of bacterial enzymes. Specifically, we investigated two enzymes essential for bacterial survival: inorganic pyrophosphatase (Mt-PPase) from *Mycobacterium tuberculosis* and NAD^+-dependent formate dehydrogenase (Sa-FDH) from *Staphylococcus aureus*. Notably, FDH lacks a direct human counterpart, while PPases differ substantially between bacteria and humans, making both enzymes attractive targets for selective inhibition. To date, no clinically used antibiotics act on these enzymes.

Mt-PPase is a 110 kDa hexamer, while Sa-FDH is an 84 kDa homodimer. We prepared uniformly $^{13}C/^{15}N/^{2}D$-labeled proteins and assigned their backbone resonances. Using NMR screening, we identified compounds binding to functional sites that modulate catalytic activity. Two complementary strategies were applied: monitoring ligand signals (STD and WaterLOGSY) and detecting ligand-induced perturbations in protein TROSY spectra. Optimization of initial hits yielded inhibitors with micromolar IC_{50} values. Importantly, these compounds display no structural similarity to known PPase or FDH inhibitors, providing promising starting points for the development of novel antibiotics.

The study was supported by the Russian Science Foundation grant No. 24-14-00081.

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AN IMPROVED q-RASAR MODELING FRAMEWORK FOR ENVIRONMENTAL TOXICITY ENDPOINTS

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The continuous quest for the quick, accurate and efficient toxicity data gap filling of commercial chemicals is the need of the hour, considering their detrimental effects on the environmental flora and fauna. Thus, it becomes essential to develop simple and improved modeling strategies aiming towards generating more accurate predictions. Recently, the quantitative Read-Across Structure- Activity Relationship (q-RASAR) modeling has been reported to enhance the external predictivity of QSAR models. However, in some studies, the cross-validation metrics of the q-RASAR models show slightly compromised values compared to the corresponding QSAR models. In this background, we have reported here an improved q-RASAR workflow [1] coupled with the Arithmetic Residuals in *K*-groups Analysis (ARKA) framework [2]. This improved workflow (ARKA-RASAR) considers two important aspects – the contribution of different QSAR descriptors to different experimental response ranges, and the identification of the similarity among close congeners based on both the selected QSAR descriptors and the contribution of different QSAR descriptors to different experimental response ranges. A simple, free, and user-friendly Java-based tool, Multiclass ARKA-v1.0, has been developed to compute the multiclass-ARKA descriptors [3]. In this study, five different toxicity datasets that had been previously used for the development of QSAR and q-RASAR models were considered. We have developed hybrid ARKA models (consisting of a combination of QSAR descriptors and ARKA descriptors). These hybrid feature spaces were used to compute RASAR descriptors and develop ARKA-RASAR models. We have used the same modeling strategies (Partial Least Squares and Multiple Linear Regression) used to develop the previously reported QSAR and q-RASAR models for a fair comparison. In addition, these modeling algorithms are simple, reproducible, and transferable. The multi-criteria decision- making statistical approach, the Sum of Ranking Differences (SRD), inferred that the ARKA- RASAR models are the best-performing models, considering training, test, and cross-validation statistics. The least significant difference procedure ensures that the SRD values were significantly different for most models, presenting an unbiased workflow. The promising results and the ease of computation of ARKA and RASAR descriptors using our tools suggest that the ARKA-RASAR modeling framework may be a potential choice for developing highly robust and predictive models for environmental toxicity data gap filling.

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ON OUR UNDERSTANDING OF AGING, PERSONALIZED MEDICINE AND GERIATRIC CARE

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The technological revolution being witnessed today largely owes to the emergence of Artificial Intelligence, and particularly machine learning, which has impacted the pharmaceutical and health care industries very significantly. The ability to ask scientific questions was greatly enhanced due to the new roads made by intelligent technologies, especially with the advent of Generative AI and large Language Models (LLMs). In this talk, I would like to bring the recent advances made in the areas of aging and personalized medicine with case studies and ongoing work from our group. Some of the fundamental questions on aging, metabolic disorders, degenerative diseases, and geriatric care will be addressed. Importantly, how these questions can be effectively addressed by using AI and ML approaches will be explained.

A NOVEL DRUG DESIGN APPROACH: QUANTITATIVE STRUCTURE-INTERACTION ACTIVITY RELATIONSHIP (QSIAR) IN ANTI-TUBERCULAR AGENTS

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Computer-Aided Drug Design (CADD) is an important tool in drug discovery, encompassing both Ligand-Based Drug Design (LBDD) and Structure-Based Drug Design (SBDD). In recent years, SBDD has gained prominence due to advancements in molecular biology, including genomics, proteomics, and the availability of structural data on novel drug targets. A key component in analysing SBDD results is the docking score, which evaluates the interactions between a molecule and the target protein. However, docking scores often do not correlate with the observed biological activity. This discrepancy can be attributed to the limitations of scoring functions used in docking algorithms, which frequently overlook important factors such as entropy changes, solvation effects, and critical interactions that contribute to binding affinity. These factors limit the accuracy of predicted binding energy changes, leading to poor correlations between docking scores and actual biological activity. To address these challenges, a novel approach known as Quantitative Structure Interaction Activity Relationship (QSIAR) has been introduced. This approach considers the specific interactions between a ligand and the amino acid residues at the active site, treating them as independent variables, while the biological activity is treated as the dependent variable. In quantitative terms, this method can explain the observed anti-tubercular activity, such as the inhibition of mycobacterium ATP synthase, across various compounds, including 4-substituted amino sulphonyl-2-methyl-7-chloroquinolines, bisquinolines, imidazo[1,2-a]pyridine ethers, and squaramides. The developed and validated quantitative models have led to the identification of novel lead compounds through virtual screening of focused libraries, offering promising candidates for the development of new anti-tubercular agents.

COMBINING MACHINE LEARNING AND STRUCTURE-BASED APPROACHES FOR THE EFFICIENT IDENTIFICATION OF NOVEL BIOACTIVE SCAFFOLDS

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Drug discovery and development is a long and costly process, with high attrition rates. Machine learning and artificial intelligence can contribute to streamlining the development cycle by intervening in various stages, including bioactive scaffold identification, hit-to-lead and lead optimization campaigns, and the design of clinical studies.

In this talk, we present the computational workflow we developed at the National University of La Plata (Argentina), a workflow that combines in-house supervised and unsupervised machine learning algorithms and structure-based approaches (molecular docking and, occasionally, molecular dynamics). Our workflow was designed to provide high efficiency and be compatible with limited computational infrastructure. However, it yields very high early enrichment rates in various small-, medium-, and large-scale experimental validation instances, including real-world applications in relevant environments, achieving confirmed hit rates in the range of 25 to 100 % across different molecular targets. We present concrete examples from the fields of antiseizure, antiparasitic, antiviral, and antibiotic drugs.

This study was supported by Agencia Nacional de Promoción de la Investigación, el Desarrollo Tecnológico y la Innovación PICTs 2021-0404 and 2021-0478, UNLP Project ID EX010 and CONICET PIP 2022-11220210100030CO.

STRUCTURE AND FUNCTIONING OF TRPV CHANNELS: INSIGHTS FROM MOLECULAR MODELING

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The human body possesses a remarkable system of molecular sensors – the TRPV (Transient Receptor Potential Vanilloid) ion channel subfamily, which function as highly sensitive thermo- and chemoreceptors. Located on sensory neurons and epithelial cells, these proteins are activated by elevated temperatures and specific ligands. For instance, TRPV1 is involved in sensations of heat and pain and evokes a spicy taste under the action of capsaicin – an active component of chili peppers. Thus, the temperature and taste sensations are closely connected at the molecular level. Apart from the above, TRPVs are involved in diverse physiological processes and are linked to chronic pain syndromes, neurodegenerative diseases, diabetes, hereditary channelopathies, etc. Temperature-insensitive TRPV5/6 mediate calcium homeostasis; their dysfunction promotes osteoporosis, nephrolithiasis, and epithelial carcinomas. The variety of TRPV functions makes them promising targets for a wide range of newly developed drugs, especially analgesic and anti-cancer compounds. This makes investigating the functioning and regulatory mechanisms of these channels relevant.

This work summarizes the results of the molecular modeling studies of TRPVs, which have been performed by our group in recent years. First, the properties of the ion conducting pore were examined in detail. Using the experimentally obtained conformational ensembles of TRPVs, it was shown that only three major states of the ion conducting pore exist that are common to the entire subfamily: α-closed, π-closed, and π-open. The closed states are distinguished by the conformation of the pore-forming helices, but both have hydrophobic patches at the surface of the activation gate – the pore region regulating the channel conduction, which is not permeable to water and ions [1]. The open gate forms a less hydrophobic environment, which favors pore hydration. A sophisticated analysis reveals highly heterogeneous water dynamics in the open pore. The curvature of the pore surface and polar residues reorganize water structure, promoting the permeation of ions through the hydrophobic gate in a fully hydrated state [2, 3].

The second focus of our studies is the ligand regulation of TRPVs, especially TRPV6. This receptor plays a crucial role in human cancer cell proliferation, making the development of effective channel inhibitors a significant topic in biomedicine. Here, we examine two small natural molecules: the phytoestrogen genistein and the phytocannabinoid tetrahydrocannabivarin (THCV). The combination of experimental methods and molecular modeling revealed that genistein functions as a pore blocker by binding to the channel and altering the structure of the TRPV6 activation gate [5]. THCV molecules do not block the pore; rather, they act as allosteric inhibitors that bind to portals connecting the pore to the membrane environment, which causes the channel transition to the α-closed state [6].

The presented results expand our understanding of TRPVs functioning, reveal new molecular mechanisms of TRPVs regulation, and provide new prospective molecular targets (binding sites) and molecular agents (ligands), opening new avenues for future therapeutic strategies and drug development. This work was supported by RSF grant 23-14-00313.

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A COMPUTATIONAL PIPELINE FOR ACCELERATING THE DESIGN OF GLYCOMIMETICS

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To accelerate the rational design of glycomimetic inhibitors, based on derivatization of a carbohydrate ligand, we introduce a computational pipeline that automates the creation and modeling of analogs, and computes their interaction energies. Putative glycomimetics are assembled by grafting small drug-like moieties onto the native carbohydrate scaffold, with the moieties chosen from a virtual library of more than 1,500 molecular fragments, selected for their synthetic accessibility. The method is illustrated for the case of glycomimetics, but is generalizable to any bound ligand. A genetic algorithm (GA) was developed to identify the most likely poses of the appended moieties in the receptor binding site. For validation, curated experimental datasets were assembled from the literature, consisting of 119 glycomimetics, with reported solution binding free energies, including 46 with corresponding high-resolution crystal structures of the glycomimetic complexes. These datasets were subdivided for protocol testing and "real-world" performance validation.

The GA search resulted in an average root-mean-squared deviation (RMSD) of 1.5 Å for the added moieties, compared to their crystallographic data. The GA-generated structures were then subjected to molecular dynamics (MD) simulation, and the performance evaluated for three post-MD approaches to computing interaction energies: the scoring function from AutoDock Vina-Carb, as well as the generalized Born and Poisson-Boltzmann surface area (GBSA/PBSA) implementations within the AMBER molecular mechanical (MM) force field. For the Test dataset of structures with reported energies, the highest coefficient of determination (R^2 = 0.67) was obtained with MM-PBSA when ligand conformational entropies were included. Current limitations of the protocol and experimental datasets are discussed.

This study was supported by the National Institutes of Health (R01 GM135473).

COMPUTER-AIDED ANTIMICROBIAL DISCOVERY: STRUCTURE–ANTIMICROBIAL ACTIVITY RELATIONSHIPS OF RECOMBINANT HOST DEFENSE PEPTIDES AGAINST DRUG-RESISTANT BACTERIA

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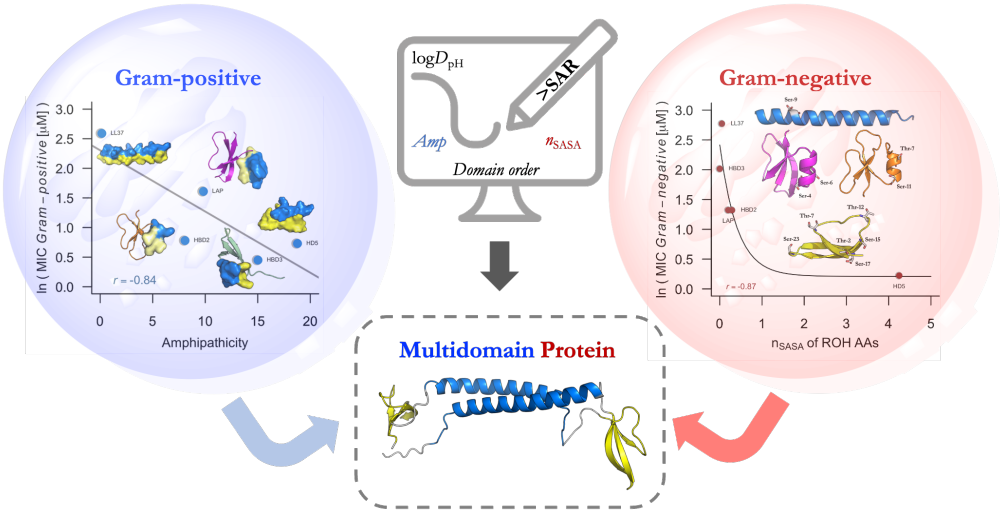
Host defense peptides (HDPs) represent a valuable class of antimicrobial agents with the potential to address the growing threat of antimicrobial resistance (AMR). Here, we have studied recombinant constructs based on combination of HDPs fused to the GFP protein and multidomain proteins combining three or four HDPs in a single polypeptide, referred as 1st and 2nd generation antimicrobials, respectively. These recombinant peptides were tested against Gram-positive and Gram-negative bacteria associated in healthcare infections. In addition, in silico studies provided insight into the antimicrobial structure-activity relationships of these biomolecules. For the 1st generation of antimicrobials, amphipathicity mainly explains the average antimicrobial activity against the Gram-positive strains. In the case of the Gram-negative bacteria, it depends on the quantity and the exposed area of the Ser and Thr amino acids. For the 2nd generation of antimicrobials, the order of domains is crucial to act against Gram-positive strains, preferably by positioning the most bioactive domain against the Gram-positive pathogen at the ends [1].



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ORAL PRESENTATIONS

THE NATURE OF ENTROPY-ENTHALPY COMPENSATION, EXOTIC ARRHENIUS PARAMETER AND KINETIC ISOTOPE EFFECT IN THE DENATURATION KINETICS OF PROTEINS

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Proteins in their native state are the key life agents having a unique functionality in the cells of all known organisms. The unfolding of a native structure, defined as denaturation, results in the loss of the proteins functionality, which can be followed by the death of the cells and organisms. The thermal heating is a most widely working factor of denaturation. Presented work is devoted to the analysis of the nature of several phenomena, being observed experimentally for the heat denaturation kinetics: enthalpy–entropy compensation (EEC) and exotic values of the Arrhenius parameters, which govern the temperature dependence of protein denaturation rate. The dissociation of polyglycine dimers into two monomer chains is considered as a model process for secondary structure unfolding of proteins. This process proceeds via breaking of interchain H-bonds between the polypeptide chains. The "completely loose" transition state (TS) model has been applied to calculate the Arrhenius parameters for the unfolding of dimers. The calculated results demonstrate EEC behavior for polypeptides of varied length and reproduce experimentally observed "exotic" Arrhenius parameters, which strongly depend on the length of unfolded chains (the number of breaking H-bonds). It is shown that EEC in solvated (hydrated, etc.) proteins is a direct consequence of EEC in proteins themselves.

Suggested model was also applied for the calculations of the Kinetic Isotope Effect (KIE) occurring upon H/D and other isotope substitution in the interchain hydrogen bonds . Heavy water D_2O is known to be an agent slowing the biological processes. The change of light water H_2O to D_2O is important for the health-related issues, including the storage of vaccines and other biological materials. The large amount of related data were reviewed recently in the monography by Chen [1]. On the basis of the experimental data, Li and Snyder hypothesized the supplement with deuterium and other heavy isotopes to promote longevity of different organisms, including the human ones [2]. The results of calculations show that KIE value for dissociation of one H-bond is small but cumulative effect of the big number of H-bonds, breaking in the unfolding process, provide large values of KIE, which provide very strong effect on the denaturation rate. It is shown that not only H/D, but $^{14}N/^{15}N$, $^{16}O/^{18}O$, and $^{12}C/^{13}C$ isotopic substitution can also provide observable values of KIE, that is in a good agreement with known experimental data.

The results of current work are presented in papers [3, 4].

This work was supported by the Russian Science Foundation, grant number 23-23-00275.

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REVOLUTIONIZING DRUG SAFETY ASSESSMENT VIA QSAR AND Q-RASAR BASED TOXICITY PREDICTION TO PROTECT HUMAN HEALTH

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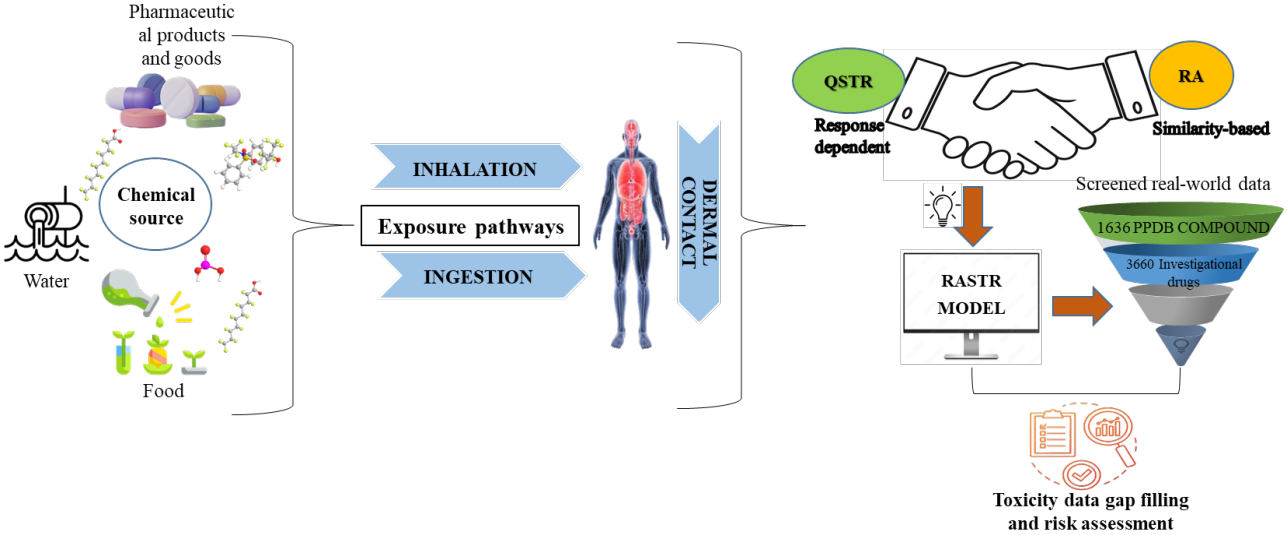
The extensive application of chemicals in the form of pesticides, cosmetics, drugs, etc., has been shown to adversely affect humans and the environment, mainly through food product residues and environmental exposure [1]. Exposure to diverse chemicals through various routes, including ingestion, inhalation, and dermal contact, is associated with multiple health risks, including endocrine disruption, cancer, and neurotoxicity. This study presents an advanced computational approach using quantitative structure-activity relationship (QSAR) and quantitative read-across structure-activity relationship (q-RASAR) models to predict the acute toxicity of diverse chemicals in humans, with the negative logarithm of the lowest published toxic dose (pTDLo) endpoint. We developed the first-ever predictive toxicity models combining QSAR and similarity-based read-across techniques to enhance accuracy, utilizing the TOXRIC database. The q-RASAR model outperformed traditional QSAR approaches, achieving robust statistical performance with internal validation metrics R^2=0.710, Q^2 = 0.658, and external validation metrics Q^2_{F1}=0.812, Q^2_{F2}=0.812, and $\Delta r^2_{m(test)}$=0.087, =0.741. The model identified key structural features, such as high coefficients and variations in similarity values among closely related compounds, the presence of carbon-carbon bonds at specific topological distances (5 and 8), and higher minimum E-state indices, all of which are linked to increased toxicity toward humans. The PLS-based q-RASAR model was further utilized to screen pesticides obtained from the pesticide properties database (PPDB) and 3660 investigational drugs from the DrugBank database for potential toxicants in humans, providing a tool to identify hazardous substances and mitigate risks. The developed models are instrumental in filling eco-toxicological data gaps and facilitating the development of novel, safe, and eco-friendly chemicals.



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ROLE OF INTERACTION FINGERPRINTS IN MACHINE LEARNING MODELS FOR SARS-CoV-2 Mpro INHIBITORS

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Interaction fingerprints (IFPs) are vectorised descriptions of protein-ligand contacts. Such 1D-encoding could be performed in different techniques, starting with each protein residue represented by several bits, one for each interaction type, and ending with deep learning embeddings of ligand surroundings. IFPs are widely employed in early drug discovery and design as a means of hit filtration (similarly to pharmacophore filtration) or descriptors for machine learning (ML) models. The latter allows one to improve the model's prognostic ability and could improve its applicability domain by infusing it with structural data.

ML requires large amounts of data, which could be hard to acquire in such field as medicinal chemistry, relying on time-consuming experimental procedures. Such data still could be accumulated when the demand is high, as we saw during COVID-19 pandemic. Previously we showed the benefits of systematic selection of protein structures for ensemble docking from all the ones available in PDB and how such virtual screening approach is able to advance the discovery of anti-coronaviral leads targeting the main protease (Mpro) [1]. Here we further used the data on the Mpro SARS-CoV-2 structure and activity of its inhibitors in order to explore the impact of ensemble docking-based IFPs on classification ability of ML models.

Three annotated libraries of Mpro inhibitors were used in the study: SMACC (225 actives, 6531 inactives), mostly consisting of the results of a large repurposing high-throughput screening; AA-Aug21 (754 actives, 451 inactives), composed from the data published in the scientific literature and COVID Moonshot Project; and AA-Feb21 (339 actives, 419 inactives), composed previously by us solely from the experimental data published in scientific literature regarding the activity against betacoronavirus Mpro [1]. All molecules were docked into the ensemble of Mpro SARS-CoV-2 structures with DOCK6.9. Simple interaction IFPs (SIF) and Protein–Ligand Extended-Connectivity IFPs (PLEC) were calculated using ODDT 1.0.9 for the best-scored protein-ligand complex of each structure in the ensemble. Morgan fingerprints, molecular weight, logP and docking scores were also used as descriptors. Random forest classifier model was selected based on previous studies. Grid search with stratified 5-fold cross-validation was performed to attune hyperparameters.

The ability of IFPs to improve the recall of actives compared to the models based only on Morgan fingerprints, appeared to depend heavily on the chemical space sampling in the training set. Repurposing data from SMACC, while ensuring high diversity, failed to provide enough examples of specific binders and actives in general, resulting in the prognosis instability of the models containing PLEC IFPs. Both AA-Feb21 and AA-Aug21 contain several analog series, since it is a common practice to publish a series of related molecules. Presence of specifically designed and tested inhibitors in the AA-Aug21 allowed to achieve high prognostic ability with F1 scores of 0.81 and ROC AUC of 0.78. The highest positive impact of PLEC IFPs infusion was achieved when the training was performed on the combined library, resulting in F1-score of 0.72 and ROC AUC of 0.98 comparing to F1 score of 0.65 and ROC AUC of 0.91 for the model including only Morgan Fingerprints and simple molecular descriptors.

Thus, description of the ligand binding modes with IFPs introduction to the ML models can improve recall only if provided with enough examples of specific binders in the training dataset. Otherwise, it reduces the classification ability of the model, with noisy interaction data of non-specific binders having a high impact on the prognosis. This observation questions the usefulness of repurposing screening data for development of ML models for virtual screening.

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CONSENSUS METHODOLOGY FOR DIRECTED SEARCH OF COMPOUNDS WITH ANTIMICROBIAL ACTIVITY AGAINST *S. AUREUS*

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The aim of the work was to develop a consensus methodology for predicting antimicrobial activity against *Staphylococcus aureus* using four different methods, as well as to conduct a directed search for promising compounds suitable for subsequent synthesis using this methodology.

The predictive dataset used is a database of 71 new 4(3H)-quinazolinone derivatives with an assumed antimicrobial activity of *S. aureus*. To evaluate the claimed activity, we applied four previously developed models: the novel architecture of fully connected convolutional neural network based on correlation convolution of multiple docking energy spectra [1], the convolutional feedforward neural network correlation based on multiple docking energies [2], the multidescriptor perceptron neural network model based on structural, physical and quantum chemical parameters [4], and also, an assessment based on a conservative strategy using the Testing73 module of the Microcosm IT system [3]. The neural network models were trained based on the local dataset of 284 structural analogs of the studied scaffold 4(3H)-quinazolinone and the verified database of 3768 antimicrobial substances with experimentally established levels of antimicrobial activity. The prediction of the antimicrobial activity of the new compounds was performed at the high or moderate level (pronounced activity, corresponds to the condition MIC<112.5 μg/ml). Compounds for synthesis were selected based on the energy value of the fully connected convolutional correlation neural network W_l for the moderate level of activity in the W_l range from 266.5 to 446.9, as well as on the presence of the consistent range of predictive estimates for the moderate level of activity by the other three methods. Generalization of predictive estimates allowed us to identify 14 promising structures among 71 new derivatives of 4(3H)-quinazolinone with moderate antimicrobial activity against *S. aureus* for further synthesis.

Thus, the consensus combination of several prediction methods enabled a directed search for promising derivatives of 4(3H)-quinazolinone with antimicrobial activity against *S. aureus* for further synthesis.

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AN INTEGRATED COMPUTATIONAL STRATEGY FOR PROFILING TERPENOID FOR DUAL-TARGET LEADS AGAINST *KLEBSIELLA PNEUMONIAE* PENICILLIN-BINDING PROTEIN 3 AND BETA-LACTAMASE

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The coexistence of altered or overexpressed penicillin-binding protein 3 (PBP3) and β-lactamases has led to a significant decrease in treatment success rates of *Klebsiella pneumoniae*. Targeting both proteins simultaneously could offer a robust strategy to overcome resistance in *K. pneumonia*e. Herein, a curated library of 147,953 terpenoids—renowned for their structural diversity and multi-targeting potential against bacterial pathways—was screened via structure-based pharmacophore modelling and molecular docking. Five terpenoids with higher binding tendencies for *K. pneumoniae* PBP3 and KPC-2 beta-lactamase were identified. These leads exhibited favourable pharmacokinetic, drug-likeness, and low toxicity profiles. The most promising leads (TP93780 and TP156670) demonstrated superior binding free energies (BFE) against *K. pneumoniae* PBP3 (–24.40 ± 5.20 and –23.46 ± 3.50 kcal/mol) and KPC-2 beta-lactamase (–15.38 ± 4.09 and –16.83 ± 3.75 kcal/mol) when compared to ceftaroline (–21.82 ± 8.64 kcal/mol) and clavulanate (–10.85 ± 34.40 kcal/mol), respectively. The energetics revealed that the promising leads were driven by balanced hydrophobic and moderate electrostatic interactions, compared to the polar-dominated binding profile of the reference standards. The post-molecular dynamics structural analysis revealed an enhanced overall stability of the TP93780 and TP156670 bound structures. The principal component analysis (PCA) revealed more constrained and localised motions in the bound structures compared to a wider range and distinct conformational states in the unbound structures. The favourable molecular orbital energies revealed from density functional theory analysis and the thermodynamically stable terpenoid-bound structures underpin their potential as dual modulators of K. *pneumoniae* PBP3 and KPC-2 beta-lactamase. Further *in vitro* studies are currently underway.

TRANSCRIPTOMIC PROFILING OF T CELLS IN 4T1 TNBC TUMORS

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Triple-negative breast cancer (TNBC) progression is accompanied by a profound immunological reprogramming of the tumor microenvironment (TME), transitioning from an early immune-active phase to a late immune-suppressed phase, and development of metastatic niches. Activated T cells are considered key players in maintaining the immunoactive status and tumor responsiveness to immunotherapies. However, as the tumor progresses, tumor cells generally induce an immunosuppressed state that is often characterized by T cell exhaustion and immunosuppression. These behaviors suggest that a temporal plasticity may exist in tumor cells, including T cells. We previously studied the plasticity of tumor cells (e.g., 4T1 TNBC cells) across different stages of tumor growth. However, the molecular plasticity of T cells *in vivo* remains poorly understood, which we aimed to investigate. To address this, we performed a transcriptomic analysis of 4T1 tumors (derived from the same batch of 4T1 cells implanted orthotopically into the mammary fat pad in female BALB/c mice) at 1 week (early), 3 weeks (intermediate), and 6 weeks (late) post-tumor implantation. Sequence quality was assessed using FastQC v.0.12.1, trimmed using Fastp v. 0.24.0, and then aligned to the GRCm39 genome using HISAT2, read counts using FeatureCounts, normalized using DESeq, and analyzed differentially expressed genes (DEGs). We further examined gene expression markers for T cells and T cell-related cytokines/chemokines and exhaustion/co-stimulatory factors. To understand the crosstalk between T cells and antigen-presenting cells (APCs), we also analyzed the signature genes for APCs, including dendritic cells (DCs), B cells, and macrophages. The expression of T cell-related genes declined from 194 genes at 1 week to 156 genes at 6 weeks, with late-stage loss of genes related to TCR diversity (TRBV2, TRBV16, TRBJ1-1, TRBJ2-1; $p<0.001$) and downregulation of genes for $CD8^+$ T cells at 3 weeks ($p<0.05$ vs. 1 week). Natural killer T (NKT) and gamma-delta (γδ) T cells displayed marked transcriptional contraction by 6 weeks ($p<0.0001$), indicating clonal restriction and functional exhaustion. Cytokine and transcription factor profiles indicated dynamic polarization of T cell subsets. For instance, early (1 week) IL-12α/β-STAT4 signaling ($p<0.01$) supported Tc1 responses; intermediate (3 weeks) IL-21 and BCL6 expression ($p<0.05$) suggested transient Tfc skewing; and late (6 weeks) AhR and IL-1β induction ($p<0.05$) reflected Tc17/Tc22 transition. Pro-inflammatory cytokines (IL-12α/β) and chemokines (CXCL9/10) were increased over time, while immunosuppressive mediators (e.g., IL-10, TGF-β3, IDO1) declined significantly at late-stage tumors ($p<0.05$). The reason for reduced immunosuppression at late-stage tumors is unclear. Interestingly, APC-T cell crosstalk also deteriorated at 6 weeks. For example, we observed a decreased expression of T cell co-stimulatory (CD28, $p<0.01$; ICOS, $p<0.001$) and antigen presentation genes at 6 weeks (CD74, H2-Aa, H2-Ab1; $p<0.001$), which coincided with a collapse in B-cell functional signatures ($p<0.0001$). Although an early dominance of M1-like macrophage polarization was observed (IL-12α/β, STAT1, CCL5, CXCL9), persistent expression of M2-associated immunosuppressive genes (ARG1, $p<0.0001$; CD163 and C3ar1, $p<0.001$) across all three stages suggests a stable tolerogenic niche despite a reduced IL-10 level at 6 weeks ($p<0.0001$). These findings highlight that TNBC progression is characterized by progressive T cell functional decline, loss of TCR diversity, and impaired APC-mediated activation that is accompanied by sustained macrophage-driven immunosuppression. These temporally coordinated immune shifts reflect possible tumor-driven adaptation toward immune evasion and metastatic facilitation, highlighting potential windows for stage-specific immunotherapeutic intervention.

A NOVEL STRATEGY TO OVERCOME PARPI RESISTANCE: TARGETING UBE2N WITH NON-COVALENT INHIBITORS

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Introduction. Ovarian cancer poses a major global health challenge, resulting in approximately 200,000 deaths annually. While Poly ADP-ribose polymerase inhibitors (PARPi) offer a promising treatment strategy, their effectiveness is primarily limited to patients with deficiencies in the homologous recombination (HR) pathway, affecting only about half of the patient population. This highlights a critical need for novel approaches to enhance PARPi efficacy and broaden its applicability in ovarian cancer. UBE2N, an E2 ubiquitin ligase, emerges as a promising target to improve the efficacy of PARPi therapy. This enzyme plays a crucial role in the HR pathway, a vital mechanism for DNA repair. By inhibiting UBE2N and disrupting the HR pathway, we aim to render ovarian cancer cells sensitive to PARPi treatment, allowing it to potentially benefit a wider range of patients. Our lab research demonstrated how UBE2N inhibition enhances ovarian cancer cell sensitivity to DNA-targeting drugs, particularly PARPi. While research on UBE2N inhibitors is in its early stages, there are promising options of covalent inhibitors like NSC697923 and BAY 11-7082, and non-covalent inhibitors like ML307 as well as Variabine B. However, none of these molecules have the necessary properties for pre-clinical or clinical development.This research aimed to develop novel, non-covalent UBE2N inhibitors to enhance PARPi effectiveness in ovarian cancer

Material and method. To identify potential UBE2N inhibitors, we utilized a combined structure- and ligand-based virtual screening approach, targeting the 19,000-compound CERMN Chemolibrary. The screening was based on three available UBE2N structures (PDB codes: 4ONM, 6UMP, and 3HCU), which capture distinct conformations of the flexible 114-124 loop. This loop, located near the active site residue Cys87, is critical for defining the shape and volume of the active site cavity. Conformational changes within the loop can therefore directly impact binding and potentially modulate the UBE2N activity. From the virtual screen, 22 compounds were selected based on interaction energy calculations and assessments of the stability of the compound-UBE2N complexes. These compounds, all targeting the UBE2N active site, underwent in vitro evaluation using SKOV3 ovarian cancer cells.

Results and discussion. Initial cytotoxicity assays demonstrated that 5 compounds significantly reduced cell viability. Further investigation using PARPi sensitization assays and clonogenic assays for colony formation identified 2 novel non-covalent UBE2N inhibitors that exhibited significantly higher potency than the known inhibitor ML307, particularly when combined with the PARPi Olaparib.

Conclusion. This study demonstrates, for the first time, successful PARPi sensitization using non-covalent UBE2N inhibitors, highlighting their potential to broaden PARPi therapy eligibility in ovarian cancer by enhancing tumor cell sensitivity to Olaparib. Future research will elucidate their precise mechanisms of action and assess their efficacy in overcoming established PARPi resistance.

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A CHEMINFORMATICS APPROACHES FOR THE IDENTIFICATION OF INHIBITORS AGAINST MACROLIDE 2'-PHOSPHOTRANSFERASE TYPE I

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Antibiotic resistance is a growing global health crisis that arises when bacteria develop mechanisms to resist the effects of drugs designed to eliminate them. One such mechanism involves the production of drug-neutralizing enzymes, such as macrolide 2'-phosphotransferase type I, which degrades macrolide antibiotics [1]. Therefore, the search for novel enzyme-targeted inhibitors is an alternative strategy for defending against resistant bacterial strains [2]. Thus, the objective of this study was to search for compounds that could inhibit macrolide 2'-phosphotransferase type I in *Escherichia coli* using a cheminformatics approach.

The 12,446 naturally occurring compounds contained in the NPASS database [3] were extracted. Through ADMET and physicochemical properties analysis (with the help of the web server Deep-PK, a deep learning for small molecule pharmacokinetic and toxicity prediction), those compounds likely to cause toxic effects (blocking hERG channels, carcinogenic, genotoxic, etc.), as well as those that did not exhibit drug-like properties, were discarded. Additionally, principal component analysis and plotting (PCA) were performed for the properties of these compounds (Fig 1).

After screening, 1,462 compounds were obtained, which were geometrically optimized with the MMFF94 force field with 10,000 steps using OpenBabel, and subsequently prepared for molecular docking analysis using the DockPrep module of the Chimera software, leaving the bridging hydrogens and adding charges using the AM1-BCC method. The target used was the macrolide 2-phosphotransferase type I enzyme from *E. coli*, which was obtained from the Protein Data Bank with the ID 5IGH. After obtaining the .pdb file, molecular dynamics in water were performed for 50 ns to obtain the optimal conformation of the protein. This conformation was used for molecular docking analysis with the help of the AutodockVina software.

Of the 12,446 compounds, 19 had binding affinities between -10 and -11.3 kcal/mol, with compound 1169 (Fig. 2) having the highest affinity (-11.3 kcal/mol); while azithromycin had an affinity of -7.2 kcal/mol.

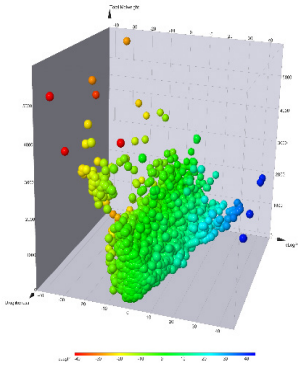

Fig 1. PCA plot of the properties of the NPASS compounds

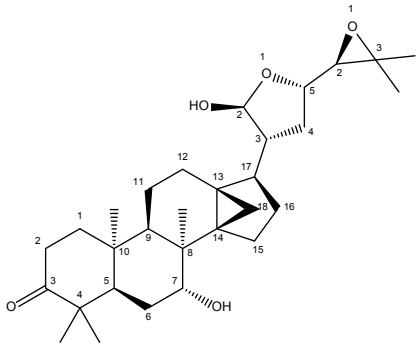

Fig 2. Lig1169

These preliminary results indicate that there are natural compounds that could act as potential inhibitors of this enzyme and restore the activity of macrolide-type antibiotics, particularly compound 1169.

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IRACEMA: A DATABASE MANAGEMENT SYSTEM FOR BIOACTIVE COMPOUNDS ISOLATED AND CHARACTERIZED BY BRAZILIAN RESEARCHERS

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Bioactive compounds, whether found in natural sources or synthetically produced, are substances with significant therapeutic potential due to their regulatory roles in metabolic processes. The discovery and elucidation of the chemical properties of these compounds have become strategically important for pharmaceutical innovation and healthcare advancement. Brazil, known for its rich biodiversity and strong expertise in organic chemistry, holds great potential for discovering bioactive molecules. The research and development of synthetic compounds, reinforced by various increasingly automated approaches, has driven a substantial grow in the amount of available chemical and biological data, transitioning between public and private sources. However, the fact that most research data is fragmented and difficult to access represents a significant challenge to efficient drug discovery and development[1].

The Brazilian scientific community has developed robust databases to hold information on natural products. These researches are following a global trend, creating solutions to organize and visualize data of compounds of interest, integrating modern tools for predicting molecular properties and descriptors. An example of these efforts is the creation of the BrNPDB (Brazilian Biodiversity Natural Products Database) and the SistematX (SISTEMAT eXtended Webservices. However, the landscape for synthetic compounds has been underdeveloped.

To address these challenges and establish the first comprehensive database of bioactive compounds isolated and characterized in Brazil, the IRACEMA (Innovative Research, Analysis and Computational Exploration of Molecules Assembled in Brazil) project was conceived. It aims to give national and international visibility to Brazilian researchers and facilitate collaboration within research groups by updating the Brazilian synthesis landscape. This platform integrates advanced cheminformatics tools for molecular analysis, including physicochemical and ADME properties prediction (e.g., pharmacokinetics and druglikeness), as well as insights into mechanisms of action through the manual curation of biological activity data from the literature. By combining chemical, physical, and biological data with predictive modeling capabilities in a user-friendly web interface, IRACEMA facilitates the exploration of structure-activity relationships and drug-like properties.

The project's technical architecture employs modern web technologies for both frontend (React) and backend (NestJS/Node.js and Python/Flask microservices) development. The system integrates specialized cheminformatics tools to deliver an interactive platform for molecular visualization and analysis, with PostgreSQL and Prisma ensuring robust data management. By overcoming these challenges, the IRACEMA database (available on https://iracema.fcf.usp.br/) strengthens Brazil's position in bioactive compound research and fosters innovation in medicinal chemistry by democratizing access to data and bridging the gap between academic discoveries and real-world applications.

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DEVELOPMENT OF A VIRTUAL SCREENING PIPELINE FOR THE DISCOVERY OF NOVEL SARS-COV-2 MPRO INHIBITORS

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The COVID-19 pandemic underscored the critical need for rapid therapeutic development. A prime drug target for SARS-CoV-2 is the main protease (M^{pro}), an enzyme essential for viral replication. Inhibiting M^{pro} effectively halts the virus's life cycle, making it a compelling target for antiviral drugs. While experimental drug screening is powerful, it remains resource-intensive and time-consuming. Virtual screening allows for the efficient prioritization of the most promising candidate molecules from millions of possibilities before they ever reach a lab.

In this work, we developed and applied a robust virtual screening pipeline specifically designed to discover novel M^{pro} inhibitors. Our integrated workflow combines QSAR modeling, molecular docking, ADMET property filtering, molecular dynamics simulations, MM-PBSA and mBAR calculations to computationally screen large compound libraries.

For QSAR modeling, we investigated a diverse set of machine learning algorithms. Crucially, we explored multiple descriptor sets and rigorously applied feature selection techniques during model optimization to identify the most relevant molecular features. This approach allowed us to select the top-performing, most generalizable model for the initial virtual screening phase.

To complement the ligand-based approaches, we implemented a structure-based virtual screening strategy that employs molecular docking. To overcome the limitations of standard scoring functions, we developed a target-specific scoring function for M^{pro} that integrates machine learning-based scoring functions to enhance the binding affinity prediction accuracy.

The top-ranking virtual hits were filtered based on the calculated ADMET properties to ensure drug-likeliness and favorable pharmacokinetic profiles early in the discovery process. The most promising candidates were subjected to molecular dynamics (MD) simulations to evaluate the stability of the protein-ligand complexes and estimate the binding free energies with the MM-PBSA method. The entire protocol was validated on known M^{pro} inhibitors to confirm its predictive accuracy.

For the most promising complexes we employed the Bennett Acceptance Ratio (mBAR) method, a rigorous statistical mechanics approach, to obtain high-precision estimates of the absolute binding free energies. This provided a robust and accurate ranking of the best compounds.

In conclusion, our approach, validated against known experimental data and adjusted for the specific target, demonstrates a significant advancement over standard virtual screening protocols. The pipeline has successfully identified several novel potential hit compounds. Future work will focus on the experimental validation of the top-ranked compounds and further structural optimization of confirmed hits.

This work was supported by the State Assignment of the Department of Chemistry, Lomonosov Moscow State University (project no. 121021000105-7).

STUDYING THE ALLOSTERIC COMMUNICATION IN BIOMOLECULES USING INFORMATION THEORY

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Intramolecular communication is the crucial internal mechanism that regulates functioning of biomolecules within the cell. Specifically, when an effector binds to an "allosteric" site, which is spatially distant from the active site of a protein, it can cause a change in the configuration of the active site and subsequent modulation of the protein activity due to communication between these two sites within the molecule, known as "allostery" [1].

We propose a systematic information-theoretical approach to studying intramolecular communication, which is implemented as the ARTEMIS software package (https://github.com/nalsur-veallam/ARTEMIS). The method is based on the analysis of mutual information (MI) between all pairs of amino-acid residues within a protein. MI data is derived from all-atom molecular dynamics (MD) simulations in the microsecond range using the PARENT software [2].

Here, we illustrate capabilities of ARTEMIS on the example of the platelet-derived growth factor alpha receptor (PDGFRα) and its variants with modulated signaling function in the cell: the pathological mutant V536E [3] and "truncated" version of the receptor without extracellular domains. Specifically, the V536E point mutation [3] and the deletion of the extracellular region resulted in the receptor activation in the absence of a ligand. Therefore, comparative analysis of these receptor variants allows identification of potential patterns in intramolecular communication, which are connected to the receptor activation and signal transduction.

For each variant of the PDGFRα, two independent replicas of 1 μs MD trajectories were analyzed. Through the analysis of the all-to-all MI matrix, highly connected positions (residues) in the protein were identified that allows construction of a mechanistic model of communication within the receptor. It was demonstrated that communication between extracellular (ligand binding) and intracellular (catalytic) domains primarily takes place through a single helix in the transmsembrane domain (TMD). Moreover, analysis of the MI matrix indicates that the intracellular domains in the truncated receptor are synchronized the most, whereas in full-length receptors, their communication is coupled to the extracellular domains. In addition, in the wild type receptor, the catalytic domains exchange information with the "active" TMD helix, while this effect is significantly reduced in the mutant. Therefore, we propose that the V536E point mutation in TMD disrupts the information transfer between the extracellular and intracellular receptor domains, leading to impaired signal transduction within the receptor.

The work was supported by the Russian Science Foundation, grant 23-14-00313.

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HOW FLAVONOID PARAMETERIZATION DETERMINES DRUG-INDECED MEMBRANE BIOPHYSICAL OUTCOMES

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This study aimed to systematically assess how the choice of molecular parameterization strategies for small molecules—specifically flavonoids—impacts the predictive power of molecular dynamics (MD) simulations in modeling flavonoid action on membrane biophysical properties. By directly linking simulation outcomes to experimental *in vitro* measurements, the research addresses a critical question in computational biophysics: can current automated parameterization protocols adequately capture subtle drug–membrane electrostatic and elastic interactions, or is quantum mechanics (QM)-guided parameter refinement required for accuracy?

While MD simulations are widely used to explore membrane-drug interactions at the atomic level, prior work has largely focused on membrane structure, thickness, and ordering, with limited direct comparison to experimentally determined membrane dipole potential changes. Previous studies have also relied predominantly on automated force field parameterization tools, potentially overlooking crucial molecular features essential for reproducing experimental trends in electrostatics. This study is the first to systematically contrast the CHARMM General Force Field (CGenFF), an automated parameter generation framework, with the QM-based Force Field Toolkit (ffTK) approach, benchmarking each against detailed *in vitro* data for three representative flavonoids—baicalein, chrysin, and luteolin.

Flavonoid parameters generated with ffTK using QM data produced MD simulation results that reliably matched experimental changes in membrane dipole potential, area per lipid, and lipid acyl chain order parameters across all three flavonoids studied. In contrast, automated CGenFF parameters were only able to recapitulate the experimental membrane effects for luteolin, but not for baicalein or chrysin. The source of this discrepancy was traced to differences in the distribution and magnitude of atomic partial charges and dihedral force constants: ffTK parameterization yielded more accurate dipole moments and conformational flexibility, improving agreement with *in vitro* results.

The superior performance of QM-refined parameters was evident in both electrostatic (membrane dipole potential) and elastic (order parameter) membrane properties. By providing a rigorous framework for benchmarking MD outputs against experimental data and demonstrating the necessity of QM-based parameter refinement, this work substantially advances the predictive power and interpretability of computational studies on drug–membrane interactions. This framework can be broadly applied to diverse classes of bioactive small molecules, enhancing the utility and accuracy of MD simulations in pharmaceutical, membrane biophysics, and computational chemistry research.

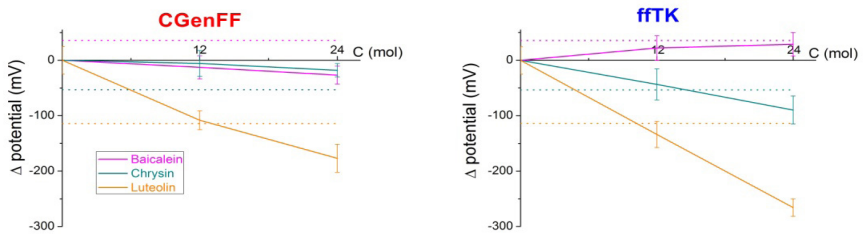

Figure. Dependence of changes in the system potential of the DOPC bilayer on membrane concentration of baicalein (*magenta*), chrysin (*dark cyan*), and luteolin (*orange*). The left graph shows the results for molecules parameterized with CGenFF, and the right graph shows the results for ffTK. *In vitro* changes in the membrane boundary potential (Δφb) at a saturation concentration (80 μM) are indicated by dashed lines.

This study was supported by the Russian Foundation of Science No. 25-14-00162.

SEARCH FOR MONKEYPOX VIRUS 2′-O-METHYLTRANSFERASE INHIBITORS BY MOLECULAR MODELING

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Monkeypox (mpox) is an infectious disease caused by the monkeypox virus (MPXV) [1]. Until recently, mpox was restricted to Central and West Africa [2]. However, two global outbreaks of the disease have now occurred. The first, in 2022, affected more than 120 countries and accounted for over 99,000 reported cases. In 2024, a second outbreak emerged, with over 15,600 confirmed cases and 537 associated deaths in Africa. Consequently, on August 14, 2024, the World Health Organization declared mpox a Public Health Emergency of International Concern for the second time.

Currently, there are no approved drugs against mpox [1,2]. In general, only symptomatic and supportive therapy is provided, and antiviral treatment is used only in severe cases. Several vaccines against mpox have been approved and may effectively prevent infection or cure patients with mild disease, but not critically ill patients. Therefore, the development of an antiviral drug against mpox is a pressing challenge. Such drugs are developed on the base of inhibitors of therapeutic target proteins.

In this study, inhibitors of the 2′-O-methyltransferase (MTase) [3] of MPXV were identified using molecular modeling methods.

As a first step, the selection and structural modeling of a suitable therapeutic protein target were required. The choice of such a target remains a matter of debate within the scientific community. Based on scientific literature and the atomic-molecular structures of proteins available in the PDB, 2′-O-MTase was selected for the study. Several protein models were constructed using different methods, and the model with the best native docking results was selected for subsequent analysis. These best results were achieved only with high parameters of the docking genetic algorithm (GA). Docking of one ligand with high GA parameters required approximately 20 times more CPU time than with standard GA parameters.

At the next stage, virtual screening of the Voronezh State University database (more than 16,000 compounds) was performed using Lomonosov-2 supercomputer. For each of the 30,349 conformers of these compounds, docking was performed using the SOL program [4] at the high GA parameters. Based on the SOL program's scoring function (assessment of the binding free energy of inhibitors to the protein), 198 best compounds were selected for further quantum chemical post-processing. Using the MOPAC program [5], the protein-ligand binding enthalpy was calculated using the PM7+COSMO method, and the hydrogen bonds between the protein and ligand atoms were calculated using the PM7 method.

Virtual screening identified 20 of the most promising inhibitor candidates for 2′-O-MTase MPXV. An experimental estimation of their antiviral activity in cell culture is planned. Experimentally confirmed inhibitors may serve as a basis for the development of direct-acting drugs against MPXV.

The young scientist E. Mandrygina is a scholarship holder of the Theoretical Physics and Mathematics Advancement Foundation "BASIS". The study was conducted under the state assignment of Lomonosov Moscow State University.

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COMPUTER MODELING OF SUPRAMOLECULAR CHEMICAL SYSTEMS PROPERTIES AND REACTIVITY AND ITS POTENTIAL IMPACT IN COMPUTER-AIDED DRUG DISCOVERY

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Computational chemistry is a powerful tool for conducting scientific research in chemistry and computer-aided drug design, which can help experimentalists with establishing the structure and studying the reactivity (and activity) of various substances and its supramolecular associates.

This report is devoted to presentation and brief discussion of the results of my scientific research in the field of computer modeling and theoretical studies of various organic/inorganic/organometallic chemical compounds and their reactivity to a greater or lesser extent relevant to drug design and discovery of pharmaceutically valuable substances (e.g., various N/O/S-heterocyclic compounds as ligands and their platinum complexes).

Formally, three main directions of my research discussed in this report could be distinguished: mechanisms, driving forces, kinetics, and thermodynamics of chemical reactions; catalysis; nature and strength of various noncovalent interactions in supramolecular chemical systems.

My studies includes modeling of charge distribution (e.g., Hirshfeld atomic charge, Voronoi deformation density atom population, Mulliken atom and basis function population analysis, Lowdin atom and basis function population, Becke atomic charge with atomic dipole moment correction, electrostatic surface potential fitting atomic charge, AIM atomic charge, etc.), analysis of natural bond orbitals and charges in the framework of the Weinhold's theory (NBO), bond order analysis (e.g., Mayer bond order analysis, Wiberg bond order analysis, Mulliken bond order analysis, Fuzzy bond order, Laplacian bond order, Intrinsic bond strength index, etc.), topological analysis of electron density distribution (within the general methodology "quantum theory of atoms in molecules" (QTAIM) using additional methods: reduced density gradient (RDG) analysis; electron localization function (ELF) analysis, localized orbital locator (LOL) analysis, etc.), visualization of weak interactions (for example, Noncovalent Interaction (NCI) analysis, Density Overlap Regions Indicator (DORI) analysis, Independent Gradient Model (IGM) analysis, Interaction Region Indicator (IRI) analysis, visualization of van der Waals potential, etc.), investigation of the influence of crystal packing effects on the structure of isolated molecular clusters stabilized by weak interactions using Hirshfeld surface analysis, calculation of molecular electrostatic potential, and identification of areas most susceptible to nucleophilic/electrophilic/radical attacks, calculation of Fukui functions; estimation of adiabatic and vertical dissociation energies of supramolecular assemblies and covalent/coordination bonds in chemical compounds.

Potentially, all these computational chemistry techniques could be applied for computer-aided drug design and discovery the nature and properties of pharmaceutically valuable compounds, and all researchers from both academia and/or industry are more than welcome to collaboration!

For my recent publications please see: https://scholar.google.ru/citations?user=n_rBOQcAAAAJ

My research has been supported by the RUDN University Scientific Projects Grant System, project № 021342-2-000.

TRANSCRIPTOMICS-BASED DRUG REPURPOSING OF SP600125 TO TARGET PRONEURAL-MESENCHYMAL TRANSITION IN GLIOBLASTOMA

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Glioblastoma multiforme (GBM) is the most aggressive type of brain tumor. Despite the use of combination therapy, including surgical resection, radiotherapy, and temozolomide chemotherapy, the median survival time after diagnosis remains approximately 15 months. One major challenge in treating GBM is its highly invasive growth into surrounding healthy brain tissue. Transcriptomic studies have classified GBM into three molecular subtypes: classical, proneural, and mesenchymal. Tumor cells can transition between these subtypes, particularly through the proneural-mesenchymal transition (PMT). PMT is accompanied by several cellular changes that enhance invasiveness, such as altered cell morphology, increased migration, elevated expression of mesenchymal markers, and the formation of pseudo-blood vessels (vasculogenic mimicry). Targeting PMT is difficult due to its regulation by a complex and stable network of signaling interactions. However, such challenges can be addressed through omics-based approaches. Our work aims to repurpose small molecule compounds to inhibit PMT by applying the connectivity map strategy. To achieve this, we analyzed RNA-Seq data from two datasets: TCGA-GBM (comprising 168 GBM patients) and GSE192710 (containing G7 mesenchymal GBM and E2 proneural GBM cell lines). We calculated a PMT score for patient GBM samples using gene set enrichment analysis (GSEA) focused on proneural and mesenchymal gene signatures. Weighted gene co-expression network analysis (WGCNA) identified 21 co-expressed gene modules, of which a module containing 694 genes, designated “blue”, showed expression levels positively correlated with the PMT score. Additionally, we identified 3,718 differentially expressed genes (DEGs) with higher expression in G7 mesenchymal cells compared to E2 proneural cells. Using the STRING database, we constructed a protein-protein interaction network from these DEGs. By intersecting this network with the “blue” module, we focused on 160 overlapping DEGs and identified 30 hub genes using the cytoHubba plugin in Cytoscape. These hub genes were included in the PMT signature. We then compared the PMT signature with expression profiles from tumor cells treated with approximately 3,000 small molecule compounds using the Connectivity Map platform, which yielded 120 candidates potentially capable of inhibiting the PMT signature. To narrow down hit compounds, chemoinformatics tools (AlzPlatform, PreADMET, LiverTow, SwissADME, and ADMETlab) and text mining via LitSense were applied using three criteria: (1) ability to cross the blood-brain barrier, (2) absence of P-glycoprotein substrate specificity, and (3) documented inhibition of epithelial-mesenchymal transition (EMT) in the literature. Five hit compounds, including SP600125, vemurafenib, FG-7142, dibenzoylmethane, and phensuximide, were mapped onto the PMT gene network using the STITCH database. Among these, SP600125 showed the strongest connection to hub genes according to cytoHubba. We validated the inhibitory effect of SP600125 on PMT *in vitro* using the U87 GBM cell model: SP600125 suppressed PMT induced by transforming growth factor beta 1 (TGF-β1) or cobalt chloride ($CoCl_2$)-simulated hypoxia by inhibiting morphological changes, cell migration, vasculogenic mimicry, and the expression of mesenchymal markers fibronectin, N-cadherin, and Slug.

Our analysis demonstrates, for the first time, that transcriptomic data combined with connectivity mapping are an effective approach to identify inhibitors of PMT. Among the hit compounds, SP600125, emerged as a promising candidate for further investigation as a therapeutic agent or as a lead for developing derivatives with enhanced anti-PMT activity.

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STEROIDAL PREGNANES AS NOVEL 11β-HSD1 INHIBITORS: INSIGHTS FROM MACHINE LEARNING–BASED QSAR AND MOLECULAR MODELING

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11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) catalyzes the conversion of inactive cortisone to active cortisol, contributing to insulin resistance, obesity, and type 2 diabetes mellitus (T2DM). Despite its therapeutic significance, existing 11β-HSD1 inhibitors suffer from limited potency, poor selectivity, and suboptimal pharmacokinetics, restricting clinical success. This study aimed to identify novel steroidal pregnane scaffolds as potential 11β-HSD1 inhibitors using an integrated computational strategy. Machine learning (ML)-based quantitative structure–activity relationship (QSAR) models were constructed with curated ChEMBL bioactivity data. Of 42 algorithms tested, the Random Forest Regressor (RFR) demonstrated the best predictive performance. A steroidal pregnane library was subsequently screened using the validated RFR models, yielding 1,112 high-confidence hits based on predicted pIC_{50} and pKi values. Structure-based virtual screening identified three top candidates: Pregnane-3,20-diol disulphate (P1, -11.4 kcal/mol), 20-Piperidin-2-yl-5α-pregnan-3β,20-diol (P2, -10.9 kcal/mol), and 12,20-di-O-benzoyl-pregnane-3β,12β,14β,20-tetraol (P3, -10.9 kcal/mol), all outperforming the reference inhibitor carbenoxolone (–10.5 kcal/mol). These ligands engaged key catalytic residues (Ser170, Tyr177, Tyr183, Lys187) in the 11β-HSD1 active site. Molecular dynamics simulations confirmed stable ligand–protein complexes over 100 ns with favorable dynamic parameters. The MM/GBSA binding free energy calculations revealed stronger binding affinities for P1 (-43.58 kcal/mol) and P3 (-44.95 kcal/mol) compared to carbenoxolone (-24.19 kcal/mol). Cluster analysis further validated stable binding conformations. Additionally, the lead compounds exhibited favorable physicochemical and pharmacokinetic profiles. Collectively, this work highlights steroidal pregnane scaffolds as promising 11β-HSD1 inhibitors with drug-like properties, warranting preclinical evaluation and rational optimization for antidiabetic nutraceutical and drug development.

HARNESSING BIOINFORMATICS FOR HPV THERAPEUTICS: ENHANCED DRUG REPURPOSING, PROTEIN HOMOLOGY, AND COMPREHENSIVE DATA MINING FOR TARGETED TREATMENT DEVELOPMENT

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Predictive modeling and computational repurposing of drugs may significantly accelerate the discovery of efficacious treatment molecules for Human Papillomavirus (HPV). In this study, we constructed a robust bioinformatics pipeline incorporating advanced methods, including deep learning, statistical filtering, and cheminformatics, to systematically screen lead therapeutic molecules against HPV [1]. Our approach began with the initial screening of compound data by some bioactivity classes and available IC_{50} values. The IC_{50} value is the concentration of a drug to inhibit a biological process by half and hence is a critical measure through which the potency of a drug can be assessed. Second, we computed descriptors using software packages such as RDKit and PaDEL. This step was of utmost significance in studying critical molecular features such as molecular weight, hydrogen bonding capacity, and the partition coefficient logarithm (LogP), which reflects a compound's hydrophobicity. To normalize the data set to allow for proper comparisons, IC_{50} values were transformed into their logarithmic equivalent, pIC_{50}, which provides a more normalized measure to assess compound activity. Our large-scale statistical analyses showed significant differences between the characteristics of active and inactive compounds. Active compounds tended to have larger LogP values, molecular weights, and hydrogen bonding capacities. These characteristics are likely to enhance the binding affinity of a compound to biological targets in the HPV pathway. We employed a fully connected neural network that used the PubChem database structural fingerprints. The neural network provided a high Pearson correlation coefficient of $r = 0.87$, with strong predictive capability for binding affinities. Nineteen of the 39 test compounds, a subpopulation of the compounds, displayed outstanding predicted affinities with pIC_{50} of 8.1 to 8.4. The findings illustrate the potential of the compounds to be repurposed as powerful therapeutics against HPV. Interestingly, our model did not experience much overfitting, suggesting that it can generalize to unseen data and provide similar performance metrics during training [2]. The findings of this study reveal the high potential of applying integrated computational methods in compound prioritization for subsequent biological screening. This strategy allows for the accelerated identification of drugs and can effectively provide new therapeutic agents for HPV. Compounds with high predicted affinities are prioritized, aiming to advance drug development in early-stage drug discovery with probable long-term consequences of successful treatments for HPV-related diseases.

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DEEP LEARNING CONVOLUTIONAL CORRELATION NEURAL NETWORK BASED ON MULTIPLE DOCKING FOR IDENTIFYING PHARMACOLOGICALLY ACTIVE COMPOUNDS

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Multiple docking methodology, in combination with feedforward neural network technology, can be effectively applied to the discovery of pharmacologically active compounds [1]. However, in the search for multitarget compounds in the case of complex systemic types of pharmacological activity, this approach becomes computationally expensive. The use of deep learning convolutional neural networks can significantly optimize the task. In this study, a classification program based on an artificial neural network was developed, implemented using the PyTorch library [2] and designed to analyze correlation convolutions of affinity matrices of biologically active compounds obtained as a result of multiple docking. The purpose of the classification is a binary separation of compounds by the severity of pharmacological activity. Models were built to predict the anxiolytic activity of chemical compounds based on multiple docking in 22 relevant target proteins and antimicrobial activity based on docking in 10 proteins associated with S. aureus. The network architecture includes two hidden layers with enumeration of the number of neurons according to the bottleneck principle from 3 to 21 and from 3 to 9, depending on the activity under study. In this case, the activation functions from the set are sorted out for hidden layers: identity, logistic, tanh, exponential, relu, leaky_relu. The output activation function is softmax. CrossEntropyLoss is used as a loss function. The program provides support for two optimizers: Adam (backpropagation of errors) and BFGS (gradient descent), with the ability to adjust the learning rate, as well as the number of epochs. During training, the input data set is randomly divided into three subsamples: train_set, test_set, validation_set in a ratio of 70, 15, 15%, respectively. The best model is selected based on the minimum value of the loss function on validation_set. A ROC curve is plotted for the selected model and the Acc, Sens, Spec values are calculated for all subsamples. The program supports calculations on both CPU and GPU, automatically detecting available devices.

Currently, the parameters of the best model for predicting pronounced anxiolytic activity are: MLP (22-3-4-2, leaky_relu); Train: Acc=70%, Sens=87%, Spec=53%; Test: Acc=62%, Sens=81%, Spec=43%; Validation: Acc=68%, Sens=95%, Spec=40%; AUC_{ROC}=68%. The parameters of the best model for predicting pronounced antimicrobial activity are: MLP (10-4-9-2, relu); Train: Acc=92%, Sens=99%, Spec=62%; Test: Acc=84%, Sens=94%, Spec=38%; Validation: Acc=93%, Sens=100%, Spec=63%; AUC_{ROC}=98%.

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TOOL FOR DIVERSITY VISUALIZATION ON THE LEVEL OF MOLECULAR SCAFFOLDS, TDV: CHEMICAL DATA AT GLANCE

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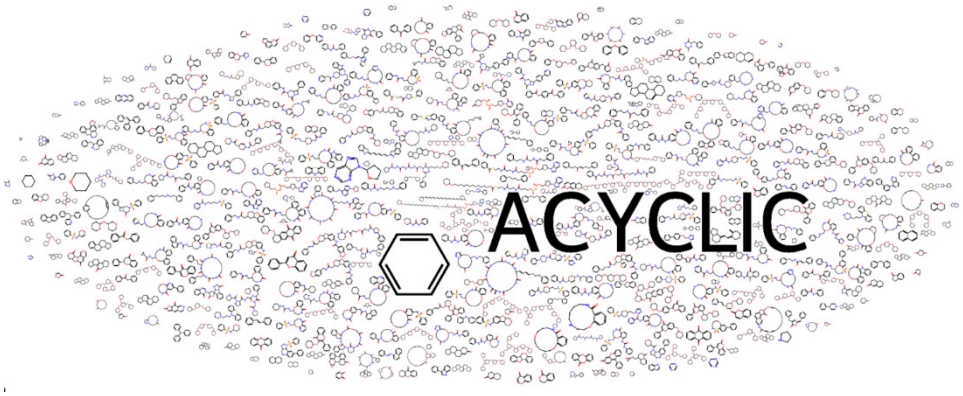
The recent growth of the available chemical data both in terms of their volume and complexity demands novel computational tools applicable to them for the purpose of the investigational data analysis. Here, we present freely available Tool for Diversity Visualization on the level of molecular scaffolds (TDV) allowing researcher to a) enumerate and visualize molecular scaffolds [1] present in the dataset consisting of up to 10k chemical structures b) use visualization as interactive interface for chemical dataset's filtering using scaffolds and biological activities or other properties (numeric values or strings).

TDV is based on the functionality of the RDKit library [2], simple approach to the assessment of diversity as the function of numbers of objects belonging to the different classes, an idea to increase the information content of the bar plot using graphical depiction of objects on 2D plane instead of simple bars on the line, which was first applied to the biological sequences by [3], to the texts in general by [4] and to the chemical structures by [5] (first – to the authors' knowledge); and original JavaScript-based realization of this approach. Also, ChEMBL [6] and PubChem [7] data combined were used to set up the baseline of the chemical diversity. An example of the TDV output for the random subset of ChEBI [8] data of 10k records (https://www.ebi.ac.uk/chebi/, accessed on 29.08.2025) is provided below.



TDV is freely available at https://www.way2drug.com/tdv/
Code is available at https://github.com/RSF-23-73-01058

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DO-NO-HARM MOLECULAR GENERATION: 12-MODEL BENCHMARK AND KRAS G12D CASE STUDY

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Popular molecule-generation benchmarks — GuacaMol [1], MOSES [2] — focus on distributional metrics (validity, uniqueness, novelty, FCD, simple goal-oracles) and light filters, which provide limited guidance for medicinal-chemistry decisions. We present a practice-driven benchmark that ranks models by their ability to propose molecules that are chemically valid, synthetically feasible, and plausible binders for a defined target.

We introduce Do-No-Harm-Molecular Generation (DNH-MolGen), a decision-oriented evaluation that mimics medicinal-chemist triage. Each generated molecule is scored through five concrete stages: (i) physicochemical descriptors: remove chemically out-of-scope candidates with descriptors (e.g., logP, TPSA), and evaluate novelty–complexity context via MCE-18 metric [3]; (ii) medicinal-chemistry structural alerts: apply rule-based sanitization (e.g., PAINS, Lilly MedChem Rules, MCF) to remove reactive, toxic, assay-interfering motifs; (iii) synthetic feasibility: calculate synthesizability estimators (e.g., SA score, RA score, SYBA score), and find synthesis path from purchasable precursors via AiZynthFinder [4]; (iv) docking to KRAS G12D 05C pocket: as a first-pass proxy for target engagement, estimate compatibility with specified binding site using gnina docking-tool; (v) formalized medicinal chemists review: encode medicinal-chemist heuristics into machine-readable checks as a final filter.

We evaluated 12 state-of-the-art models of pocket-based and ligand-based generators (10,000 molecules per each setup; 120,000 total) for conditional generation on a biologically relevant KRAS G12D target. Despite notable candidates, there are still no approved drug to treat KRAS G12D, thus some progress has been made in targeting KRAS G12C isoform with approved inhibitors as sotorasib [5]. Only 3144 (2.62%) molecules passed four filtering gates, and fewer then 1% clear the final review stage, quantifying the gap between attractive generations and actionable starting points for synthesis and assay.

DNH-MolGen yields a strict, multi-angle readout — chemical validity, "red-flag"-free structures, routeable synthesis, and target-site plausibility — that complements classic leaderboard metrics. It helps prioritize models and their generations with real downstream value, tightening the design-make-test loop. Reproducible pipelines will be released on our GitHub (https://github.com/LigandPro).

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CONSENSUS QSAR APPROACHES FOR PREDICTING PLACENTAL BARRIER PERMEABILITY IN REPRODUCTIVE TOXICOLOGY

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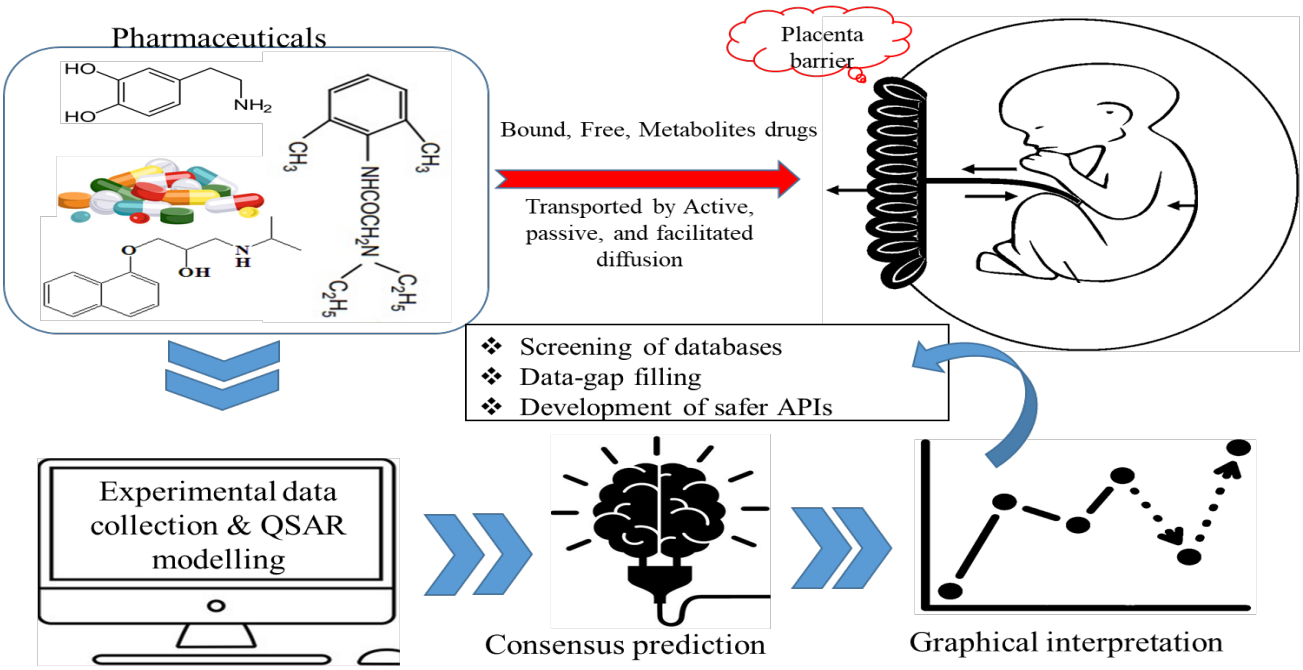
The placental barrier functions as a selective physiological interface that mitigates fetal exposure to potentially harmful xenobiotics and toxicants. Evaluating the permeability of drugs across the human placental barrier is essential for drug development and ensuring their safety during pregnancy. The in vivo permeability testing in pregnant women is unethical and has some limitations. Owing to some limitations in the traditional method, developing an *in silico* technique is essential for predicting the permeability of drugs across the placental barrier, which is cost-saving and an alternative to animal testing. The principle is straightforward if a molecule is incapable of crossing the placental barrier, it is unlikely to pose reproductive toxicity risks. In the present study, the partial least squares (PLS) modelling procedure was applied for the prediction of the permeability of drugs. To construct these models, the fetal-maternal blood concentration ratio (F/M ratio), clearance (CI), or transfer (TI) indices are selected as endpoints, which are suitable for the placental barrier transfer of drugs. Additionally, an intelligent consensus method was enforced to enhance the external predictivity. The final models are statistically significant, reliable, and robust, which have internal parameters R^2= 0.694-0.711, $Q^2_{(Loo)}$=0.593-0.567, external parameters Q^2_{F1} =0.635 & Q^2_{F2} =0.619 for CI, R^2= 0.815-0.771, $Q^2_{(Loo)}$=0.759-0.691, external parameters Q^2_{F1} =0.691 & Q^2_{F2} =0.690 for TI, R^2= 0.662-0.649, $Q^2_{(Loo)}$=0.608-0.584, external parameters Q^2_{F1} =0.611 & Q^2_{F2} =0.611 for F/M. Model analysis suggests that the number of primary amides, polar surface area-molecular size ratio, and minimum ssCH2 are key determinants influencing placental barrier permeability. Furthermore, the DrugBank database was screened and predict the permeability of new and untested pharmaceuticals using the model. The adoption of consensus modelling can therefore support early-stage drug development and chemical risk assessment, enabling safer therapeutic design and better protection of maternal-fetal health.



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ADVERSE REACTIONS OF WORLD-WIDE APPROVED DRUGS

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Side effects are any unintended effects of a drug related to its pharmacological action and may be beneficial, neutral, or harmful, whereas adverse drug reactions (ADRs) are the specifically harmful, unintended responses that occur at normal doses with a causal link to the drug. ADRs are a major contributor to clinical trial attrition, endanger patients, and add to the burden on the healthcare system. Accordingly, identifying potential ADRs for investigational compounds during the preclinical stages of research and development is critical. Because many ADRs are difficult to predict with current experimental models, *in silico* approaches are increasingly used to support toxicity prediction and risk assessment. Most computational methods for evaluating the adverse effects of known drugs rely on carefully selected reference and training datasets. However, the scope of many publicly available online resources that catalogue such datasets is often limited or they are outdated, which can hinder ADR analyses.

Accordingly, the previously developed World Wide Approved Drugs (WWAD) database [1] has been expanded to include information on adverse drug reactions for known pharmaceutical substances. These data were curated from official sources - documents published and maintained by national medicines agencies across 39 countries. To standardize ADR terminology, the internationally accepted systems were applied: the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization's classification of ADR frequency.

Data collection was conducted using a four-stage, semi-automatic algorithm tailored specifically for this purpose. The new adverse drug reaction section of WWAD contains more than 100,000 records spanning 2,300 unique low molecular weight pharmaceutical substances and over 5,000 unique MedDRA Preferred Terms. Compared with other web resources, this section offers clear advantages in both the quantity and quality of the information provided. In WWAD, ADR knowledge is integrated with data on molecular targets, therapeutic indications, and other biological activities of pharmaceutical substances, enabling comprehensive analyses across diverse areas of biomedical research. The inclusion of standardized drug structural formulas further facilitates *in silico* approaches to predicting ADR-related biological activities. Thus, the expanded WWAD database (https://www.way2drug.com/wwad/) facilitates early-stage safety evaluation of therapeutic substances during drug development.

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IN SILICO REVERSE FRAGMENT BASED DRUG DISCOVERY APPROACH (R-FBDD): CORE IDEAS, CURRENT STATUS AND FUTURE DIRECTIONS

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Fragment Based Drug Discovery (FBDD) approach [1, 2] has gained significant share of the sources of new drugs during the last two decades [3]. Within FBDD successful lead compounds are obtained from the analysis of binding of small molecules (fragments) in the pockets of the molecular target. By linking and merging the pertinent fragments occupying the pockets of the studied binding site it is possible to create larger drug-like structures with high efficiency of binding. An important non technological advantage of the FBDD is the fragment related language, which is in fact inherit to medicinal chemists thinking and is often warranted practically via numerous linear free energy relationships established in terms of constituting fragments. Despite the many advantages of the FBDD approach, the main bottleneck to its wide adoption and application in academia is the reliance of the approach on the state-of-the-art experimental equipment and highly experiences experts in the field.

In order to preserve the benefits and address the deficiencies of FBDD we have recently proposed an *in silico* based counterpart of FBDD – the Reverse Fragment Based Drug Discovery (R-FBDD) approach [4, 5]. Within R-FBDD the fragment centered thinking is preserved but the main thinking direction is reversed compared to FBDD. In R-FBDD we propose to estimate the contributions of the fragments of an entire ligand to the binding, provided the structure of a ligand-receptor complex is available. The initial estimation was based on scoring functions (SFs) but the approach itself is not limited to SFs context.

In the presentation it will be shown how R-FBDD can be successfully applied in several scenarios typical for *in silico* medicinal chemistry and drug discovery in order to guide researchers in their discovery projects. Additionally, current extensions of the R-FBDD approach are described including statistical mechanical estimates of binding free energies (via MM/GBSA) and automatic fragmentation [6] of drug-like ligands in order to preserve in resulting fragments the interaction patterns existing in entire ligands.

Thus it is shown that R-FBDD approach is a new versatile tool for *in silico* part of drug discovery, capable of providing additional valuable information out of the regular data, and especially applicable for lean drug discovery projects, in which the discovery risks are minimized via judicious re-use of the scaffolds and aid of *in silico* tools.

The study was conducted under the state assignment of Lomonosov Moscow State University, project № 121021000105-7.

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CHRONOBIOTICSDB AS THE FORERUNNER DATABASE OF AI-POWERED PERSONILISED CHRONOPHARMACOLOGY

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Chronobiotics constitute a class of pharmacological agents, encompassing both experimental compounds and those employed in clinical practice, which are chemically heterogeneous yet unified by their capacity to modulate circadian rhythm parameters [1]. These modifications pertain to fluctuations in a spectrum of physiological and biochemical processes, including the expression of core circadian clock genes in model organisms and cell cultures, alongside the expression of clock-controlled genes. The conceptualisation of chronobiotics has been established for over half a century, originating with the discovery and detailed clinical characterisation of the hormone melatonin, nevertheless the field remains fragmented; a unified classification system for these agents - which include categories such as natural chrononutrients, synthetic targeted circadian rhythm modulators, hypnotics, and chronobiotic hormones - is presently lacking. Consequently, the creation of the world's first curated and dynamically updated database of chronobiotic drugs (circadian rhythm modulators), with access provisioned via the global Internet, represents a critical and timely objective for the disciplines of chronobiology, chronomedicine, and pharmacoinformatics. The present study aims to address this need through the development of a relational database, "ChronobioticsDB" (chronobiotic.ru) [2], utilising the Django framework with PostGreSQL as the database management system. The database is filled with data on chronobiotics manually extracted and annotated from PubMed-indexed and other sources. Each compound entry will comprise a detailed profile featuring links to primary sources, a molecular structure image, the chemical formula in machine-readable SMILES format, and the systematic name according to IUPAC nomenclature, also exhaustive literature citing. To enhance the depth and relevance of each entry, the database is synchronised with external chemical repositories [2]. Furthermore, its biological and pharmacological utility will be augmented through integration with resources such as the FDA, Selleckchem, KEGG Drugs. In instances of data overlap, entries will be curated to highlight the unique properties of each chronobiotic. Subsequently, the database is intended to serve as a training set for artificial intelligence algorithms directed towards the discovery of novel chronobiotic compounds; full-text literature sources will become the training set for the agent AI-chronopharmacologist LLM.

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TOXAI ASSISTANT - AN IN SILICO ALTERNATIVE TO RATS TESTING FOR ACUTE TOXICITY

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Existing QSAR models for predicting acute mammalian toxicity often suffer from limitations such as small or narrowly focused datasets, classification-based endpoints, and insufficient regulatory compliance. In contrast, this study introduces ToxAI Assistant - a novel web platform that leverages large, curated datasets (9843 oral and 2323 intravenous rat LD_{50} values) to develop robust regression QSAR models for acute toxicity prediction [1]. The best-performing QSAR models developed using 2D RDKit descriptors and the Cat Boost method achieve $Q^2_{test} = 0.66$ at a data coverage of at least 77% within an applicability domain (AD) during validation of test sets. All models adhere to OECD QSAR principles, featuring well-defined endpoints, transparent algorithms, and a rigorously characterized AD.

A key advancement of this work is the integration of regression models into an openly accessible web application, enabling precise LD_{50} value prediction and subsequent toxicity categorization according to WHO guidelines. The platform supports structural interpretation of toxicity mechanisms by identifying atom- and fragment-level contributions to acute toxicity, thereby facilitating rational compound optimization. Additionally, ToxAI Assistant incorporates medicinal chemistry filters (Brenk, PAINS) and toxicophore detection to alert users to high-risk structural motifs.

The platform was validated on external test sets and benchmarked against existing tools (e.g., TEST, ADMETLab 3.0, STopTox), demonstrating superior chemical space coverage, prediction accuracy, and interpretability. Case studies illustrate how the tool can guide toxicity mitigation through structural modification without compromising pharmacological activity. For instance, substitution of an amino group with a phosphido ligand in an HDAC2 inhibitor reduced predicted oral LD_{50} from 2412 mg/kg to 4950 mg/kg while maintaining inhibitory potency.

ToxAI Assistant represents a significant step forward in computational toxicology by combining large-scale data, regression modelling, mechanistic interpretation, and regulatory compliance into a single, user-friendly platform. It is publicly available at https://tox-ai-assistant.streamlit.app/ and is positioned to aid in early-stage toxicity screening, drug candidate optimization, and regulatory decision-making.

Part of this work was supported by the budget of the Institute of Physiologically Active Compounds of the Russian Academy of Sciences (IPAC RAS) State Targets – 2024 [topic No. FFSG-2024–0019].

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FULLY-CONNECTED CONVOLUTIONAL NEURAL NETWORKS BASED ON MULTIPLE DOCKING: A NEW MACHINE LEARNING METHOD FOR SEARCHING BIOLOGICAL ACTIVE COMPOUNDS

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The aim of this study is to develop a novel architecture of modular multi-target fully-connected convolutional neural network based on different types of convolution of energy spectra of multiple docking and to apply this new machine learning method to in silico search for biological active compounds.

The principles of the original multiple docking methodology developed by the authors for vector assessment of ligand affinity to biotargets are presented [1]. A mathematical description of two methods of convolution of energy spectra of multiple docking is given: correlation convolution [2] and matrix convolution [3].

A method for constructing a fully-connected convolutional neural network for the case of multiple docking into one biotarget is considered. A method for constructing a modular multi-target fully-connected convolutional neural network for the case of multiple docking in several biotargets is considered.

Using the new original architecture of fully-connected convolutional neural networks developed by the authors, a series of highly accurate models for in silico prediction of the biological activity of chemical compounds have been formed.

1. Two sets of fully-connected convolutional neural networks were constructed based on matrix convolution of energy spectra of multiple docking into one biotarget: a) for 22 human biotargets relevant for anxiolytic activity, gamma correlation coefficients R_{Gamma}=-0.164–0.104; b) for 10 relevant biotargets of S.aureus, R_{Gamma}=-0.165–0.226.

2. Two sets of fully-connected convolutional neural networks were constructed based on correlation convolution of energy spectra of multiple docking into one biotarget: a) for 22 human biotargets relevant for anxiolytic activity, R_{Gamma}=0.233–0.302; b) for 10 relevant biotargets of S.aureus, R_{Gamma}=0.395–0.590.

3. A fully-connected convolutional neural network was constructed based on the correlation convolution of energy spectra of multiple docking into S.aureus peptide deformylase to predict the antimicrobial activity of monotarget compounds; R_{Gamma}=0.632, balanced accuracy *BAcc*=72%, area under the ROC curve AUC_{ROC}=76%, statistical significance p=$6.1 \cdot 10^{-7}$.

4. A modular fully-connected convolutional neural network was constructed based on the correlation convolution of energy spectra of multiple docking into 10 relevant biotargets of S.aureus to search for multi-target antimicrobial substances; R_{Gamma}=0.805, *BAcc*=75%, AUC_{ROC}=75%, p=$2.4 \cdot 10^{-9}$.

The resulting models are used to search for new substances with antimicrobial and anxiolytic activities.

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IN SILICO SCREENING OF PROBIOTIC-DERIVED METABOLITES AS LUXS QUORUM SENSING INHIBITORS IN OTITIS MEDIA PATHOGENS

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Quorum sensing (QS) plays a pivotal role in the pathogenesis and persistence of otitis media, and the LuxS-mediated autoinducer-2 (AI-2) system is a key regulator of bacterial communication, biofilm formation, and immune evasion. Inhibiting LuxS offers a promising anti-virulence strategy that bypasses conventional antibiotic resistance. In this study, we employed molecular docking and virtual screening to evaluate the interactions of probiotic-derived metabolites with LuxS from clinically relevant otitis media pathogens. Structural modeling and binding affinity analyses were performed using advanced bioinformatics tools to identify potential inhibitors that can disrupt AI-2 synthesis.

This study evaluated the potential of *Lactobacillus reuteri* to produce metabolites capable of inhibiting *Haemophilus influenzae* LUXS activity. An *in silico* workflow combining genomic mining, molecular docking, and structural analysis was used. The 3D structure of *Haemophilus influenzae* LUXS (PDB ID: 1J6W) was retrieved from the RCSB Protein Data Bank. Biosynthetic gene cluster analysis of *L.reuteri* was conducted using AntiSMASH v8.0, which identified four predicted secondary metabolites: bacilysin, citreohybridinol, trehangelin A, and viguiepinol. All ligands were energy-minimized using Avogadro (MMFF94 force field), and the files were converted using Open Babel. Blind molecular docking was performed using AutoDock Vina via PyRx with a maximized grid to ensure broad binding site coverage. The results were validated through re-docking on the DockThor platform. Visualization and interaction analyses were conducted using ChimeraX and BIOVIA Discovery Studio 2025.

The binding affinity analysis showed that Viguiepinol had the highest binding affinity -7.5 kcal/mol followed by Citreohybridonol (-7 kcal/mol), Trehangelin_A with an affinity equal to -6 kcal/mol and finally Bacilysin with the lowest binding affinity equal to -5 kcal/mol with Root Mean Square Deviation (RMSD) equal to 1 Å. The structural analysis showed that Bacilysin had the highest number of hydrogen bonds equal to 4 with the amino acids residues: LYS 23, ARG65, ILE76, ASP5 followed by Trehangelin_A with 3 hydrogen bonds with SER160, ALA22, ILE21 as amino acids residues. Both Citreohybridonol and Viguiepinol did not had any hydrogen bonds and only had hydrophobic interactions with some amino acids from the receptor. These hydrogen bonds have a significant impact on the LUXS receptor, suggesting potential interference with LUXS function. Although these *in silico* findings are promising, further *in vitro* validation is necessary to confirm their biological activity.

This study highlights the potential of *L. reuteri*-derived metabolites as natural quorum-sensing inhibitors and proposes their application in smart delivery systems. Probiotic-loaded biodegradable polymers could enable the localized and responsive release of inhibitory agents in the presence of otitis media pathogens. Such systems may offer innovative solutions for improving otitis media treatment and reducing antibiotic-associated resistance.

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POSTERS

MOLECULAR DYNAMIC AND DFT BIOPROSPECTING OF POLYOL PATHWAY ENZYME MODULATORS FROM SOUTH AFRICAN ESSENTIAL OILS FOR DIABETIC COMPLICATION MANAGEMENT

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This study explores essential oils from South African medicinal plants (*Agathosma betulina, Cymbopogon citratus, Artemisia afra*) as inhibitors of aldose reductase (AR) and sorbitol dehydrogenase (SDH) key enzymes implicated in diabetic complications. Advanced computational techniques identified quercetin-7-O-glucoside as potential dual inhibitor of AR (-51.80 kcal/mol) and SDH (-34.41 kcal/mol), while quercetin-3,7-diglucoside also demonstrated potent SDH inhibition (-70.52 kcal/mol) superior to epalrestat (−30.55 kcal/mol). 120 ns molecular-dynamic simulations confirmed enhanced enzyme stability with reduced root mean square deviation of 1.39 – 1.48 Å against AR-apo 1.56 Å and 2.48 – 2.86 Å against SDH-apo 2.95 Å. These compounds stabilize enzyme structures through hydrogen bonding and π-π interactions with catalytic residues. A robust correlation ($0.5 \leq |r| \leq 0.95$) between maximum electrostatic potential, polarizability, LUMO and binding free energy suggested electrostatic interactions as primary determinants in compound-AR/SDH binding. Pharmacokinetic analyses of the compounds showed minimal blood-brain barrier penetration and no significant inhibition of CYP450 enzymes, suggesting reduced potential for CNS-related adverse effects and drug-drug interactions. These phytochemicals, particularly Q7G, represent promising therapeutics to prevent diabetic complications like retinopathy, neuropathy, nephropathy, cardiomyopathy and cataracts by comprehensively regulating the polyol pathway through simultaneous inhibition of AR and SDH. Investigation of in vivo efficacy and development of targeted drug delivery systems for Q7G and Q37DG is encouraged.

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NOVEL $GABA_B$ RECEPTOR MODULATOR AS AN ALTERNATIVE TO PHENIBUT VIA MOLECULAR MODELING AND IN VIVO STUDIES

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Background. Phenibut, a γ-aminobutyric acid type B ($GABA_B$) receptor agonist, is commonly used to treat anxiety and insomnia but is limited by adverse effects such as sedation, tolerance, and withdrawal symptoms. This study aimed to discover a novel $GABA_B$ receptor modulator with improved efficacy and safety compared to phenibut.

Methods. A library of 15,000 drug-like compounds was screened in silico, with initial selection based on Tanimoto similarity. Identified candidates were subjected to molecular docking to assess binding affinity, followed by molecular dynamics simulations to evaluate receptor-ligand stability while pharmacokinetics were analyzed to assess oral bioavailability and blood-brain barrier penetration. Among these, 3-[(2-oxo-2-phenylethyl)amino]benzoic acid (novel hit) emerged as the lead compound. Its pharmacological efficacy was tested in vivo using a stress-induced Wistar rat model (n = 20, male, 200-250 g), with phenibut as the reference. Anxiety-like behavior was evaluated using the elevated plus maze.

Results. The novel hit displayed stronger binding affinity (ΔG_{bind} = -8.5 kcal/mol) and greater complex stability than phenibut (-8.0 kcal/mol), with MMGBSA and MMPBSA analyses corroborating these results. Pharmacokinetic evaluation revealed favorable oral bioavailability and efficient central nervous system penetration. In behavioral studies, rats treated with the novel hit spent significantly more time in the open arms of the elevated plus maze (110.80 ± 26.10 s) compared to phenibut-treated rats (57.80 ± 9.40 s, $p < 0.05$), indicating a robust anxiolytic effect.

Conclusion. Collectively, these findings highlight the novel hit as a promising alternative to phenibut, demonstrating enhanced efficacy and an improved safety profile. Further preclinical evaluation is warranted to confirm long-term safety, dose optimization, and translational potential toward clinical application.

DEVELOPMENT OF A PROBABILITY FACTOR BASED ON BLIND AND TARGET-SITE DOCKING ANALYSIS FOR IMPROVED IC_{50} PREDICTION OF CANDIDATE COMPETITIVE ENZYME INHIBITORS

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Docking analysis is widely used for screening compounds as promising enzyme inhibitors in novel drug development. Docking to a specific binding target, such as an active or allosteric site, is often used for compound screening. However, this approach has the drawback that compounds showing promising *in silico* results may not be truly effective in practice. This may be the result of preferential binding to alternative sites on the enzyme that do not induce inhibition, diminishing the probability of binding to the target site, and leading to lower inhibitory action. On the other hand, the blind docking method targeting the entire enzyme, can elucidate the preferential binding sites (active or allosteric or sites that do not cause inhibition), but the estimated binding energy at the target site is calculated based on a more restricted number of binding poses at this site and the prediction of Ki based on this energy still don't take into account stable binding to other sites. So, the prediction may not coincide with the *in vitro*-calculated value.

In the present study, we propose a probability factor (PF) that is extracted based on the combined results of docking analysis targeted at the active site of DPP4 and docking analysis targeted to the entire enzyme. The PF is calculated from the Eest exported from docking to the target site box ($Eest_{ts}$), by abstracting a factor (d) produced using the results of docking to the whole enzyme at all positions (x) with lower binding energy ($Eest_x$) than that of the target site ($Eest_t$). $PF = Eest_{ts} - d$

$d = \sum(\Delta E_x \bullet (v_x/100)) \bullet 10$, where $\Delta E_x = Eest_x - Eest_t$ and v_x is the frequency (%) of binding to the specific site x with the specific pose which corresponds to Estimated binding Energy $Eest_x$.The correlation of probability factor PF with $\log_{10}(IC_{50})$ calculated by in vitro experiments is better described by an exponential curve described by the equation:

$\log_{10}(IC_{50}) = 4.752098 - 0.1679366 \bullet 10^{-0.3980433 \cdot PF}$, with $R^2 = 0.9983$ and p-value $= 1.09 \bullet 10^{-8}$.

A total of nine compounds were used to create the curve, six of which were 3-(benzo[d]thiazol-2-yl)-2-aryltiazolidin-4-one derivatives and three were plant-derived compounds (methyl rosmarinate, Calceolariside A and 2(3,4-dihydroxy) phenylethyl-glucopyranoside) from *Thymus Thracicus Velen*. All compounds were competitive inhibitors according to Lineweaver-Burk diagrams with IC_{50} values from 12 nM to 37200 nM. The exponential curve better describes the correlation compared to the linear curve proposed previously [1].

The results suggest that the model could be used to accurately predict the IC_{50} of competitive inhibitors of different core structures.

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MOLECULAR DOCKING ON DNA POLYMERASE III AND REGRESSION ANALYSIS IN THE SEARCH FOR THE BINDING SITE OF ANTHRANILIC ACID DERIVATIVES WITH ANTIBACTERIAL ACTIVITY

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Research in the field of searching for promising biologically active substances involves screening large amounts of data and significant time costs. Using databases based on big date and multiple regression models "structure-activity", allows you to reduce the search to several hours. The aim of the work is to search for the binding site of anthranilic acid derivatives with antibacterial activity against *E.coli* by DNA polymerase III. The relationship with biological activity is described by the equations of multiple linear regression analysis. Ligand–receptor interactions were modeled using the AutoDock 4.0 program as part of the MGL Tools 1.5.6 software package. During molecular docking, we used a three-dimensional model of the *E.coli* DNA polymerase III molecule, information about which was obtained from the RCSB Protein Data Bank database: PDB ID code: 3D1G [1]. When constructing the Grid maps, the coordinates of the ligand were taken as the center, chain A: x = -41.22, y = -110.93, z = -36.04; and chain B (x = -37.95, y = -145.04, z = 13.18) with coordinates of points (60 × 60 × 60) around each simulated area. Based on multiple linear regression analysis by the Statistica 10 program, the relationship of antibacterial activity of 20 derivatives of anthranilic acid against *E.coli*, the binding site of anthranilic acid derivatives to chains A and B of the DNA polymerase molecular target with the highest values of statistical criteria was determined (R=0.938, F=15.40). The experimental result of antimicrobial activity against *E.coli*: MIC (mkg/ml) was converted to the logarithm: log(1/MIC). Mathematically, the interaction is described by a composite model containing 16 descriptors of molecular docking according to the conformations of 1-10 chains A and B: log 1/MIC exp. (*E.coli*) = chains A: $Be4_{DNApolIIIA}$, $Ki4_{DNApolIIIA}$, $Be7_{DNApolIIIA}$, $Ki7_{DNApolIIIA}$, $Be8_{DNApolIIIA}$, $Ki8_{DNApolIIIA}$; and chains B: $Be1_{DNApolIIIB}$, $Ki1_{DNApolIIIB}$, $Be3_{DNApolIIIB}$, $Ki3_{DNApolIIIB}$, $Be4_{DNApolIIIB}$, $Ki4_{DNApolIIIB}$, $Be5_{DNApolIIIB}$, $Ki5_{DNApolIIIB}$, $Be8_{DNApolIIIB}$, $Ki8_{DNApolIIIB}$. The intermolecular interaction of anthranilic acid derivatives with the sites of the DNA polymerase molecular target was evaluated, and the amino acid residues of the interaction model were determined. The interaction site number 1 of chain A contains the following amino acids: ARG152A, TYR153A, TYR154A, LEU155A, LEU159A, THR172A, GLY174A, HIS175A, LEU177A, SER192A, VAL193A, ILE194A, PHE241A, ASP243A, ARG246A, VAL247A, TYR323A, THR341A, SER346A, TYR354A, VAL360A, VAL361A, MET362A, MET364A, ARG365A; section number 2 (Chain B) contains: ARG152B, TYR153B, TYR154B, LEU155B, THR172B, GLY174B, HIS175B, LEU177B, VAL247B, ASP243B, ARG246B, SER346B, TYR354B, VAL360B, VAL361B, MET362B. Thus, a site of interaction of anthranilic acid derivatives with antibacterial activity was found. The orientation of the studied biologically active substances in the coordinates of the interaction sites will allow searching for compounds with antibacterial activity against *E.coli* based on a multiple regression model.

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RISK ASSESSMENT OF INDUSTRIAL CHEMICALS TOWARDS SALMON SPECIES AMALGAMATING QSAR, Q-RASAR, AND ARKA FRAMEWORK

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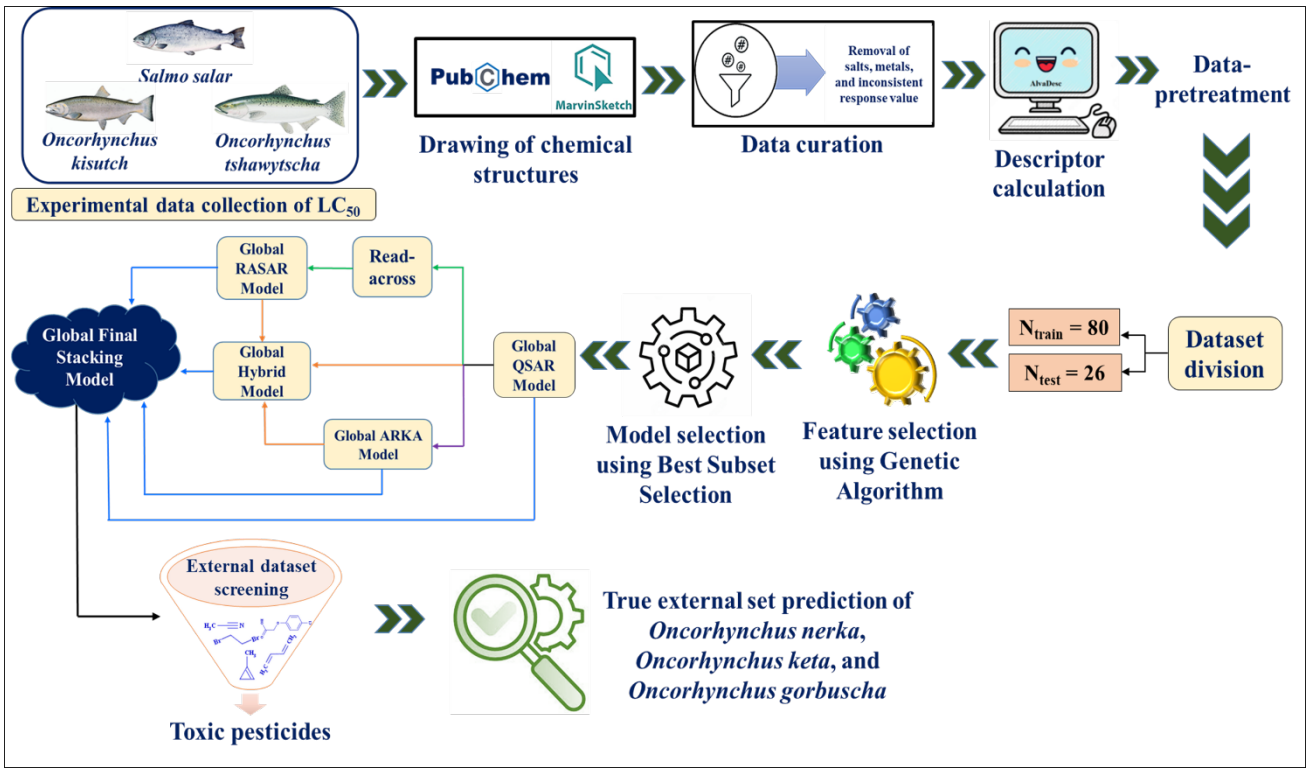
The extensive use of industrial chemicals poses a serious threat to aquatic species such as the salmon species, which, when consumed, can affect human beings via their dietary intake. Salmon fish is a vital source of protein for maintaining human health. The present study aims to estimate the toxicity of diverse chemicals using an *in silico*-based global model involving three different salmon species: *Salmo salar*, *Oncorhynchus kisutch*, and *Oncorhynchus tshawytscha,* encompassing the toxicity endpoint median lethal concentration (LC_{50}). LC_{50} signifies the amount of chemical inhaled by the test organism that causes death in 50% of the population during the toxicity test study. Primarily, a quantitative structure-activity relationship (QSAR) model is developed using molecular descriptors. QSAR model descriptors are integrated with the similarity and error-based measures of read-across to develop the read-across structure-activity relationship (RASAR) model. Another emerging dimensionality reduction modeling algorithm, arithmetic residuals in *K*-groups analysis (ARKA), is employed to enhance the model's degree of freedom. Model quality was improved by hybrid model development, which combined the feature matrix of the QSAR model with those of the RASAR and ARKA descriptors. Finally, to attain more trustworthy results and address the limitations of individual models, a partial least squares (PLS)-based stacking model is developed using the predicted response values of QSAR, RASAR, ARKA, and hybrid models as descriptors. The stacking model outperforms the quality [1] of the individual models, which is evident from the determination coefficient R^2 (0.713), cross-validated leave-one-out Q^2_{LOO} (0.697), predictivity Q^2_{F1}, Q^2_{F2} (0.797, 0.795), and a lower value of root mean square error of prediction RMSEp (0.652). The developed stacking model can thus be used in environmental risk assessment, aiding in toxicity data-gap filling and design of safe and green chemicals.



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INTEGRATING CHEMOMETRICS AND DUAL 2D-QSAR MODELS WITH MOLECULAR DOCKING FOR LEAD IDENTIFICATION ADDRESSING TRYPANOSOMA CRUZI IN CHAGAS

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We developed dual quantitative structure–activity relationship (QSAR) models targeting Chagas, a widespread Neglected Tropical Disease (NTD). Existing therapies are limited by relapse, toxicity, and extended treatment periods. The causative Protozoan parasites *Trypanosoma cruzi* is transmitted by infected «kissing bug» but congenital, transfusional, transplant-associated and food-borne routes also contribute to infection [1]. Recent studies employed two distinct models for *T.cruzi* inhibition one with diverse chemical compounds and another focused on 2-aminobenzimidazole scaffold targeting a key enzyme in Chagas pathology. Although the observed (IC_{50}) showed moderate potency, the compounds demonstrated limiting toxicity *in vivo* motivating the development of 2D-QSAR models for *T. cruzi* inhibition, using descriptors for interpretability, allowing identification of structural features correlated with inhibitory activity, guiding the design of new molecules. The first model was developed using 2D QSAR approach based on partial least squares (PLS) method in compliance with OECD guidelines, prediction accuracy was enhanced by Intelligent Consensus Prediction (ICP) yielding robust acceptable statistical parameters, internal (= 0.784, = 0.725 etc.) and external (= 0.824, and = 0.821) validation metrics. Similarly the second model was also developed using PLS method adhering to OECD guidelines and was validated using different globally accepted internal (= 0.774, = 0.658 etc.) and external (= 0.697, and = 0.686) validation parameters. Statistical parameters of both models demonstrate reliability, robustness, accuracy, and predictive ability. Structural features like- hydrophobicity, aromaticity, hydrogen bond acceptors/donors, and heteroatoms were found to strengthen inhibitory activity. These two developed models were applied individually to predict the *T. cruzi* inhibitory activity of compounds from the coconut database and QSAR-guided structural modifications were implemented to develop potential analogs of the top candidates from each models. Molecular docking was used to evaluate the binding affinity and interactions of these set analogs generated from both models and compared to a known *T. cruzi* inhibitor at the active site. In-depth *in silico* ADMET profiling was conducted to assess the least toxic compounds with potential application in Chagas treatment.

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IN SILICO ANALYSIS OF BIOACTIVE COMPOUNDS FROM *VITEX AGNUS-CASTUS*: PHARMACOKINETICS AND TARGET PREDICTION

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Vitex agnus-castus is a medicinal plant with a well-documented history of use in managing premenstrual syndrome (PMS), a condition that significantly impacts the quality of life for many women [1]. Although its clinical efficacy is established, the specific molecular mechanisms and pharmacokinetic properties of its main bioactive compounds—including flavonoids, iridoids, and terpenes—are not fully elucidated, limiting their rational development into standardized phytopharmaceuticals. This study aimed to perform a comprehensive *in silico* characterization of three key compounds from *V. agnus-castus*—casticin, agnuside, and 1,8-cineole—to deepen the understanding of their therapeutic potential. The primary objective was to evaluate their ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiles and predict their principal molecular targets, thereby elucidating potential mechanisms of action and justifying the plant's ethnopharmacological use on a molecular level.

Computational methods were employed using established bioinformatics platforms. A broad range of ADMET properties, including physicochemical characteristics, compliance with Lipinski's Rule of Five, blood-brain barrier (BBB) permeability, and toxicological endpoints such as carcinogenicity and skin sensitization, were assessed using the ADMETlab 3.0 platform [2]. The SwissTargetPrediction server, which operates on a ligand-based approach combining 2D and 3D similarity measures, was utilized to identify the most probable protein targets for each compound [3].

The pharmacokinetic analysis revealed distinct profiles for each compound. Casticin and 1,8-cineole demonstrated favorable oral bioavailability profiles, complying with all criteria of Lipinski's Rule of Five. Notably, 1,8-cineole, a small lipophilic monoterpene, was predicted to cross the blood-brain barrier, suggesting a potential direct mechanism of action on the central nervous system that could explain its effects on mood-related PMS symptoms. Conversely, agnuside showed two violations of Lipinski's rules (molecular weight > 500 Da and >10 H-bond acceptors), indicating a lower probability of good oral absorption and systemic availability. The consolidated target prediction analysis revealed a diverse interaction profile, with proteases emerging as the most predominant target class (25.0%). Other key classes, including enzymes, Cytochrome P450, and transporters, were also significantly represented (16.7% each), highlighting a multi-target mechanism consistent with phytocompounds. This is exemplified by casticin's predicted affinity for Aldo-Keto Reductase (AKR1B1), an enzyme implicated in inflammatory signaling, and 1,8-cineole's interaction with aromatase (CYP19A1), the crucial enzyme responsible for estrogen biosynthesis, providing a direct link to hormone modulation.

In conclusion, this *in silico* analysis provides significant molecular-level justification for the therapeutic application of *V. agnus-castus*. The findings highlight 1,8-cineole as a promising neuroactive compound, while the identification of targets like aromatase offers a plausible mechanism for the plant's well-known hormone-modulating effects. This work establishes a solid foundation for future experimental validation towards the rational development of new treatments for PMS.

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IN SILICO STUDIES OF THE INTERACTION OF ANTIMICROBIAL PEPTIDES WITH PROTEINS FROM MICROORGANISMS BY TARGET FISHING AND DOCKING APPROACHES

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The rise of antimicrobial resistance represents a major global health challenge, driving the urgent need for novel therapeutic strategies. Antimicrobial peptides (AMPs) have emerged as promising candidates due to their broad-spectrum activity and multi-target mechanisms of action, which may reduce the likelihood of resistance development. In this project, hybrid antimicrobial peptides designed in our laboratory, which combine structural motifs from cecropin and cathepsin, and their potential molecular targets were investigated using computational approaches. Through target fishing, several microbial proteins essential for vital cellular processes—such as DNA replication and repair, metabolic pathways, nutrient transport, and adhesion—were identified. The most relevant predicted targets included DNA gyrase B (PDB_{ID}: 1EI1), thymidylate synthase (PDB_{ID}: 1AOB), DNA glycosylase MutY (PDB_{ID}: 1WEI), PotF (PDB_{ID}: 1A99), Dr hemagglutinin (PDB_{ID}: 1USQ), and xanthosine phosphorylase (PDB_{ID}: 1YR3), highlighting the multi-target potential of the peptides. Subsequently, molecular docking simulations were performed to evaluate peptide-protein interactions in detail, identifying key binding residues and estimating binding affinities. Among the analyzed peptides, CECB1_CATL1.2 demonstrated the most favorable interactions, suggesting a mechanism of action involving the simultaneous inhibition of multiple essential proteins. Overall, this study demonstrates the value of in silico tools, such as target fishing and docking, for drug discovery, supporting the identification of new therapeutic targets and guiding the rational development of novel treatments against multidrug-resistant microorganisms.

COMPUTATIONAL MODELING OF BIOACCUMULATION POTENTIAL OF PER- & POLY-FLUOROALKYL SUBSTANCES: MACHINE LEARNING BASED QUANTITATIVE READ-ACROSS STRUCTURE-PROPERTY RELATIONSHIP APPROACH

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Per- & poly-fluoroalkyl substances (PFASs) contain aliphatic carbon chains where the hydrogen atoms are completely or partially substituted with fluorine and are characterized by their enhanced durability and resistance to chemical and biological degradation due to the presence of strong carbon-fluorine bonds. PFASs contamination represents a non-avoidable environmental threat because of its tendency to bioaccumulate in aquatic organisms and cause adverse impacts on human health. To address this problem, experimental bioconcentration factor (log BCF) data of freshwater fish (Teleostei taxonomic class) for representative PFASs [1] were used to develop the quantitative structure-property relationship (QSPR) and machine learning (ML)-based quantitative Read-Across Structure-Property Relationship (q-RASPR) models. We utilized various ML algorithms to capture both linear and non-linear relationships. The best-performing ML q-RASPR model exhibited better external prediction (Q^2_{F1}= 0.930, Q^2_{F2}= 0.917, MAE_{test}= 0.491, $RMSE_{test}$= 0.653) compared to both the corresponding QSPR model and the previously reported model. In compliance with the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) guideline, a true external set prediction of 2411 unknown PFASs was performed, and they were classified into bioaccumulation categories as per Annex XIII. The bioaccumulation factor (log BAF) of PFASs was predicted using the Read-Across approach, and the predictivity and reliability of the method were assessed. Furthermore, we have developed a Python-based tool named "PFAS (BCF) Predictor-v1.0" to predict the BCF value of a true external set and classify PFASs into bioaccumulation categories according to the REACH guideline (Annex XIII), thus emphasizing the overall applicability and accessibility of this study. Statistical analysis suggests that the bioconcentration factor of PFASs depends on the number of CF_2 groups, the atomic distribution properties, and the similarity and error-based features. The developed models will further support the design of an environmentally conscious strategy and control measures for managing PFAS contamination [2].

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STRUCTURAL INSIGHTS INTO PLASMEPSIN INHIBITION BY PHENOLIC COMPOUNDS FROM AFRICAN MISTLETOE (*TAPINANTHUS GLOBIFERUS*) PARASITIZING *VITEX DONIANA*

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In Nigeria, *Tapinathus globiferus* is used in traditional medicine in the managements of hypertension, diabetes, ulcers, infections, and skin itching, while aiding childbirth. In Europe, it addresses circulatory/ respiratory issues, cancer, epilepsy, and acts as a nervous tonic. Malaria remains a devastating parasitic disease, with Plasmodium falciparum resistance to current therapies necessitating new drug targets. Plasmepsins I and II (Plm-I/II), aspartic proteases critical for hemoglobin degradation in the parasite's life cycle, represent promising candidates. This study investigated four Tapinanthus globiferus-derived compounds—catechin (Y10), catechin-3-gallate (Y11), 4-methoxyphenyl acryl aldehyde (Y12), and 4-hydroxy-3-methoxy acryl aldehyde (Y13)—for their Plm-I (PDB: 3QS1) and Plm-II (PDB: 1LF3) inhibitory potential using molecular docking and ADMET profiling.

Molecular docking revealed binding affinities ranging from −5.0 to −6.7 kcal/mol (Plm-I) and −5.6 to −8.4 kcal/mol (Plm-II). Catechin-3-gallate (Y11) exhibited the highest affinity for both enzymes (−6.7 and −8.4 kcal/mol, respectively), surpassing other ligands though lower than native co-crystallized inhibitors. Notably, Y11 formed a critical hydrogen bond with Asp214 (Plm-II catalytic dyad), explaining its enhanced binding. ADMET predictions indicated favorable drug-likeness: all compounds followed Lipinski's rule, with catechin (Y10) classified as least toxic (Class VI). These findings highlight T. globiferus metabolites, particularly catechin-3-gallate, as promising plasmepsin inhibitors. The strong affinity and low toxicity profiles underscore their potential as antimalarial leads. Further in vitro and in vivo validation is warranted to advance their therapeutic development.

PREDICTION AND STUDY OF THE ANTI-INFLAMMATORY ACTIVITY OF THE MEDICINAL PLANT PORTULACA OLERACEA, BASED ON THE MODEL OF BINDING OF BIOLOGICALLY ACTIVE SUBSTANCES OF THE FLAVONOID GROUP TO THE ASSOCIATED LEUKOTRIENE B4 RECEPTOR 1

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Portulaca Oleracea L. It is an annual succulent plant of the Portulacacea family, subclass Caryophyllidae. It is widespread and cosmopolitan. Portulaca oleracea contains a wide range of biologically active substances, such as polysaccharides, flavonoids, alkaloids, macro- and microelements, etc [1]. A metastatic analysis of scientific literature data for the period 2019-2024 revealed that Portulaca Oleracea extract has the ability to influence the inflammatory response system. It is worth noting that the induction of pro-inflammatory markers such as interleukin 1,2,6; leukotrienes; Cyclooxygenases play an important and fundamental role in the development of various autoimmune diseases, vascular vascularization, as well as in the development of both tumors and cancer metastases. This makes it a very relevant topic to study a promising source of a valuable type of medicinal plant raw materials with a pronounced anti-inflammatory effect. The aim of the study is to conduct computer modeling of a number of biologically active compounds, namely the flavonoid spectrum of Portulaca Oleracea, which provide anti-inflammatory activity by molecular docking.

Cluster modeling is based on the analysis of multiple linear regression and spatial (Cartesian) three-dimensional coordinates of biologically active purslane molecules. Ligand–receptor interactions were modeled using the SwissADME program (absorption, distribution, metabolism, excretion). For visualization, a two-dimensional model of the studied substances was used, as well as a three-dimensional model of interactions with receptors. The information was obtained from the CHEMBL ID database, and the forecast was performed for Homo sapieCluster cluster modeling based on the analysis of multiple linear regression and spatial (Cartesian) three-dimensional coordinates of biologically active purslane molecules. Ligand–receptor interactions were modeled using the SwissADME program (absorption, distribution, metabolism, excretion). For visualization, a two-dimensional model of the studied substances was used, as well as a three-dimensional model of interactions with receptors. The information was obtained from the CHEMBL ID database, and the prediction was performed for Homo sapiens. During the molecular docking of 15 molecules from the flavonoid group of the medicinal plant Portulaca Oleracea, the following data were obtained. The leukotriene B4 1 receptor (LTB4R) is the leader in the ligand-target interaction as a receptor providing a high level of anti-inflammatory activity. The parameters for studying this selected model give the following ratio predictions: Molar refractive index is 88.39; TPSA is 67.82 Å2; Solubility is 2.80e-02 mg/ml.; 8.57e-05 mol/l. The results of the study make it possible to identify the descriptor of biologically active molecules of the portulaca/LTB4R flavonoid group, build predictive search models: “structure – anti-inflammatory activity” and build a cluster of “active” molecules using molecular docking.

The work is part of a study of medicinal plant raw materials LRS Portulaca Oleracea herba. With the further possibility of creating a dietary supplement, as well as registering a patent for a technology for creating dietary supplements or medicinal products.

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DISCOVERY OF HIGH-AFFINITY LIGANDS TARGETING THE PUL56 SUBUNIT OF HUMAN CYTOMEGALOVIRUS TERMINASE USING COMPUTATIONAL APPROACH

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Human cytomegalovirus (HCMV) remains a major cause of morbidity and mortality in immunocompromised individuals, including bone marrow and solid organ transplant recipients. Current antiviral therapies primarily target viral DNA polymerase and are limited by nephrotoxicity, with drugs such as ganciclovir, valganciclovir, foscarnet, and cidofovir posing significant clinical challenges. The viral terminase complex, composed of the ATPase subunit pUL56 and the nuclease pUL89 (with occasional involvement of pUL51), has emerged as a promising alternative target. Letermovir, the first antiviral agent targeting pUL56, demonstrates efficacy and tolerability but is associated with adverse events such as gastroenteritis, nasopharyngitis, dyspnea, and elevated serum creatinine.

In this study, we employed AlphaFold 3 to model the pUL56 subunit, followed by loop refinement using our Alpha-Loop algorithm and binding site analysis using CASTp. The resulting model aligns with literature data, exhibiting structural and amino acid composition similarities in the binding site. From a database of ~15,000 compounds, molecules with a Tanimoto similarity coefficient ≥ 0.6 relative to letermovir were selected. Initial binding energies were evaluated using AutoDock Vina, and the most promising ligands were further analyzed with AutoDock 4. A ligand was considered effective if its binding affinity was ≤ -6 kcal/mol. Letermovir exhibited binding energies of -8.7 kcal/mol (Vina) and -7.8 kcal/mol for AutoDock 4). The most promising candidate, the hit compoud, demonstrated superior affinity (-10.1 kcal/mol for Vina and -10.7 kcal/mol for AutoDock 4). Toxicity was assessed in silico using the ProTox and TEST. methods. While ProTox classified letermovir as toxicity class 4 (LD_{50} = 500 mg/kg), experimental data suggest higher tolerability (LD_{50} > 2000 mg/kg). TEST predicted even greater toxicity for letermovir. For NL, in vitro cytotoxicity was evaluated via MTT assay on MRC-5 cells (human lung fibroblasts), yielding a CC_{50} of 2.87 mg/mL — approximately 9-fold less cytotoxic than letermovir (CC_{50} = 0.29 mg/mL). However, without EC_{50} data or confirmation via additional cytotoxicity assays (e.g., ATP, LDH), this comparison remains preliminary.

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NEW NITROGEN-CONTAINING HETEROCYCLES WITH *GEM*-DICHLOROCYCLOPROPYL FRAGMENT: SYNTHESIS AND *IN SILICO* ANALYSIS BIOLOGICAL ACTIVITY

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Nitrogen-containing heterocyclic compounds are included of the majority of modern drugs. Enhancement and modification of the biological effects is achieved by varying and combining various functional groups in the molecule. It is known that the presence of a *gem*-dichlorocyclopropyl fragment in the molecule imparts compounds with a selective hypolipidemic activity, for example, as in the drug ciprofibrate.

Based on chalcone **1**, with a *gem*-dichlorocyclopropyl fragment, we have synthesized new, previously unreported nitrogen-containing heterocyclic compounds: 2-pyrazolines **2**, **3**, **4**; spiropyrrolidineoxindoles **5**, **6**; and pyrazole **7**.

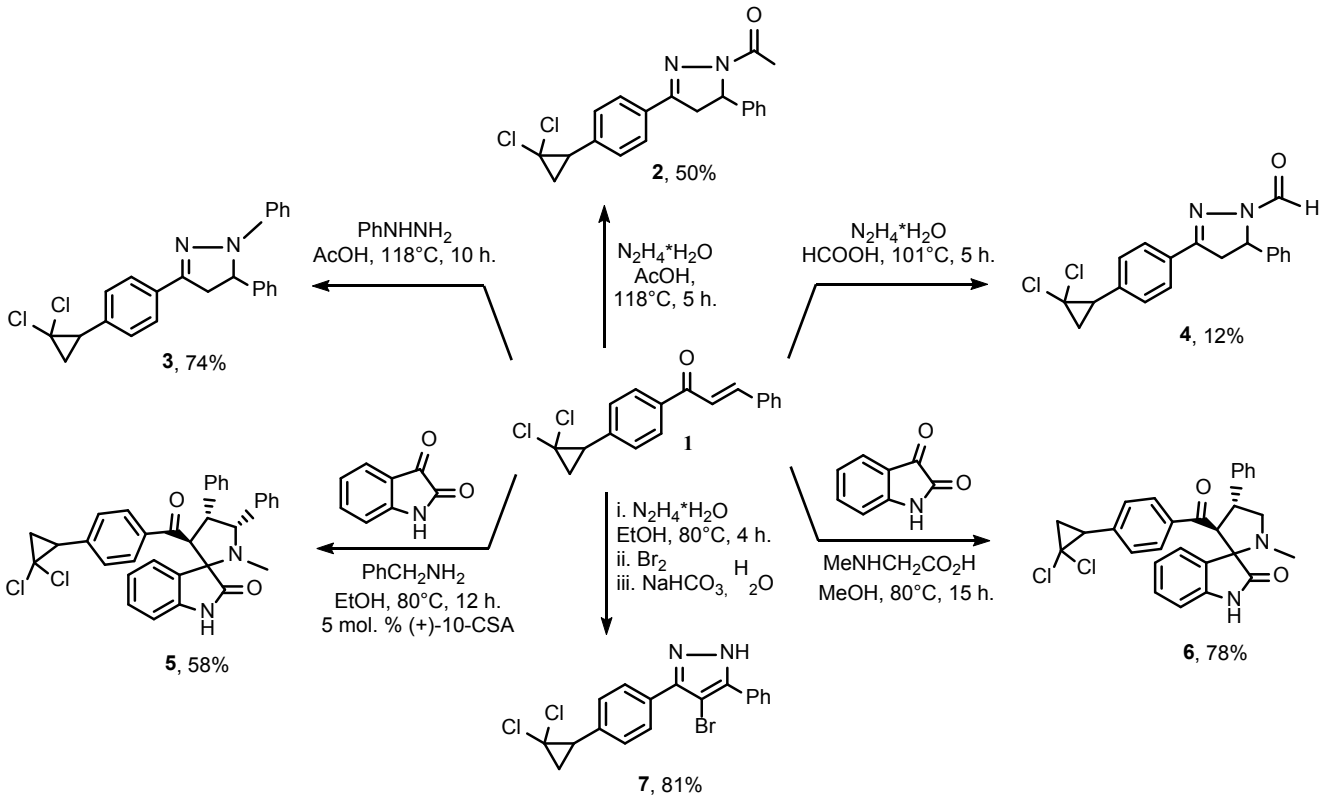

Figure 1. Structures and yield of all new compounds **2-7**.

A comprehensive preliminary analysis of the biological properties of the drugs was carried out on the platform PassOnline (https://www.way2drug.com/PASSOnline/services.php) to go online using services PASS Targets, CLC Pred, Acute Rat Toxity, DIGER-Pred, KinScreen, MetaTox.

The results indicate the possibility of further *in vivo* testing of the obtained bifunctional heterocyclic compounds in order to study the synergistic effect caused by the presence of heterocyclic and cyclopropane rings.

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A LARGE-SCALE DATASET OF QUANTUM CHEMICAL PROPERTIES OF DRUG-LIKE MOLECULES FOR Δ-LEARNING MODELS

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Quantum chemical calculations provide essential information for reactivity estimation, molecular force-field construction, and offer valuable features for QSAR studies. However, accurate ab initio methods are computationally expensive and not feasible for large-scale datasets, which limits their applicability in practical tasks. The development of approaches for approximating quantum chemical properties with ML models is of growing importance in cheminformatics and drug discovery. One promising way to reduce computational costs is the Δ-learning scheme [1], where machine learning models refine low-cost quantum chemical predictions to approximate higher-level calculations.

In this study, we present a newly prepared dataset, QURES, derived from the DrugBank database [2]. For nearly 10,000 drug-like molecules, conformational search and frequency calculations were performed at the GFN2-xTB level, followed by geometry and frequency refinement at the r2SCAN-3c level. Final single-point calculations were carried out with the ωB97X-D4/def2-TZVP method on the optimized conformers. The resulting dataset was then employed to systematically benchmark a range of machine learning algorithms, including classical regression models, tree-based ensembles, and graph neural networks.

Our analysis shows that Δ-learning substantially improves the accuracy of all tested models in predicting high-level quantum chemical properties. Classical machine learning approaches achieved performance comparable to graph-based deep learning methods, suggesting that Δ-learning can narrow the gap between traditional algorithms and neural networks. These results highlight the potential of integrating Δ-learning with low-cost quantum chemical methods for scalable and precise estimation of the properties of drug-like molecules.

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DENR+POL: THEORETICALLY CONSISTENT POLARIZABLE EMPIRICAL CHARGES FOR DRUG-LIKE AND BIOLOGICAL MOLECULES

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Molecular mechanics force fields and scoring functions are indispensable tools for *in silico* drug design. The electrostatic interactions play an important role in the ligand-receptor binding, and the development of more accurate models to describe electrostatics is one of the main ways for force fields and scoring functions improvement. In the practice of molecular modeling, electrostatic interaction energy is usually evaluated by the Coulomb law applied to the point atomic charges, calculated for the modeled organic and biomolecular system. There exist numerous methods for atomic charge calculation for organic molecules. Among them, empirical charge models based on electronegativity equalization have a special place. The advantages of this group of methods are theoretical and computational simplicity as well as the model's extensibility. However, the development of empirical charge models implies that the researcher should make his own choice about which theoretical principles will be integrated in his approach. The choice of erroneous or mutually inconsistent principles results in a nonphysical charge calculation method. One way to maintain the consistency is to adhere to the natural hierarchy of the electronic effects that control intra- and intermolecular interactions. In the past we have suggested the DENR [1] charge model that provides a theoretically correct description of the inductive effect [2-3]. Our actual work aims to introduce a new empirical charge calculation method, DENR+POL, that accounts for inductive and polarization effects in drug-like and biological molecules in a hierarchically consistent manner. The parameters of DENR+POL are fitted to the quantum chemical (QC) reference molecular electrostatic potential (MEP) of a combined molecular set that includes drug-like molecules from the PDBBind refined set as well as some molecules from the training set of the MMFF94 charge model. The accuracy of the MEP reproduction around an organic molecule is a natural metric to estimate the electrostatic component of the intermolecular interactions at typical distances where molecules form appreciable interactions. It is the primary and mandatory requirement for the pertinent charges relevant to drug discovery tasks. So parameter fitting to QC MEP is an additional advantage of our model. To illustrate DENR+POL possibilities in this work, we will inspect specific cases in which the explicit account of polarization is the most significant and evaluate the correctness of the description of charge distribution on specific molecular systems. For our analysis we have selected one drug-like molecule with an intramolecular H-bond and two drug-like molecules that are capable of forming an intermolecular H-bond. H-bond is interesting for us because in this case the polarization effect should play an important role.

The performed analysis revealed that the DENR+POL is able to polarize bonds much stronger than its predecessor, DENR. DENR+POL (inductive and polarization effects simultaneously) polarizes the entire network of atoms involved in intramolecular hydrogen bond formation, whereas DENR (inductive effect only) predicts almost identical charges at both polar hydrogens—that which forms H-bond and that which does not form it. The account of this additional intramolecular polarization helps to improve the quality of the quantum chemical reference MEP reproduction using DENR+POL. In the case of the intermolecular hydrogen bond complex, DENR+POL correctly predicts that the magnitude of the polarization response to perturbation is reasonably smaller compared to the magnitude of the unperturbed molecular electrostatic potential of the unperturbed electronic density of a non-interacting molecule and also polarizes all involved hydrogen bonds in the right direction. So the correct account for polarization on the basis of the correct account for inductive effect has improved an electrostatic description of the hydrogen bond in medicinal chemistry-related molecules. Based on the observed theoretical consistency and low computational cost (due to the empirical nature) of DENR+POL, we can recommend it as an appealing method of the first choice for ligand-protein complex simulations.

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NUTRICHRONOBIOTICS

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Circadian rhythms are endogenous biological oscillations with a period of approximately 24 hours, synchronized with the light–dark cycle. They regulate fundamental physiological processes such as energy metabolism, hormonal secretion, immune defense, cognitive performance, and sleep–wake cycles. Proper functioning of circadian clocks ensures metabolic homeostasis and overall health. Disruption of circadian rhythms, caused by factors such as irregular feeding patterns, night-shift work, jet lag, or exposure to artificial light at night, has been strongly associated with metabolic syndrome, obesity, type 2 diabetes, cardiovascular diseases, depression, neurodegeneration, and certain types of cancer [1].

In parallel with pharmacological chronobiotics, a related but distinct concept has recently emerged — nutrichronobiotics. These are dietary bioactive compounds of natural origin that exert regulatory effects on circadian timing systems. Unlike synthetic drugs, nutrichronobiotics are consumed as part of the daily diet and may therefore provide a safer, more accessible, and long-term approach to circadian modulation.

The objective of this study is to provide a structured overview of nutrichronobiotics, their mechanisms of action, and their potential health applications. Unlike synthetic drugs, nutrichronobiotics are naturally consumed in food and may represent a safer and more accessible approach to circadian modulation. However, the field still lacks a unified classification system and standardized clinical protocols. A structured framework [3,4] that integrates nutrichronobiotics into the broader landscape of circadian modulators is required. Such a framework should consider compound origin, molecular targets, chronopharmacological properties, and clinical potential. Establishing this knowledge base would advance chronobiology and nutritional science, opening opportunities for personalized dietary interventions to support circadian health and healthy aging.

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REPURPOSING ANTIVIRAL COMPOUNDS AS PUTATIVE LEADS AGAINST MONKEYPOX VIRUS A42R PROFILIN-LIKE PROTEIN: A MOLECULAR DYNAMICS SIMULATION, FREE ENERGY LANDSCAPE, AND DENSITY FUNCTIONAL THEORY STUDY

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Repurposing existing antivirals offers a rapid strategy to develop therapeutics against the global rise in MPXV cases. Herein, the molecular docking of Small Molecule Antiviral Compound Collection (SMACC) (3,146) for putative lead against MPXV A42R protein afforded the top 20 hit antivirals. Ensemble docking further identified the top six ACs viz: CHEMBL2172308, CHEMBL3110004, CHEMBL3133947, CHEMBL3133949, CHEMBL399129, and CHEMBL4454132 with favourable drug likeness and ADMET properties, alongside favourable safety profiles. Thermodynamic binding free energy (BFE) calculation of the hits identified CHEMBL3110004 (-30.64 kcal/mol), CHEMBL2172308 (-29.29 kcal/mol), and CHEMBL3133947 (-26.93 kcal/mol) as putative leads. The leads maintained thermodynamic stability and a compact A42R conformation throughout the 300-ns MD simulation. The BFE per-residue decomposition analysis unravelled a balance of favourable electrostatic and van der Waals contributions from binding site residues, including Thr39, Phe40, Asp19, Pro88, Thr84, and Pro107, as the complexes most stabilising terms. Moderate structural variation across MD clusters suggests key interactions with A42R binding site residues were preserved. The principal component analysis and free energy landscape analyses revealed that the CHEMBL2172308-, CHEMBL3110004-, and CHEMBL3133947-bound systems exhibited distinct, localized dynamic motions, suggestive of stabilization into functionally relevant conformations state. The balance between electrical stability, reactivity, and biological compatibility of the leads further position them as putative candidates to be repurposed as anti-MPXV compounds targeting the A42R protein. Further preclinical analyses are needed to verify the anti-MPXV of these leads.

A MODEL TO PREDICT LOGBB OF MOLECULES ACTIVE AGAINST THE H1 RECEPTOR

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In 2019, the World Allergy Organization reported that between 20% and 25% of the world's population suffers from allergies [1]. In Mexico, 40% of the population suffers from some form of allergy [2]. Most allergies have no cure, but antihistamine treatments can help relieve the symptoms of allergic reactions related to histamine H1 receptor activity, such as rhinitis, conjunctivitis, urticaria, atopic dermatitis, some anaphylactic reactions, nausea, and vomiting [3]. Despite their effectiveness in combating allergies, first- and second-generation antihistamines have multiple side effects, such as drowsiness, fatigue, and dizziness, among others. This is caused by their lack of selectivity for the H1 receptor, coupled with their high permeability to the blood-brain barrier, which allows them to enter the central nervous system, causing daytime drowsiness, difficulty with auditory stimuli, and impaired selective attention [4]. The permeability of a compound to the BBB can be measured by its LogBB value [5]. However, obtaining this value experimentally is complex, which is why the creation and optimization of mathematical models capable of effectively predicting the LogBB of molecules of interest is a necessity for the development of new drugs.

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EXPLANATION OF THE ANTIBACTERIAL IMPORTANCE OF SOME SYNTHESIZED DERIVATIVES OF THE TWO ANTIBIOTICS: CIPROFLOXACIN AND NORFLOXACIN *VIA IN SILICO* DOCKING STUDIES

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Staphylococcus aureus is recognized as a leading cause of bacterial infections in humans worldwide. While many infections remain asymptomatic, they can lead to life-threatening conditions such as pneumonia, meningitis, and septicemia particularly in immunocompromised individuals. Moreover, *S. aureus* is associated with high morbidity in clinical settings, especially in low-resource countries where access to medical treatment is limited [1]. On another hand, Ciprofloxacin and Norfloxacin are two prescription antibiotic used to treat a wide range of bacterial infections. They are part of a class of antibiotics called fluoroquinolones. Furthrmore, the identification of bioactive compounds from extensive molecular libraries is a critical phase in the drug discovery process. To facilitate this, computational and molecular modeling techniques have become indispensable, providing deep insights into the molecular mechanisms underlying biological systems. Notably, methods such as molecular docking techniques are extensively used to uncover novel hits across a range of therapeutic targets [2].

Motivated by these findings, we carried out theoretical studies to explore the biological potential of derivatives of these two well-known antibiotics. Specifically, we focused on molecular docking to predict their inhibitory mechanisms against target bacteria. The results revealed notable intermolecular interactions with key amino acids in the active site, indicating promising inhibitory potential.

According to the results obtained, the hydrazide fragment linked to the antibiotic by organic synthesis and the molecular docking is carried out against the target: 'carotenoid dehydrosqualene synthase from *S. aureus* (pdb: 2zcq)', a significant improvement in the antibacterial potential is observed and this is justified by the binding energy values of the docking complexes which show that the derivative showed a higher score (a lower binding energy value) than the corresponding antibiotic. On the other hand, this information is consolidated by the analysis of the intermolecular interactions formed between the docked ligand and the amino acids of the active site of the target used. The ciprofloxacin derivative showed 4 H-Bonds including one with the amino acid Gln165 by the fluorine atom of ciprofloxacin while the hydrazide function formed three H-Bonds with the residues: Asp48 and Asp52. On another hand, the norfloxacin derivative also showed four hydrogen bonds similar to those of ciprofloxacin derivative while norfloxacin could not form any. The above results show that the derivatives of antibiotics (Ciprofloxacin and Norfloxacin) and especially closing the hydrazide function showed a very significant antibacterial potential against the strain *S. aureus*.

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ANTIBACTERIAL ACTIVITIES OF MELDRUM'S ACID DERIVATIVES: *IN VITRO* AND MOLECULAR DOCKING STUDIES

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Antimicrobial resistance (AMR) is a growing global health threat, caused by the rise of antibiotic-resistant bacteria, which makes infections harder to treat. In 2019, AMR was linked to an estimated 1.27 million deaths worldwide. This issue increases treatment costs, risks outbreaks, and limits the effectiveness of antibiotics. Meldrum's acid derivatives are among the promising candidates due to their versatile structure and potential biological activity. This study evaluates the antibacterial potential of five synthesized Meldrum's acid derivatives through both *in vitro* and *in silico* approaches. Antibacterial activity was tested against *Bacillus cereus*, *Bacillus spizizenii*, *Shigella sonnei*, and *Proteus vulgaris* using the disk diffusion, minimum inhibitory concentration (MIC), and minimum bactericidal concentration (MBC) methods. Molecular docking was performed using SwissDock against *Bacillus subtilis* DNA gyrase subunit B (PDB ID: 4URM). Among the tested compounds, **M3A** exhibited moderate antibacterial activity as shown by visible inhibition zones in the disk diffusion assay, along with quantifiable MIC and MBC values. Molecular docking against *B. subtilis* DNA gyrase subunit B (PDB ID: 4URM) revealed a binding affinity of -7.1 kcal/mol, indicating a moderate interaction. The compound formed a key hydrophobic contact with an isoleucine residue at 3.4 Å, which may contribute to stabilizing its position within the active site. However, no significant hydrogen bonds were observed, and interaction with ASN54 was weak due to the longer distance (5.2 Å). In contrast, the positive control, Cefotaxime, showed a slightly stronger binding score of -7.4 kcal/mol and formed two hydrogen bonds with ARG144 at optimal distances (2.9 Å and 3.1 Å), indicating a more stable and specific binding. These findings suggest that while **M3A** can engage the target protein through hydrophobic interactions, further structural modification could enhance its binding strength and antibacterial potential. To conclude, **M3A** shows potential as a lead antibacterial compound, supported by both experimental and computational results. Further structural optimization and biological evaluation could enhance its efficacy and broaden its antibacterial spectrum, contributing to the ongoing search for effective alternatives to combat AMR.

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FROM *IN SILICO* DESIGN TO EXPERIMENTAL IMPLEMENTATION: DEVELOPMENT OF A NOVEL GLUCOKINASE ACTIVATOR

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Type 2 diabetes is a prevalent disorder characterized by dysregulation of glucose homeostasis. One of the most promising therapeutic targets for the development of novel hypoglycemic agents is the enzyme glucokinase (GK), which plays a central role in maintaining glucose homeostasis [1]. Activation of GK enhances hepatic glucose utilization and insulin secretion by the pancreas.

The objective of the present study was to perform computational modeling, synthesis, and in vitro experimental evaluation of novel imidazo[4,5-*b*]pyridine derivatives as potential GK activators. Virtual screening of a compound series was conducted using molecular docking with the Schrödinger software suite (Maestro 11.8, XP mode). The human glucokinase crystal structure (PDB ID: 3H1V) was used as the target [2]. Binding efficiency was assessed using the XP-GSCORE function, which estimates the ligand–enzyme complex energy. For high-ranking compounds, ADME parameters were calculated to predict oral bioavailability and pharmacokinetic profiles.

The most promising derivatives were synthesized and subjected to initial *in vitro* evaluation of biological activity. Hypoglycemic effects were assessed in rat liver homogenates using the Long method, with glucose concentrations determined by the Somogyi–Nelson assay.

From the primary screening of the focused library, 30 compounds were selected. Analysis of interactions with the allosteric GK site revealed the presence of unoccupied pockets potentially available for ligand optimization. Within the framework of *de novo* design, benzyl-substituted derivatives were developed, demonstrating a substantial increase in binding energy. The highest efficacy was observed for compound **2e** (XP-GSCORE = –12.23 kcal/mol), whose high affinity was attributed to π–π stacking interactions between a benzyl fragment and the TYR214 residue, as well as optimal occupancy of the binding pocket. ADME calculations confirmed that compound **2e** meets the criteria for oral bioavailability.

In vitro experiments demonstrated dose-dependent activation of GK by the synthesized compound **2e**. The results highlight the effectiveness of the strategy of modifying imidazo[4,5-*b*]pyridine derivatives for the development of GK activators. Compound **2e** was identified as the most potent ligand *in silico*, successfully synthesized, and exhibited significant activating activity in biological assays. These findings support the consideration of compound **2e** as a lead structure for further preclinical development of novel antidiabetic agents.

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USING THE MOLECULAR DOCKING METHOD TO EXAMINE A SOME SUBSTITUTED-PIPERIDINE-3-CARBOXAMIDE DERIVATIVES AS ACTIVE INGREDIENTS IN THE TREATMENT OF CROHN'S DISEASE

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In this study, I investigated the feasibility of using some substituted piperidine-3-carboxamide derivative compounds, which have never been synthesized before and have not been included in the literature, for the treatment of Crohn's disease, a chronic, inflammatory bowel disease that can affect any part of the digestive system, by molecular docking method. For this purpose, fifty different piperidine-3-carboxamide derivative molecules were used in molecular docking studies with nine different proteins using the Auto Dock Vina program. Among the molecules, the highest docking score of -12.8 kcal/mol was obtained between the compound 1-[2-(2-(4-bromophenyl)-4-[(E)-2-phenylhydrazinylidene]-1,2-dihydro-1,3,5-triazin-6-yl)ethyl] piperidi- ne-3-carboxamide and the protein with PDB code 1KMV. Boiled-egg graphs and bioavailability radars were drawn for the ten molecules with the highest docking scores among the fifty molecules studied.

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IN SILICO ADMET PROFILING OF SUBSTITUTED PIPERIDINE-3-CARBOXAMIDE DERIVATIVES AS POTENTIAL CROHN'S DISEASE

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In this study, I have carried out ADME studies on seven different substituted-piperidine-3-carboxamide derivatives compounds, which we have considered as drug active ingredients that can be used in the treatment of Chron's disease with dokking studies I have done in our previous studies. In this context, these molecules were examined in terms of physicochemical properties, lipophilicity, water solubility, absorption property, distribution property, metabolism property, toxicity property, environmental toxicity property, tox21 pathway property, and medicinal chemistry property. According to the results obtained, it was concluded that (E)-4-((4-(((4-bromopyridin-1(2H)-yl)methylene)amino)-3-(4-methoxyphenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)methyl) piperazine-1-carboxylic acid molecule is the most ideal molecule that can be used in the treatment of Chron's disease in terms of ADME properties among the molecules studied.

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THEORETICAL MODELING OF HOW POLYCAPROLACTONE SURFACE MODIFICATION AFFECTS THE SORPTION OF BANEOCIN COMPONENTS

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Wound healing is associated with high risks of bacterial infection. One effective approach to mitigating potential complications is the use of wound dressings based on nanofiber materials. These dressings prevent the formation of scar tissue and promote accelerated regeneration by mimicking the extracellular matrix and creating an optimal environment for cell attachment. To enhance the therapeutic effect and speed up regenerative processes, modern wound dressings are enriched with antimicrobial peptides (AMPs), growth factors (GFs), enzymes (ENZs), and various pharmaceutical agents.

A significant number of studies have been conducted on the incorporation of the following antibiotics into wound dressings: gentamicin, ciprofloxacin, vancomycin, mupirocin, and tetracycline. However, these drugs are only effective against specific bacterial strains, can exhibit toxicity upon topical application, and may inhibit tissue regeneration.

The biopolymer polycaprolactone (PCL) is widely used in biomedicine for wound healing. It constitutes a dense and porous substrate composed of a repeating chain [-$(CH_2)_5$-CO-O-]n. Surface modification with various functional groups enhances the sorption properties of the polymer. The antibiotic Baneocin, which consists of bacitracin and neomycin, was selected for this study. It is active against both Gram-positive and Gram-negative bacteria; its high bioavailability minimizes toxicity risks, and it is well-tolerated by skin tissues.

The aim of this work is to utilize theoretical modeling to study the effect of polycaprolactone surface modification on the sorption of components of the antibacterial drug Baneocin: bacitracin and neomycin.

Geometry relaxation and energy calculations for the structures were performed using the Density Functional Tight Binding (DFTB) method within the DFTB+ software package. The third-order parameter set 3OB for biological and organic systems was employed.

Quantum chemical analysis showed that surface modification increases the sorption capacity for the components of Bacitracin compared to the unmodified surface. The main mechanism for improving sorption is the formation of a network of hydrogen bonds and electrostatic interactions. Surface activation with EDC further enhances binding, ensuring the formation of covalent amide bonds with the substrate, which is accompanied by a significant redistribution of charge, primarily along the C–N bond.

Thus, our simulated suture material represents a new approach to creating wound dressings based on polycaprolactone immobilized with Bacitracin. The resulting material is biocompatible, works against both Gram-types of bacteria, is non-toxic, and promotes fibroblast survival.

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EXPLORING SMALL CYCLIC PEPTIDES AS POTENTIAL MODULATORS OF NEUROTENSIN RECEPTOR 1

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Diketopiperazines (DKPs) are small, stable cyclic dipeptides that are gaining attention as promising drug-like molecules [1]. In this study, we looked at five Type I DKPs including ABOTOB, BEMYEY, BOCSIV01, BUVKEJ01, and CEWFER, to see if they could interact with the Neurotensin Receptor 1 (NTSR1), a Class A G-protein coupled receptor (GPCR) involved in brain function and some types of cancer. We used molecular docking to check how well these DKPs could bind to NTSR1, based on crystal structure (PDB ID: 4GRV) obtained from PDB bank [2].

The docking was carried out using AutoDock 4.2 [3], and the results showed that all five DKPs could interact with important amino acids inside the receptor's binding pocket. Among them, BUVKEJ01 showed the strongest predicted binding, forming several hydrogen bonds that suggest a stable and specific interaction with the receptor.

These results suggest that DKPs may have the potential to become useful tools or even lead compounds in drug discovery for diseases related to NTSR1. Further testing and development are needed to explore this possibility in more depth.

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NEW STEROID CARBAMATES: SYNTHESIS, *IN VITRO* BIOLOGICAL ACTIVITY AND *IN SILICO* ADMET AND DOCKING STUDIES

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Steroids have significant role in the regulation of many biological processes. They manifest their activity by binding for steroid receptors. These receptors are predominantly expressed in hormone-dependent cancers. Androgen receptors (AR) are highly expressed in prostate cancers, while glucocorticoid receptors (GR) are expressed in multiple epithelial cancers, and their presence is associated with increased aggressiveness of many cancers.[1,2] Because of that, ligand-binding domains of these receptors represent a good target for design of new molecules that could be their potential ligands. Aldo-keto reductases (AKR) represent a large family of enzymes which have a crucial role in metabolism, cell protection and tumorigenesis. AKR1C3 and AKR1C4 are involved in tumorigenesis in cancer cells as well as in the development of therapy resistance.[3,4] On the other hand, carbamates represent a large group of organic molecules, that have hydrogen bond-donor and hydrogen bond-acceptor atoms. This group can establish interactions with amino acid residues in the active center of an enzyme or ligand-binding domain of a receptor.[5] Because of that, we synthesized new 17-carbamate steroids in testosterone series with aliphatic substituent at nitrogen atom and examined their *in vitro* biological activity. Two of three newly synthesized compounds showed binding affinity to the ligand-binding domain of androgen receptor (LBD-AR), while one of them showed binding affinity to LBD-GR. All tested compounds showed inhibitory activity against AKR1C4 isoform over 74%. Only one of them showed significant inhibitory activity against AKR1C3. For all of these molecules, *in silico* ADMET predictions were performed. All tested compounds belong to fifth class of toxicity with LD_{50} = 4000 mg/kg and they showed immunotoxicity, respiratory toxicity and they could penetrate the blood-brain barrier and be apsorbed in gastrointestinal tract. Docking was performed for molecules that showed the best *in vitro* results. Compounds **1** and **3** showed about 75% and 71% binding to the LBD-AR compared to control. Compound **3** also showed 74% binding for LBD-GR for antagonistic form. Compound **1** showed 69% binding for AKR1C3 compared to control docking.

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REPURPOSING SOME BETA-BLOCKER DRUGS AS ANTI-CANCER: *IN SILICO* STUDY

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Drug repurposing represents a strategic approach to identify novel anticancer therapies by repurposing existing drugs with known safety profiles, thereby accelerating development timelines. Beta-blockers, traditionally used for cardiovascular disorders, have shown promising anti-tumor effects through modulation of beta-adrenergic signalling pathways implicated in cancer progression. This study focuses on evaluating the potential of FDA-approved beta-blockers and their derivatives as inhibitors of the androgen receptor (AR), a key target in prostate cancer.

An *in silico* pipeline integrating virtual screening and molecular docking was utilized. A library of beta-blockers was sourced from PubChem, prepared by energy minimization using the MMFF94 force field in PyRx 0.8, and converted to PDBQT format via Open Babel. The AR structure (PDB ID: 5T8E) was prepared using AutoDock Tools v1.5.7 by removing water molecules, adding polar hydrogens, and assigning Gasteiger charges. Virtual screening was performed with AutoDock Vina (exhaustiveness = 8), followed by redocking of top hits (exhaustiveness = 108). Binding affinities were assessed, and interactions were visualized using Discovery Studio Visualizer v21.1.0 and PyMOL v2.5.

Virtual screening identified three top-ranking ligands based on binding affinities and pharmacophoric features: 4,4,4-trifluoro-1-(4-nitrophenyl)-3-(trifluoromethyl)butane-1,3-diol (a Nifenalol derivative; -9.1 kcal/mol), Idropranolol (-8.9 kcal/mol), and Indenolol (-8.9 kcal/mol). Molecular docking revealed stable ligand-receptor complexes primarily stabilized by hydrogen bonds (key interactions with polar residues), van der Waals forces, and π–π stacking. Hydrophobic contacts and electrostatic interactions further contributed to binding specificity. Docking poses highlighted critical amino acid residues in the AR active site, underscoring the role of non-covalent interactions in ligand recognition and orientation.

This computational study provides evidence for the repurposing of beta-blockers as AR inhibitors for prostate cancer therapy. The selected ligands exhibit high binding affinities and favorable interaction profiles, positioning them as promising leads for lead optimization and in vitro validation. These findings advocate for further exploration of synergistic effects in combination therapies to enhance anticancer efficacy, potentially reducing resistance and side effects in clinical settings.

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FERROSTATIN-1: A PROMISING NEUROPROTECTIVE AGENT AGAINST DEGENERATIVE DISORDERS

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Ferroptosis is a form of regulated cell death that occurs as a consequence of iron-mediated accumulation of intracellular reactive oxygen species, leading to accelerated lipid peroxidation and irreversible damage to the cell membrane. Inhibition of ferroptosis has been considered a promising strategy for the prevention and treatment of various diseases, including cancer, ischemia, iron toxicity, neurological disorders, single or multiple organ injuries, infarction, and stroke. Ferrostatin-1, a member of the free radical scavenging antioxidant group, exerts inhibitory effects on ferroptosis by capturing peroxyl radicals. Due to this property, it has emerged as a potential candidate for the prevention or treatment of neurodegenerative diseases. The objective of the study is to investigate the physicochemical and pharmacokinetic characteristics, possible targets, biological activity related with neurodegenerative disorders and toxicity profile of ferrostatin-1 using various in silico tools including pkCSM, SwissADME, PASSTarget, and PASSOnline Total, respectively. The obtained results revealed that ferrostatin-1 fully complies with Lipinski's Rule of Five as well as Ghose, Veber, Egan, and Muegge druglikeness rules. The most reliable possible direct protein target of ferrostatin-1 is cytochrome P450 2J2 in terms of confidence score (CS=0.523). This has been followed by serine/threonine-protein kinases PFTAIRE-1, NEK6, PCTAIRE-2, and alpha-synuclein with CS of 0.499, 0.481, 0.456, and 0.444, respectively. Nuclear receptor subfamily 0 group B member 1 (NR0B1), nuclear receptor coactivator 1 (NCOA1), sphingomyelin phosphodiesterase, and signal transducer and activator of transcription 1-alpha/beta are predicted as mediated protein targets of with a CS higher than 0.5. Ferrostatin-1 demonstrated membrane permeability inhibitor activity with the maximum activity probability (Pa) score of 0.757. Ubiquinol–cytochrome-c reductase, 3-hydroxybenzoate 6-monooxygenase, methylenetetrahydrofolate reductase (NADPH) and oxidoreductase inhibitory effects, with corresponding Pa values of 0.751, 0.682, 0.611, 0.581, respectively was also determined. Additionally, the compound estimated to treat phobic disorders, and acute neurologic disorders with Pa values of 0.678 and 0.500, respectively. Although there is a possibility of activity for other neurodegenerative diseases such as dementia, Parkinson's, Huntington's, Prion, and amyotrophic lateral sclerosis diseases, their Pa was found to be less than 0.5. Ferrostatin-1 has also been estimated to have inhibitory effects on antioxidant and anti-inflammatory enzyme systems that may be associated with neurodegeneration. Superoxide dismutase, lipid peroxidase, and peroxidase inhibitory effects, as well as antagonistic effects on TNF-α and interleukins was determined. ADVERPred predicted nephrotoxicity for ferrostatin-1 with a Pa value of 0.271. Since ferrostatin-1 has been considered a potential candidate for treating neurodegenerative diseases, we conducted analysis using several in silico tools, and our results further supported this assumption. In conclusion, our results indicate that ferrostatin-1 meets drug-likeness criteria, and displays a selective toxicity profile, suggesting therapeutic potential in ferroptosis-related disorders. The direct and mediated protein targets of the compound are found to be associated with the nervous system. However, as its activity against any specific disease is not particularly pronounced, further studies are required to clarify its pharmacological role, particularly in neurodegenerative diseases and safety profile.

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TIP: WEB APPLICATION FOR PREDICTING DRUG–TRANSPORTER INTERACTIONS

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Drug transporters play a key role in the absorption, distribution, metabolism, and excretion (ADME) processes of drugs, determining their pharmacokinetic profile. Understanding the drug-transporter interaction profile is critically important for enhancing therapeutic efficacy, modulating drug delivery to target organs, and overcoming multidrug resistance. Transporters also serve as major mediators of adverse drug interactions and cause significant individual variability in therapeutic response, which is often associated with genetic polymorphism. Moreover, they influence tissue distribution and accumulation of drugs, which is directly related to their toxicity and safety. The need to create a universal model for predicting interactions with all human transporters stems from the critical importance of these proteins in assessing ADME properties, determining bioavailability, and predicting drug interactions during drug development.

For preliminary assessment of interactions of drug candidate compounds, quantitative structure-activity relationship (Q)SAR analysis methods are used, based on which (Q)SAR models are created, including those incorporated into freely available web services. Web services such as preADMET, SwissADME, pkCSM, and Deep-PK mainly provide the ability to predict compound interactions with P-glycoprotein and some OCT and OATP1B transporters, which limits their application. The PASS Online web service is capable of predicting interactions with a larger number of transporters, though this prediction constitutes only a small fraction of the predicted biological activity spectrum. A specialized freely available web application for predicting the interaction profile of organic compounds with human transporter proteins has not been created to date.

In this work, based on information from the ChEMBL v.35 database, a training set of more than 37,830 compounds experimentally tested on 177 human transporters with determination of IC_{50} or K_i values was created. After removing duplicates and performing classification annotation of compound-transporter interactions (using a 10 μM threshold) to assign compounds to active and inactive classes, structure-activity classification models were developed using the PASS computer program [1]. The average invariant accuracy of prediction (IAP) of the obtained models for assessing interactions with 94 human transporters was 0.966 (by leave-one-out cross-validation procedure). The obtained models were implemented in a new freely available web application for predicting compound interactions with human transporters based on their structural formulas (Mol format, SMILES, drug name) TIP - Transporter Interaction Predictor (https://way2drug.com/TIP/). The prediction results provide a list of transporters with which interaction is predicted, along with Pa values (probability that the compound belongs to the active compound class) and Pi values (probability that the compound belongs to the inactive compound class), as well as ChEMBL identifiers, UniProt identifiers, and TCDB (Transporter Classification Database) classifications for each transporter.

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ON MECHANISM OF REACTION OF PENICILLIN-BINDING PROTEIN WITH BORONIC ACID UP TO TRICOVALENT ADDUCT FORMATION

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Penicillin-binding proteins (PBPs) are an enzyme family that catalyzes the final stages of bacterial cell wall formation. Inhibition of PBPs leads to disruption of bacterial cell wall formation and bacterial death. *Pseudomonas aeruginosa* is a pathogenic microorganism for humans which causes nosocomial infections. Among all PBPs of *Pseudomonas aeruginosa*, penicillin-binding protein 3 (PaPBP3) is the main drug target, since only its inhibition leads to bacterial death[1]. Treatment of *Pseudomonas aeruginosa* is limited due to its high resistance to β-lactam antibiotics. Boronic acids, among non-β-lactam antibiotics, are promising due to their ability to form a covalent adduct with the catalytic serine residue in the active site, mimicking the tetrahedral transition state of the natural transpeptidation reaction. Structural studies have shown formation of a tricovalent adduct not only with the catalytic serine, but also with a serine from the SXN motif and a lysine from the KTG motif[2]. The formation of such an adduct increases the residence time of the inhibitor. To date, the mechanism of tricovalent adduct formation has not been thoroughly studied. Understanding the reaction mechanism may help in the development of new boronic acid–based inhibitors.

In this study, molecular modeling of the proposed five-stage reaction mechanism of PaPBP3 and ((2-nitrobenzamido)methyl)boronic acid was performed. For a monocovalent complex structure establishment, classical (MM) and hybrid (QM/MM) molecular dynamics (MD) were used. The reaction mechanism was investigated using QM/MM umbrella-sampling free-energy simulations. Additionally, difference in reaction paths between ((2-nitrobenzamido)methyl)boronic acid and (S)-(1-(2-nitrobenzamido)ethyl)boronic acid were studied using QM/MM MD simulations. An experiment has shown that (S)-(1-(2-nitrobenzamido)ethyl) boronic acid does not form the tricovalent adduct, only the monocovalent one[3]. Collective variable (CV) components related to the further monocovalent adduct transformation were investigated.

The quantum part was composed of an inhibitor molecule, side chains of Ser294, Lys297, Asn351, Lys484, backbone of Lys348, Ser350, Ser485, Ala488, entire Ser349, Gly486, Thr487 and a water molecule in contact with free H_Z atom of Lys487. The QM subsystem was calculated with the PBE0 functional with D3 dispersion correction and the 6-31G** basis set. MM subsystem was described using the CHARMM36 force field for enzyme molecule, CGenFF for boronic acid molecules and TIP3P for water molecules.

It was found that the final product is lower in energy than the non-covalent enzyme-inhibitor complex by 21.3 kcal/mol, which confirms the adequacy of the proposed mechanism. Analysis of CV components for ((2-nitrobenzamido)methyl)boronic acid and (S)-(1-(2-nitrobenzamido)ethyl)boronic acid shows that components distributions for the first one are slightly shifted toward lower values, corresponding to better binding. Pearson correlation coefficients between CV components distributions have smaller absolute values for the second one, therefore reaction for (S)-(1-(2-nitrobenzamido)ethyl)boronic acid proceeds with greater difficulty.

This research was carried out using the equipment of the shared research facilities of HPC computer resources at M.V. Lomonosov Moscow State University.

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COMPUTATIONAL WORKFLOW FOR PREDICTING DRUG METABOLISM BY GUT MICROBIOTA

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The human gut microbiota plays a crucial role in drug metabolism, with microbial enzymes capable of transforming pharmaceutical compounds, leading to altered drug efficacy, toxicity, or activation of prodrugs. Understanding these drug-microbiota interactions is essential for drug development and personalized medicine. To address this challenge, we have developed the HGMMX database and the MDM-Pred prediction model, designed to advance *in silico* analysis of drug metabolism by gut microbiota.

The HGMMX (Host Gut Microbiota Metabolism Xenobiotics) database contains curated information about 678 unique chemical compounds, including 368 substances metabolized and 310 not metabolized by human gut microbiota. Each entry provides comprehensive data: parent compound structure, metabolite structures, bacterial species responsible for biotransformation, reaction types, and metabolism-related information. The database includes approved drugs, dietary supplements, and other xenobiotics with their PubChem and DrugBank identifiers. Search tool enables users to query the database by compound name, structural similarity (using MNA and QNA descriptors), compound type, bacterial genus, and biotransformation reaction type.

The MDM-Pred web application provides predictions of drug metabolism by gut microbiota using PASS (Prediction of Activity Spectra for Substances) algorithm. Three classification models were developed: (1) prediction of microbiota-mediated drug metabolism (accuracy 0.85), (2) identification of responsible bacterial genera (average accuracy 0.92), and (3) prediction of biotransformation reactions (average accuracy 0.92). The models were trained on over 600 compounds from more than 80 publications and validated using leave-one-out cross-validation.

Studying drug metabolism by the microbiota is a complex and often unpredictable task. We believe the key to solving this problem lies in a smart combination of curated data and computational methods. To that end, we have established a complete computational workflow. It begins with the HGMMX database, the comprehensive resource of its kind, providing standardized chemical and biological data. This curated information then feeds into the MDM-Pred predictive model, which transforms the data into high-accuracy predictions of metabolizing bacterial genera and reaction types. This entire workflow, accessible via a freely available web interface, provides a tool for modern drug discovery.

Both resources are freely available at www.way2drug.com.

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THE FIRST CHEMOMETRIC REPORT ON ACUTE TOXICITY PREDICTION OF INSECTICIDES TOWARDS MULTIPLE SPECIES OF GRASSHOPPERS

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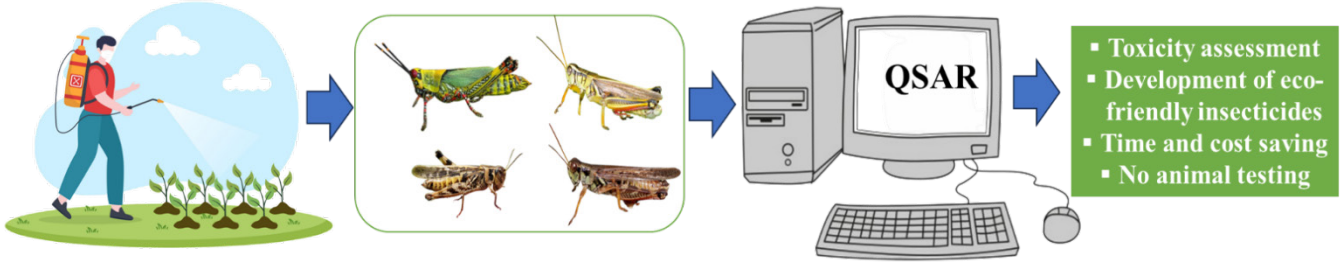
Insecticides are excessively used in agriculture to prevent insects from crops (crop destruction) which results in the fulfillment of the food demand of the population. These are also used to prevent airborne diseases, weeds in public places, etc. However, these insecticides are designed to be toxic for insecticides. But it has also serious adverse effects on humans and the environment. So, it is very essential to assess the toxicity of these insecticides before coming into use. Grasshoppers are one of the common pests in agricultural fields [1-2]. Experimental toxicity prediction requires high costs, lengthy, complex laboratory conditions, and a large number of animal sacrifices. Thus, *in silico* approaches such as Quantitative-Structure-Activity-Relationship (QSAR) are one best alternatives. In this present study, we have developed several multiple linear regression (MLR) models to assess the acute toxicity of insecticides towards multiple grasshopper species (*Zonocerus variegatus* (LC_{50}), two-stripped grasshopper (LD_{50}), migratory grasshopper (LD_{50}), and clear-winged grasshopper (LD_{50})) [1-2] strictly following the Organisation for Economic Co-operation and Development (OECD) guidelines. Final models were developed using simple and reproducible 2D descriptors. Statistical results of the developed models (R^2=0.730-0.787, Q^2_{LOO}=0.564-0.681, Q^2_{F1}=0.612-0.798, Q^2_{F1}=0.606-0.839) showed that the models are robust, reliable, and predictive. Several biomarkers (such as ether groups, mean atomic polarizability, etc. enhance the toxicity) are also reported in this study, which will be helpful in the development of eco-friendly and safer insecticides. There is no in-silico study available on acute toxicity prediction of insecticides towards grasshoppers. This study will be helpful in toxicity data gap filling, strictly adhering to the reduction, replacement, and refinement (RRR) guidelines. Therefore, it will be helpful to maintain a healthier and safer ecosystem.



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THE POLAR PATCH IN THE HYDROPHOBIC GATE OF THE TRPV1 CHANNEL AND ITS FUNCTIONAL ROLE

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TRPV1 (Transient Receptor Potential Vanilloid 1) is a polymodal ion channel activated by high temperatures (>43 °C), acidic pH (<5.9), and chemical ligands. In humans, TRPV1 mediates temperature and pain sensitivity, and its dysfunction is associated with pathological pain syndromes, making it an important pharmacological target for analgesic development.

The ion-conducting pore of TRPV1 is formed by four transmembrane helices S6 and adopts three major conformational states: α-closed, π-closed, and π-open [1]. The activation gate corresponds to the hydrophobic region of the pore that regulates ion conduction. In the π states, the gate is formed by the hydrophobic I679 side chains together with the polar N676 residues exposed to the pore lumen, while in the α-closed state these residues rotate outward, L678 and M682 form the highly hydrophobic region in the gate. Here, we investigated the role of N676 in TRPV1 gating using molecular dynamics (MD), the "dynamic molecular portrait" (DMP) approach [1], and *in silico* mutations.

Based on the MD simulation data, the S6 helix was mapped in the vicinity of the gate. Three types of parameters were plotted on the maps: molecular hydrophobicity potential (MHP), showing the distribution of hydrophobic and hydrophilic properties on the molecular surface [2], and complementarity of S6 contacts with neighboring helices and with water, thus reflecting the consistency of MHP between the contacting molecules. Mapping revealed that N676 forms a local polar patch in the hydrophobic environment of I679, promoting its hydration in the π-open state, thereby facilitating water and ion penetration. Interestingly, N676 also introduces a non-complementary region in the inter-helix contacts. Apparently, this can result in lowering the energetic barrier for TRPV1 transitions between the states.

Using the method of "alchemical" transformation, relative free energies (ΔΔG) were calculated for a few mutations of N676. It was shown that substitutions of this residue with either more hydrophobic (N676A – $\Delta\Delta G_{mut} \approx$ -12 kJ/mol, N676L – $\Delta\Delta G_{mut} \approx$ -24 kJ/mol) or more hydrophilic (N676S – $\Delta\Delta G_{mut} \approx$ -7 kJ/mol) amino acids shifted the equilibrium toward closed states, consistent with experimental evidence that the N676A variant produces a non-conductive TRPV1 phenotype [3].

Overall, N676 stabilizes the hydrated π-open state, thereby promoting pore conduction. The evolutionary conservation of this residue likely reflects its unique balance of polarity and steric properties, ensuring proper gating dynamics across the entire TRPV family.

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MODULATING POTENTIAL OF SPILANTHOL ON NEUROINFLAMMATION: *IN SILICO* ANALYSIS IN BV2 MICROGLIA

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Neuroinflammation is a fundamental process in the central nervous system (CNS), mediated primarily by microglia and astrocytes, which regulate the immune response to external aggressions. Although it plays a protective role, its excessive activation can compromise neuronal homeostasis, favoring the release of pro-inflammatory cytokines and contributing to the progression of neurological diseases. This condition directly impacts synaptic plasticity and cognitive processes and is associated with the worsening of neurodegenerative conditions. In this context, interest in natural compounds as modulators of this response is growing, given their chemical diversity and low toxicity profile. Among these, spilanthol stands out, an alkaloid found in jambu (*Acmella oleracea*), traditionally used in the Amazon region and recognized for its broad spectrum of biological activities, including analgesic, anti-inflammatory, and anxiolytic effects. Despite its pharmacological potential and potential ability to cross the blood-brain barrier, the molecular mechanisms underlying its role in neuroinflammation remain poorly explored. To address this gap, the present study conducted in silico analyses focusing on the transcriptomic profile of lipopolysaccharide (LPS)-induced microglial activation in BV2 cells. Public RNA-seq data available in the GEO repository (accession GSE79898) containing profiles of cells stimulated with LPS or maintained under control conditions for 4 hours were analyzed. A differential analysis was performed with the DESeq2 package, considering genes with padj < 0.05 and $|\log2FC| \geq 1$, and using the lfcShrink function to reduce fold change values. Subsequently, spilanthol target prediction was performed using different systems pharmacology platforms, including SwissTargetPrediction, SuperPred, PASS, and CTD, and the results were standardized for integration with differentially expressed genes. Functional enrichment analyses revealed coordinated activation of classic innate immunity pathways, such as TNF, NF-κB, IL-1/IL-6, and IL-17, as well as processes associated with the inflammatory response. Gene repression, in turn, was limited and less organized. Integration with spilanthol target prediction highlighted four convergent genes: TLR2, NFKB1, MMP2, and KCNA3, directly related to microglial activation, transcriptional regulation, and tissue remodeling. These findings suggest plausible mechanisms by which spilanthol could modulate neuroinflammation by interfering with strategic inflammatory response points in the CNS. In conclusion, the study confirmed that stimulation of BV2 microglia with LPS triggers a robust and reproducible inflammatory response, validating the experimental model used. Furthermore, evidence has emerged that spilanthol may act as a modulator of critical neuroinflammation pathways, highlighting it as a promising candidate for the development of innovative therapeutic approaches for central nervous system diseases. Future experimental investigations are timely to deepen the understanding of its mechanisms of action and consolidate its clinical potential.

INHIBITION OF *HELICOBACTER PYLORI* UREASE BY *PERSEA* AMERICANA SEED COMPOUNDS *IN SILICO* AND *IN VITRO*

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Helicobacter pylori is a gram-negative bacterium who infects over 40% of world's population and is major cause of gastric cancer. Its persistence on gastric mucosa relies on virulence factors such as urease, an enzyme that converts urea into ammonium, neutralizing the stomach acid. Even though infection may be treated by antibiotics, the emergence and spread of resistant strains compromises therapy efficacy and highlights the need for new bioactive compounds. *Persea americana* (Laureaceae), known as avocado, is an meso-american native vegetal specie mostly destinated to alimentary and cosmetic applications of the pulp, which the seed is treated as industrial waste. However, it is known that avocado seeds are rich in bioactive compounds. Within this context, this study aimed to evaluate urease inhibition by bioactive compounds in avocado seed extract.

Hydroalcoholic seed extract was prepared by 7 days maceration of previously dried and grounded avocado seeds. The result solution was filtered, and the solvents were eliminated by rotary evaporation and lyophilization to obtain the crude extract. Urease inhibition was analyzed in vitro, and enzyme activity was monitored by ammonium production. Chemical characterization was performed by high resolution mass spectrometry, and the proposed compounds analyzed *in silico*. Way2Drug PASS Online was applied to select compounds with Pa higher than Pi as "Urease inhibitor". The selected compounds were optimized on physiological pH using MMFF94 on OpenBabel and docked on *H. pylori* urease chain B (available on Protein Data Bank, code 1E9Y using AutoDock Vina. The macromolecule was protonated by AMBER force field on Poisson-Boltzman and the gridbox was centered on active site, covering all important residues (20 x 26 x 22 A). Protocol was validated by RMSD < 2 A with co-crystallographic ligand acetohydroxamic acid (AHA). Finally, compounds' pharmacokinetic properties were predicted by SwissADME and analyzed according to Lipinsky rule of five.

Avocado crude extract showed 47.0 % of urease inhibition at 64 ug/mL. Mass spectrometry revealed the presence of long chain unsaturated fatty acids and acetogenins, such as avocadene, avocadyne, persediene, perseitol, persenone and persin. Twenty of twenty-three proposed compounds have Pa > Pi for urease inhibition, with higher value for palmitic and stearic acid (Pa = 0.665), and acetogenins Pa< 0.300. Only avocadyne, avocadyne acetate and chlorogenic acid don't have urease inhibition between the listed activities and therefore were excluded for molecular docking. In the molecular docking, palmitic (-4.7 kcal/mol) and stearic acid (-4.9 kcal/mol) showed binding energies lightly superior to AHA (-4.3 kcal), while the best result was for perseitol, which presented a binding energy of -6.3 kcal/mol. This suggests that perseitol may act by new mechanisms, that differ from AHA and from PASS models. Perseitol-target complex was stabilized by hydrogen bond interactions between ligand hydroxyl groups and protein residues Ala169, Asp362 and Ala365, in addition to nickel complexation. In SwissADME prediction, perseitol follows the Lipinski rule with one violation, due to large number of hydroxyl groups. In addition, the substance has low gastrointesinl permeation and is bot permeant to blood-brain barrier. Also does not inhibit methabolism enzymes neither is a glycoprotein P substrate. These findings indicate that avocado seed may have potential for *H. pylori* treatment, and perseitol is a possible lead compound for urease inhibitor. Theses findings must be better evaluated by further studies, to understand perseitol isolated effect *in vitro* and propose possible molecular modifications to enhance its action before drug development.

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DESIGN OF IRIDOIDS BASED ON THE STRUCTURE OF GENIPIN THROUGH *IN VITRO* AND *IN SILICO* STUDIES AGAINST CERVICAL CANCER

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Cervical cancer is a malignant neoplastic disease associated with human papillomavirus infection that originates in the cervix, ranking second in incidence and mortality in our country among the types of cancer that affect women. Some iridoids have been shown to have cytotoxic effects against different types of cancer *in vitro*, including geniposide and genipin [1]. In this study, *in vitro* cytotoxic activity of geniposide and genipin was evaluated in three cervical cancer cell lines, and iridoids were designed *in silico* based on the structure of the most active iridoid [2].

***In vitro* evaluation.** The cytotoxic activity of geniposide and genipin was evaluated using the sulforhodamine B technique in three cervical cancer cell lines: CaLo [VPH18, IIB], INBL [VPH18, IVB) and CaSki [VPH16, metastatic] during 72 h. The IC_{50} was obtained by regression analysis using the Prisma program [2].

***In silico* studies.** The literature was searched for iridoids with reported cytotoxic activity against cervical cancer. Those most structurally similar to geniposide and genipin were selected, and a SAR analysis was performed. The molecules were constructed in 3D, obtaining their lowest energy conformer with optimized geometry using the Spartan'20 program. A QSAR mathematical model was constructed using multilinear regression in Excel, using the molecular descriptors obtained from the optimized structures. Subsequently, a 2D and 3D molecular similarity analysis was performed. Finally, iridoids were designed based on the structure of the most active iridoid evaluated in this study and on the results of the SAR and QSAR analyses [2].

Genipin was found to have cytotoxic activity against all cell lines tested, especially against CaLo and CaSki (IC_{50}: 59 and 66 μM, respectively); however, geniposide was inactive.

It was observed that the presence of an aldehyde, a carboxylic acid, or a hydroxymethyl group at C4, as well as hydroxyl groups at C1, C6, and C8, and the absence of a double bond at C7-C8 increases the activity of iridoids. It was also observed that the dipole moment (ρ) is essential for cytotoxic activity against HeLa, as in some antiulcer compounds and also in some cytotoxic compounds against leukemia.

The following QSAR model was obtained from the 13 selected iridoids, including genipin:

$-\ Log\ IC_{50} = 0.1118(p) - 0.07433(\Delta PSA) + 2.56022(LogS) + 0.02923(\Delta Polarizability^2) + 1.2684$, which reveals that dipole moment is essential for cytotoxic activity, as is its polarizability. ($\Delta Polarizability^2$), its polar surface area (ΔPSA) and its water solubility ($LogS$). Ten iridoids designed based on the genipin structure were obtained, with higher predicted activity than the most cytotoxic iridoid in the literature (IC_{50}: 0.2 μM), according to the QSAR model. Ten iridoids designed based on the genipin structure were obtained, with higher predicted activity than the most cytotoxic iridoid in the literature (IC_{50}: 0.2 μM), according to the QSAR model.

Genipin showed low potency against the cell lines tested, so it was considered a lead compound. For this reason, iridoids were designed based on the structure of genipin, yielding ten candidates with IC50pred values between 0.001 and 0.147 μM.

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INTELLIGENT CONSENSUS PREDICTION (ICP) FOR TOXICITY ASSESSMENT OF DIVERSE CHEMICALS IN MAYFLY: A STEP TOWARDS ECOLOGICAL RISK MANAGEMENT

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Humans along with both aquatic and terrestrial species are exposed to toxicological threats as a result of the substantial use of pesticides in agriculture, which dramatically increases risk. Conventional methods are not widely accepted since they are expensive, time-consuming, and raise concerns about animal sacrifice. The quantitative Structure-Activity Relationship (QSAR), on the other hand, offers a distinct benefit for predicting the toxicity of substances. Using LD_{50} as a predetermined endpoint and adhering to OECD guidelines, the current study develops a partial least square (PLS)-based QSTR model for estimating the harmful effects of various chemicals against mayfly (Ephemera vulgata) species. Mayfly is useful in providing food for fish and is regarded as a standard species that maintains freshwater ecosystems and indicating heavy metal contamination. The generated model is reliable and robust, according to the results of the internal and external validation parameters (R^2 = 0.684-0.689, $Q^2_{(LOO)}$ = 0.648-0.661, Q^2_{F1} = 0.665-0.694, and Q^2_{F2} = 0.661-0.690). The model's external predictivity is improved with the application of intelligent consensus prediction (ICP) (Q^2_{F1}=0.726 and Q^2_{F2}=0.722) [1]. The information extracted that the key bio-markers for pesticide toxicity are presence of electronegative atoms, bulky fragments, number of aliphatic (CHR3) groups, less polar atoms, existence of toxic phosphate group, and high number of saturated single bonds. Additionally, the model is employed for screening the Pesticides Properties Database (PPDB) to identify new toxicants and ranking them according to their ecotoxicity. This validates the external predictability of the established model, facilitates regulatory decision-making, helps design eco-friendly chemicals, and contributes to build a sustainable earth.

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IN-SILICO EVALUATION OF SILYMARIN COMPOUNDS AS INHIBITORS OF HELICOBACTER PYLORI'S HOPQ ADHESIN

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Helicobacter pylori is a bacterium that is able to colonize the human stomach and induce chronic inflammation of the organ's epithelium, which can lead to the development of stomach cancer, and since the bacterium already shows resistance to the main antibiotics used in its treatment, there is the need for the development of new therapies against it. In order to colonize the stomach, *H. pylori* express a number of virulence factors that allow the bacterium to survive in such environment, and one of these virulence factors is the HopQ adhesin, which binds to members of the carcinoembryonic antigen-related cell adhesion molecule family (CEACAM), allowing the bacterium to adhere to the surface of cells that express such structures. In such context, silymarin, a compound made of flavolignans extracted from *Silybum marianum L. Gaertn.* seeds have already shown anti-*H. pylori* properties *invitro* essays and can represent a new way of treating the infection [1], but there is no clear information about the mechanism of action. Therefore, this work aimed to evaluate the possibility of the silymarin main compounds, silybinin A and B, isosilybinin A and B, silychristin, isosilychristin, taxifolin and silydianin, to act upon *H. pylori's* HopQ adhesin via molecular docking.

The compounds (ligands) were drawn in MarvinSketch and their geometry and protonation were optimized in the Avogadro software, while the HopQ structure complexed with one of its biological targets (CEACAM1), was obtained in the Protein Data Bank (PDB: 6GBG) [2] and optimized in the PDB2PQR platform. The binding site was obtained through the SuperStar software and docking was performed in the GOLD software, both contained within the CCDC library, using 10Å as the binding site radius and ChemPLP as scoring function and the results were analyzed in the DiscoveryStudio software.

The molecular docking resulted in fitness scores ranging from 47,95 (silydianin) to 66,42 (silychristin), which show that all the analyzed compounds possess a favorable interaction profile with the HopQ binding site. Moreover, it has been identified that all the compounds are able to stablish hydrogen bonds with multiple amino acid residues of the binding site, including those that are known to mediate the CEACAM1 binding by HopQ, such as SER135, THR136 and THR147, and also hydrophobic interactions with the residues within a hydrophobic pocket in the HopQ binding site. Silydianin, which got the highest fitness score is, were able to stablish strong hydrogen bonds with CYS103, THR129 and ASN131 while interacting with ILE102 and ILE242 of the hydrophobic pocket.

In conclusion this study found that all the eight main silymarin compounds are able to stablish strong interactions with amino acid residues in the binding site of HopQ, which can possibly result in its blocking and thus the disruption of the ability of *H. pylori* to bind to cells that express CEACAM molecules when in the presence of these compounds, hindering the establishment of the infection.

This study was supported by UFES and FAPES.

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COMPARATIVE EFFICIENCY OF STRUCTURE ACTIVITY RELATIONSHIP AND PROTEOCHEMOMETRIC MODELLING

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Virtual screening is widely applied in modern drug discovery. Well-known structure-activity relationship (SAR) methods rely on chemical structure comparisons. Proteochemometrics (PCM), which incorporates protein target descriptors, has emerged as a complementary approach, expanding SAR capabilities and enabling predictions for novel targets with little-known or unknown ligand spectra. While both SAR and PCM can predict ligands for well-characterized proteins, PCM is increasingly applied to this task without clear justification for its superiority.

This study rigorously compares the performance of SAR and PCM in predicting ligands for proteins with known ligand spectra, employing a novel validation scheme specifically designed to avoid biases inherent in standard PCM validation procedures. Our results demonstrate that PCM offers no significant advantage over SAR in this context. Furthermore, we demonstrate that the conventional validation techniques frequently used for PCM models produce artificially inflated performance scores, leading to potentially misleading conclusions regarding PCM's effectiveness compared to SAR. This highlights the critical importance of employing transparent and unbiased validation schemes when comparing different virtual screening methodologies, ensuring accurate assessment and informed selection of the most appropriate approach for a given drug discovery task [1].

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COMPUTATIONAL DRUG DESIGN OF 1,5-DISUBSTITUTED TETRAZOLES: A CHEMOINFORMATIC AND DE NOVO STRATEGY

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1,5-Disubstituted tetrazoles (1,5-DS-T) represent a class of privileged scaffolds with considerable potential across diverse therapeutic areas. In this work, we employed a comprehensive computational approach integrating chemoinformatic analysis, ligand-based target prediction, and *de novo* design to investigate this scaffold. Four virtual libraries were generated, including a set of 158 *in*-house compounds synthesized via the Ugi-azide multicomponent reaction [1-3]. Physicochemical property calculations and principal component analysis (PCA) confirmed that these libraries possess drug-like characteristics and structural heterogeneity. Unsupervised clustering using the *K-means* algorithm revealed notable chemical resemblance between our synthesized molecules and bioactive compounds cataloged in ChEMBL. This analysis guided the selection of CXCR3, a chemokine receptor implicated in cancer progression and drug resistance, as a key therapeutic target [4]. Molecular docking simulations, conducted with the crystal structure of CXCR3, identified several *in*-house and ChEMBL compounds with strong predicted binding affinities and favorable interactions within the orthosteric site. Subsequently, the compound with the lowest binding energy and a better ligand efficiency than the co-crystallized compound, was chose to create a pharmacophore model. The pharmacophore model was used in the PGMG server to guide bioactive molecules generation, these molecules [5], were filtered based on pharmacodynamic and pharmacokinetic parameters. The molecule that fulfills the filtering criteria, was chose as a template for a design by intuition, the designed molecules were filtered by molecular docking with CXCR3. As a result, a computational hit was obtained that will be submitted to synthesis and *in vitro* testing. These findings underscore the therapeutic relevance of 1,5-DS-T derivatives and demonstrate the effectiveness of computational methodologies in guiding early-stage drug discovery.

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COMPUTATIONAL CHARACTERIZATION OF PHYTOCHEMICAL INHIBITORS TARGETING CATHEPSIN B FOR POTENTIAL CANCER THERAPY

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Cysteine cathepsin proteases play a significant role in cancer progression, making them attractive targets for therapeutic intervention. Although several synthetic inhibitors have been developed, their use is often limited by adverse side effects. In contrast, phytochemical-based inhibitors offer a promising alternative due to their biocompatibility and reduced toxicity. This study aimed to identify potential phytochemical inhibitors of cathepsin B using a multi-parametric computational approach. A high-throughput virtual screening of 109 phytochemicals with reported anticancer activity, along with four FDA-approved drugs, was performed. Molecular docking revealed that isoquercetin exhibited the highest binding affinity (G-score: −8.010 kcal/mol), outperforming the reference drugs. Density functional theory (DFT) calculations were employed to analyze the structural, geometric, and electronic characteristics of the top-performing compounds. HOMO–LUMO energy gaps and molecular electrostatic potential surfaces supported their electronic stability and reactivity. Further, ADME profiling demonstrated favorable pharmacokinetic properties. Molecular dynamics (MD) simulations of 100 ns were carried out for the top phytochemical–cathepsin B complexes and sorafenib reference complex. Structural stability of the systems was evaluated using RMSD, RMSF, SASA, radius of gyration (Rg), and hydrogen bond interactions. Principal component analysis (PCA) and free energy landscape (FEL) analysis confirmed the dynamic stability and conformational flexibility of the complexes.

This integrated in silico investigation highlights isoquercetin as a potential natural inhibitor of cathepsin B, paving the way for the development of phytochemical-based cancer therapeutics.

NEW DIHYDROPYRIMIDINYL-2-HYDRAZONES: SYNTHESIS AND *IN SILICO* ANALYSIS OF BIOLOGICAL ACTIVITY

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The pyrimidine nucleus with a Schiff base moiety and a nitrile group is an excellent substructure for the development of agrochemicals and pharmaceuticals. In particular, some representatives of such compounds possess anticonvulsant and antiviral activities.

Our research group have obtained 6-oxo-4-pentyl-1,6-dihydropyrimidinyl-5-carbonitrile-2-hydrazones of substituted benzaldehyde (**6a-c**), isatin (**7a-c**), and salicylic aldehyde (**8a-e**), which have not been previously described in the literature, as a result of a condensation reaction between a hydrazine derivative **5** and the corresponding carbonyl compounds (Fig. 1). The building block of 3,4-dihydropyrimidine-2(*1H*)-thione **4**, required for further synthesis of the compound **5**, was constructed by the multicomponent Biginelli reaction between ethyl cyanoacetate **2**, thiourea **3**, and hexanal **1**.

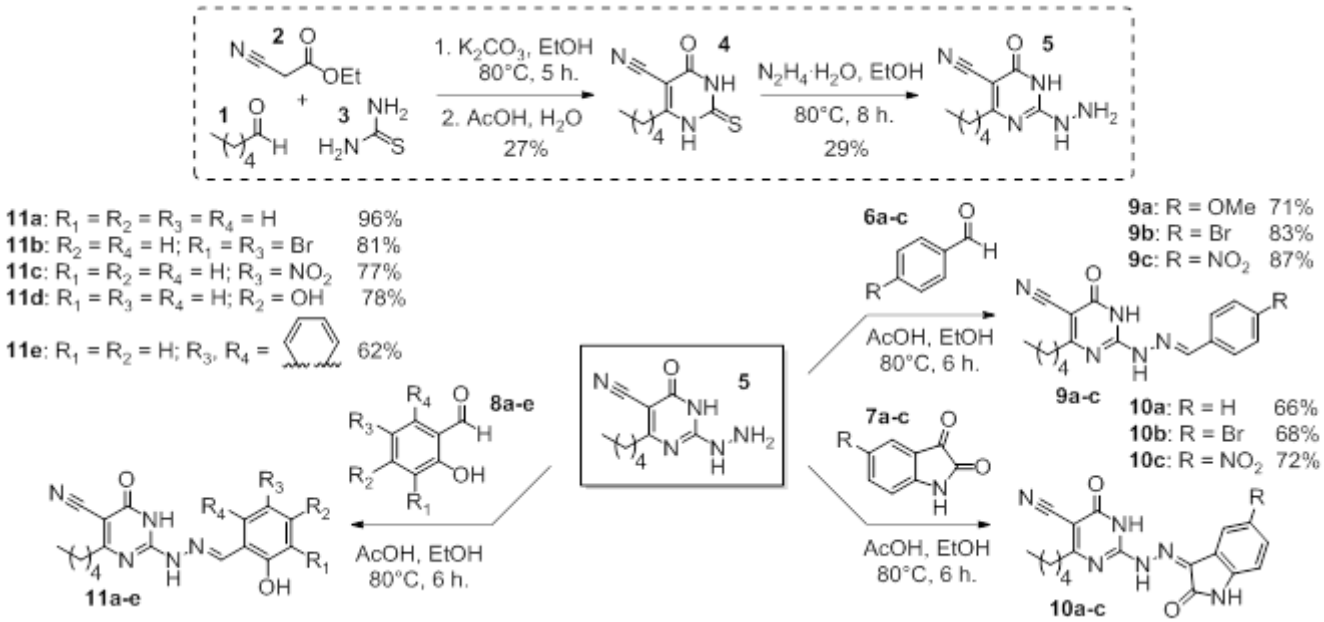

Figure 1. Structures and yield of all new compounds **9a-c**, **10a-c** and **11a-e**.

The analysis of pharmacological activity of obtained compounds was carried out using computer technologies *in silico* on the PassOnline platform (http://way2drug.com/passonline/predict.php). Calculations of acute rat toxicity using GUSAR, rodent organ-specific carcinogenicity using ROSC-Pred, *in silico* prediction of adverse drug effects ADVERPred, prediction of interaction with the undesirable targets (antitarget prediction), prediction of drug-induced changes of gene expression profile using DIGEP-Pred, prediction of interaction of pharmacological substances with human kinome using KinScreen, prediction of toxicity taking into account the metabolism of drug using MetaTox, prediction of interaction with molecular targets, prediction of substrate/metabolite specificity were performed. Possible effective interactions with molecular targets are calculated and predictions of various types of activity are made. A prediction of interaction with tumor and non-tumor cell lines has been made.

The results obtained indicate the possibility of obtaining new heterocyclic compounds for the purpose of creating unique molecular tools and drug prototypes.

This work was supported by the SPSR (Belarus) no. 20240340.

AMIACTIVE (AIA): A LARGE-SCALE QSAR BASED TARGET FISHING AND POLYPHARMACOLOGY PREDICTIVE WEB TOOL

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Computer-aided drug design (CADD) has become a cornerstone in modern drug discovery, with approaches such as ligand-based methods (e.g., QSAR modeling, pharmacophore analysis) and structure-based methods (e.g., molecular docking, molecular dynamics) driving innovation. Ligand-based strategies remain essential, especially with the increasing availability of large-scale biological activity data from public repositories such as ChEMBL. Within this context, we present AmIActive (AIA), a large-scale QSAR-based predictive web tool designed to facilitate target fishing and polypharmacology assessment for both molecular and non-molecular targets.

Over the years, several highly impactful QSAR-based predictive platforms have shaped the field. PASS [1] pioneered the prediction of biological activity spectra using thousands of models. More recently, PLATO [2] introduced a polypharmacology-oriented predictive system with thousands of regressor models, and SwissTargetPrediction [3] became widely adopted for its intuitive similarity-based framework. Together, these platforms have provided invaluable resources to the scientific community, lowering the barriers for non-specialists to apply advanced chemoinformatics methodologies. AIA seeks to further enhance this ecosystem, complementing existing solutions.

The AIA platform integrates 3,239 statistically validated QSAR models covering 2,277 distinct targets, including single proteins (69% of models), protein complexes, protein families, cell lines, organisms, and tissues. Pharmacological data was extracted from ChEMBL30, followed by rigorous cleaning and standardization. Datasets with fewer than 30 compounds or unsuitable activity measures (not based on a dose-response curve) and units were removed, and activities were converted to a negative log of mols/L formats (pIC50, pAC50, etc.). For classification, thresholds separating active and inactive compounds were determined using a binary search algorithm with the objective to make the classes as balanced as possible. Molecular fingerprints were generated using ECFP4 descriptors (1024 bits), which served as input features for machine learning moddeling.

All models were built using the Random Forest algorithm, selected for its robustness and resistance to overfitting. To ensure reliability, randomization tests with five-fold cross-validation were performed using the Matthews Correlation Coeficient (MCC) as the performance metric, and only models with p-values < 0.05 and a MCC ≥ 0.5 were retained. Further optimization was conducted through Bayesian hyperparameter tuning with nested cross-validation, in order to produce high-quality classifiers. The trained models demonstrated strong performances, with mean accuracies around 0.82, F1-scores of 0.82, and MCC values of 0.65. Applicability domains were formally defined using using a normalized euclidean distance metric, ensuring predictions are only considered reliable within the chemical space represented by the training data, in line with OECD QSAR guidelines.

The AIA system is freely available at https://amiactive.ccen.ufpb.br/, through an intuitive graphical interface powered by Chemaxons MarvinJS applet. Users can either draw chemical structures or input SMILES strings, after which predictions are generated and downloadable in CSV format. Output files include detailed information such as predicted probabilities of activity, thresholds, applicability domain reliability, and full validation metrics of the models employed.

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IN SILICO ANALYSIS OF BIOACTIVE COMPOUNDS FROM *PLECTRANTHUS AMBOINICUS* (LOUR.) SPRENG

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The development of therapies from medicinal plants has been gaining increasing relevance, as these species contain promising molecules for the treatment of several diseases. In this context, *in silico* studies are essential tools to analyze and better understand such compounds, allowing preliminary investigations that strategically guide future experimental approaches. Therefore, this study aimed to evaluate the pharmacokinetic and pharmacological properties of three bioactive compounds identified in *Plectranthus amboinicus* (Lour.) Spreng., namely luteolin, rutin, and thymol, selected based on the available literature. The study was conducted using the AdmetLab 3.0 platform, based on Lipinski's rule of five, utilizing the SMILES codes for each compound collected from the PubChem database. Additionally, molecular target predictions were performed with SwissTargetPrediction, considering the four most probable targets for each compound.

The pharmacokinetic analysis revealed that luteolin and thymol did not violate Lipinski's parameters, suggesting favorable oral absorption, whereas rutin failed in four out of five parameters, indicating a large molecular size and low oral bioavailability. Target prediction highlighted luteolin as a multitarget compound, with potential antioxidant and anti-inflammatory activities mediated by modulation of oxidative stress. Thymol was predicted to interact with inflammation-related pathways, particularly through cyclooxygenase-1 inhibition, as well as with central nervous system targets, including GABA and serotonin receptors.

Taken together, these findings indicate that luteolin and thymol, bioactive constituents of *Plectranthus amboinicus*, exhibit promising pharmacokinetic profiles and potential therapeutic activities. This *in silico* investigation provides a rational basis for future in vitro and in vivo studies, aiming to validate their pharmacological relevance and explore the development of plant-based therapies.

3D PHARMACOPHORE MODELING OF THE ERβ TUMOR SUPPRESSOR: A NOVEL STRATEGY FOR IDENTIFYING CLINICALLY SAFE DRUGS AGAINST BREAST CANCER

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The estrogen receptor beta (ERβ), recognized as a tumor suppressor in cancer, has garnered increasing interest in targeted therapy. Clinically, elevated levels of ERβ have been correlated with favorable prognosis and improved survival rates in patients with triple-negative breast cancer. This highlights that the activation of ERβ by selective ligands represents a promising therapeutic strategy in cancer treatment.

The central proposal of this work focuses on identifying FDA-approved drugs with the minimum required characteristics for ERβ selectivity, as a viable alternative for the treatment of breast cancer.

We developed an *in silico* strategy based on multicomplex-based pharmacophore (MCBP) for the modeling of an ERβ map, useful for the large-scale exploration of DrugBank and FDA drug libraries. Through virtual screening, we identified drugs whose structures met the necessary chemical-structural interactions for the modulation of ERβ activity. The promising drugs were evaluated in breast cancer cell lines using cytotoxicity, proliferation, apoptosis, and migration assays.

We identified drugs with the necessary molecular interactions to activate ERβ. GC-1, AH-5158, and PR1 demonstrated a reduction in cell proliferation and viability, with IC50 values of 206, 146, and 36 μM, respectively, in MDA-MB-231 cells, and 170, 127, and 21 μM, respectively, in MCF-7 cells. Additionally, they induced apoptosis and significantly decreased cell migration. The developed pharmacophoric map matched the experimental interactions described in the literature and was validated with agonist compounds supported by clinical and biological assays. The evaluated promising drugs reduced proliferation and induced apoptosis, even in cells with nearly undetectable ERβ expression, an effect correlated with the reported up-regulation activity of ERβ agonists. AH-5158 impacted the migration of MDA-MB-231 cells with 40% inhibition of wound closure, reflecting a decreased capacity for cellular invasion in vivo, which is associated with the agonistic effects of the ERβ receptor.

The development of a multicomplex based pharmacophoric map aimed at ERβ, using novel computational tools, allowed identifying by virtual screening and molecular docking, drugs with high affinity for the ERβ receptor, which demonstrated antiproliferative activity in the MCF-7 and MDA-MB-231 breast cancer cells. This poses a viable alternative for the possible repositioning of clinically safe drugs, to be used in the therapy against luminal breast cancer and aggressive triple negative.This finding provides a feasible alternative focused on drug repurposing, with the associated advantages of increasing the success rate, reducing costs, and shortening the time required to establish a new therapeutic indication for breast cancer.

MULTICOMPONENT SYNTHESIS OF PYRAZOLONE DERIVATIVES OF 2-AMINO-3-CYANO-4*H*-CHROMENE AND *IN SILICO* EVALUATION OF THEIR POTENTIAL BIOLOGICAL ACTIVITY

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Multicomponent reactions (MCR) are a promising, economical and simple method for obtaining 2-amino-3-cyano-4*H*-chromene derivatives, which are valuable in everything from agriculture to medicine [1]. In this work, two problems are solved: 1) solving the problem of introducing 1,3-dicarbonyl components into the composition of Hantzsch MCR products using the DMAP catalyst, which has not been studied previously; 2) combining the synthetic MCR method (Figure 1) and in silico approaches to assess the potential biological activity of the obtained derivatives (Table 1) using the PASS Online service (http://way2drug.com/passonline/predict.php).

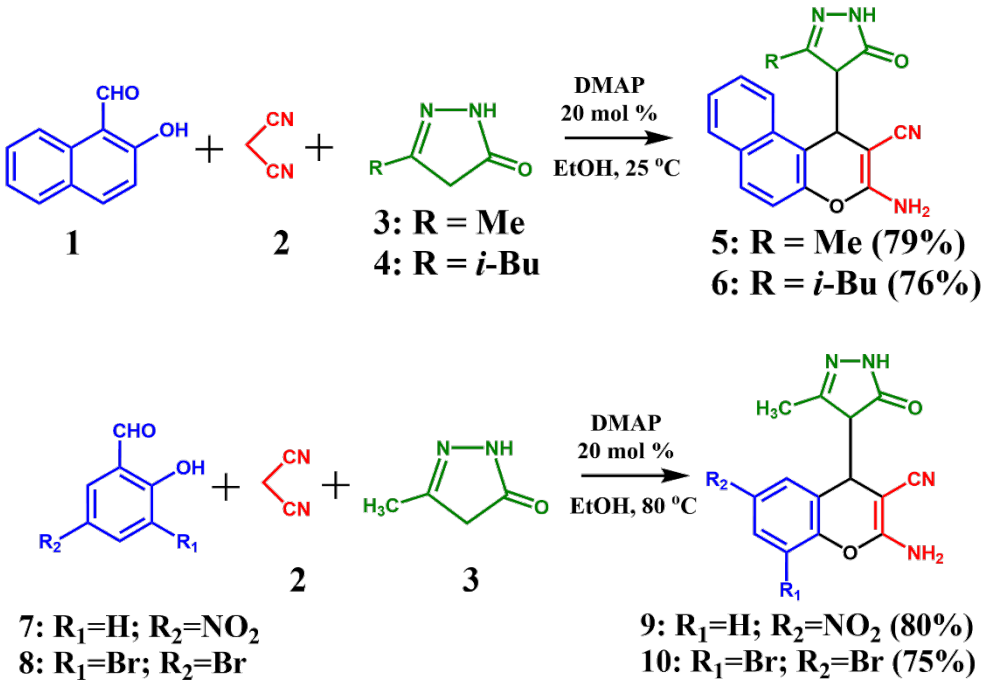

Figure 1. MCR products and corresponding yields

Table 1. Types of biological activity and P_a-index for MCR products

Parameter	P_a-index for MCR products			
	5	***6***	***9***	***10***
Catalase stimulant	0.721	0.668	0.707	0.774
Cystinyl aminopeptidase inhibitor	0.713	0.687	0.744	0.728
Neurodegenerative diseases treatment		0.789		
Autoimmune disorders treatment		0.759		
HMGCS2 expression enhancer			0.616	0.710

Thus, the functionalization of 2-amino-3-cyano-4*H*-chromene derivatives with various pyrazolones increases the likelihood of exhibiting a wide variety of biological activities, information about which may be in demand in various fields.

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IN SILICO–GUIDED IDENTIFICATION AND BIOLOGICAL EVALUATION OF TRITERPENOID-TYPE P-GLYCOPROTEIN INHIBITORS

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Multidrug resistance (MDR) represents a current issue which limits the efficacy of cancer chemotherapy. The key mechanism of MDR development is associated with the overexpression of transmembrane transporters from the ATP-binding cassette (ABC) family, which facilitate the removal of chemotherapeutic drugs from cells. The most studied ABC transporter is P-glycoprotein (P-gp/ABCB1) which is responsible for the active efflux of numerous antitumour drugs. While third-generation P-gp inhibitors (e.g., zosuquidar, elacridar, tariquidar) reached clinical trials, dose-limiting toxicities and drug–drug interactions stalled their translation, motivating computationally guided searches for safer scaffolds, especially among semisynthetic natural metabolites.

Here we combine chemoinformatics, molecular modeling, and mechanism-resolved cellular assays to identify two semisynthetic pentacyclic triterpenoids that exhibited direct inhibitory activity on P-gp transport without affecting its expression: (a) soloxolone N-3-(dimethylamino)propylamide and (b) a 3-meta-pyridine 1,2,4-oxadiazole derivative of 18β-glycyrrhetinic acid.

Molecular docking revealed strong binding affinities of both compounds to the P-gp transmembrane domain. Functional assays in P-gp–overexpressing human cervical carcinoma KB-8-5 and murine lymphosarcoma RLS40 cells revealed that both compounds markedly increased the intracellular accumulation of the P-gp substrates rhodamine-123 (Rho123) and doxorubicin (DOX), thereby restoring cellular sensitivity to the cytotoxic action of DOX in a synergistic manner, as confirmed by Bliss model analysis. Notably, these effects occurred without downregulation of P-gp expression. Further kinetic studies indicated that compound (a) inhibited P-gp efflux activity through competitive and non-competitive mechanisms for DOX and Rho123, respectively, resulting in sustained drug retention.

These findings highlight pentacyclic triterpenoids as promising scaffolds for the development of effective, biocompatible P-gp modulators. By enhancing intracellular drug accumulation without impairing normal cellular function, these compounds offer a potential strategy to overcome MDR in aggressive cancers.

This research was supported by the Russian Science Foundation, grant No. 23-14-00374.

PREDICTING THE ADVERSE EFFECTS OF PASSIFLORA INCARNATA ALKALOIDS THROUGH COMPUTATIONAL METHODS

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The prediction and assessment of potential adverse effects of medicinal substances play a critical role in modern healthcare. Understanding these effects is essential for ensuring the safety and well-being of patients. With advancements in computational methods, particularly *in silico* analysis, researchers can now predict and evaluate the adverse effects of chemical compounds more efficiently. In this study, we focus on *Passiflora incarnata* alkaloids, exploring their potential harmful impacts on the human body and emphasizing the significance of such analyses in contemporary medical research.

When discussing modern medicine, a crucial aspect is the components of drugs. Alongside their therapeutic benefits, understanding the potential adverse effects of medicinal substances, whether derived from herbs or synthetics, is paramount for human health and requires careful evaluation. Typically, these properties are established through clinical trials of drugs. Presently, advancements in information technology have significantly impacted various fields, including chemistry, medicine, and pharmacy. In particular, *in silico* analyses have emerged as a valuable tool for predicting the adverse effects of chemical compounds [1]. This study aims to elucidate the potential adverse effects of harmine, harmaline, harmol, harmalol, and harman alkaloids found in *Passiflora incarnata* on the human body, alongside their potential benefits [2, 3]. The analysis was conducted using the ADVER-Pred service on the Way2Drug platform. The results underscored the importance of such computational methods in understanding and mitigating the risks associated with medicinal substances [4].

The findings reveal a notable impact of these substances on the cardiovascular system, with arrhythmia, cardiac failure, and myocardial infarction emerging as significant concerns across all alkaloids. Particularly noteworthy is the elevated risk of cardiac failure associated with harmol (Pa 0.500, Pi 0.056), while arrhythmia is a prevalent issue with the other compounds. Harmine stands out with the highest likelihood of inducing arrhythmia (Pa 0.589, Pi 0.052). Additionally, the study highlights hepatotoxicity as an important consideration, with harmol and harman exhibiting probabilities of Pa 0.337, Pi 0.314 and Pa 0.404, Pi 0.256, respectively.

In conclusion, this study underscores the critical importance of utilizing computational methods to predict the adverse effects of *Passiflora incarnata* alkaloids in modern medicine. By elucidating the potential adverse impacts of harmine, harmaline, harmol, harmalol, and harman alkaloids on the human body, alongside their potential benefits, we provide valuable insights for healthcare practitioners and researchers. Our findings highlight the predominant cardiovascular effects of these alkaloids, including arrhythmia, cardiac failure, and myocardial infarction, with harmol showing a particularly high propensity for cardiac failure. Additionally, the identification of hepatotoxicity in harmol and harman underscores the multifaceted nature of their effects. Moving forward, continued advancements in predictive analyses and comprehensive examinations of substance effects will be pivotal in safeguarding public health and ensuring the safe and effective use of medicinal compounds. Thus, investing in further research efforts in this direction is crucial for advancing the field of pharmacology and ultimately promoting a healthier society.

We appreciate the encouragement received from the Pharmacy faculty of Azerbaijan Medical University, whose expertise has greatly contributed to the success of this study.

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EXPLORING AQUATIC TOXICITY OF DIVERSE PESTICIDES AGAINST *CHIRONOMUS RIPARIUS* (HARLEQUIN FLY) AND *LEMNA GIBBA* (SWOLLEN DUCKWEED): APPLICATIONS OF QSTR AND NOVEL Q-RA APPROACHES

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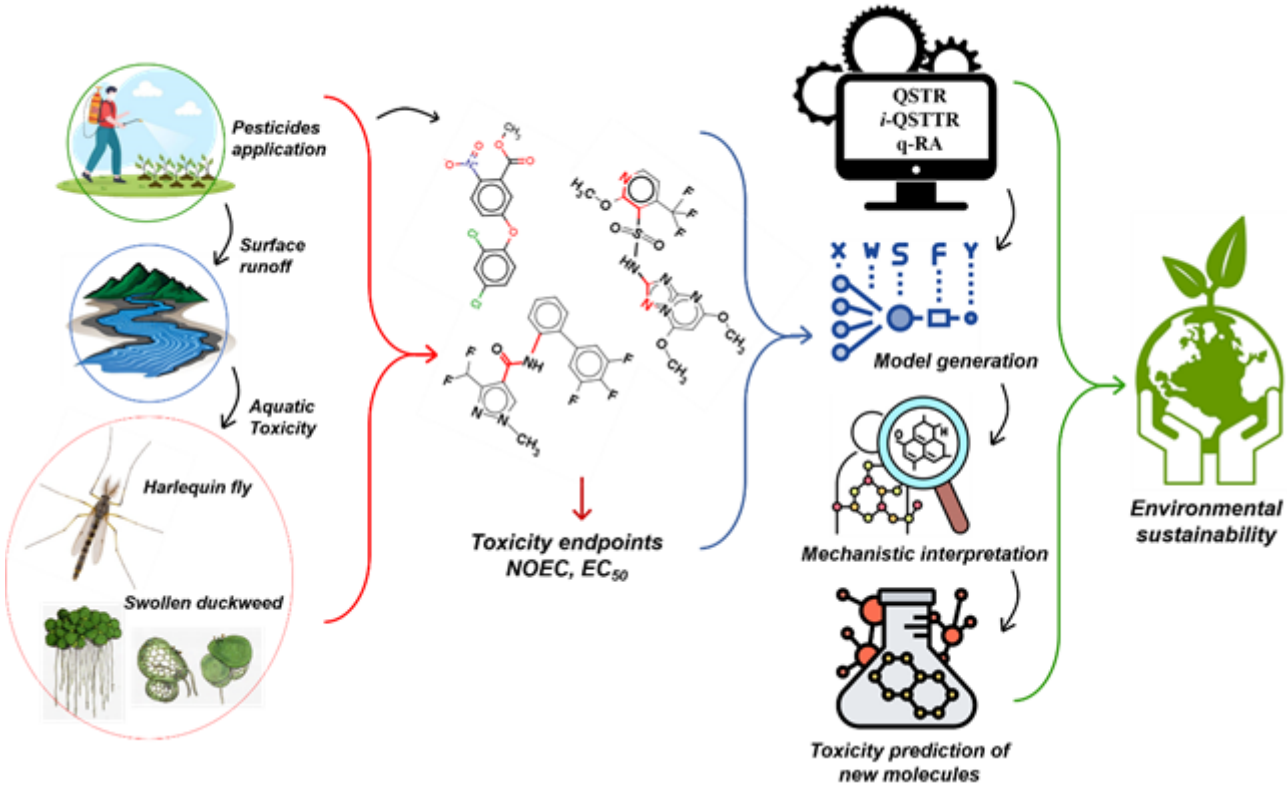
Organic pesticide molecules pose toxicity risks to aquatic species such as *Chironomus riparius* and *Lemna gibba*. However, limited toxicity data and resource-intensive laboratory tests impede comprehensive assessment. To overcome these obstacles, computational techniques like Quantitative Structure-Toxicity Relationship (QSTR) offer an efficient and effective approach. In this study, we performed QSTR modeling by employing these two species. The models demonstrated strong statistical reliability, as indicated by robust internal validation metrics (R^2 = 0.711−0.777 and Q^2_{LOO} = 0.619−0.676) and consistent external validation results (Q^2_{F1} = 0.75−0.76 and Q^2_{F2} = 0.738−0.75). Furthermore, a new "quantitative read-across (q-RA)" method improved the accuracy of predictions. The study also identified key structural features of chemicals that contribute to their toxicity. Finally, we screened a large number of chemicals to predict their toxicity levels and to identify the ten most and ten least harmful ones, along with the structural patterns responsible for their toxicity. These insights play a vital role to design safer pesticide molecules towards a sustainable management of aquatic ecosystems.



PARTIAL ATOMIC CHARGES LOCALITY STUDYING IN MACHINE-LEARNING MODELS

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The molecular electrostatic potential (ESP) most fully characterizes the electrostatic properties of molecules, which are important for modeling the interactions of ligands with targets in the methods of molecular dynamics and molecular docking. The prediction of the electrostatic properties of molecules using machine learning is actively developing due to the flexibility, scalability, speed and high accuracy of machine-learning (ML) models with optimally selected parameters [1]. An important property of ML models for charge prediction is their transferability, i.e., the ability to correctly predict charges for structures dissimilar to those in the training set.

The objective of this study was to investigate the relationship between partial atomic charges and their locality in case of prediction of the charges for drug-like molecules using ML models. In this work, two model architectures were analyzed in predicting of partial atomic charges and ESP (Figure 1): a random forest (RF) and a fully connected multilayer perceptron (MLP).

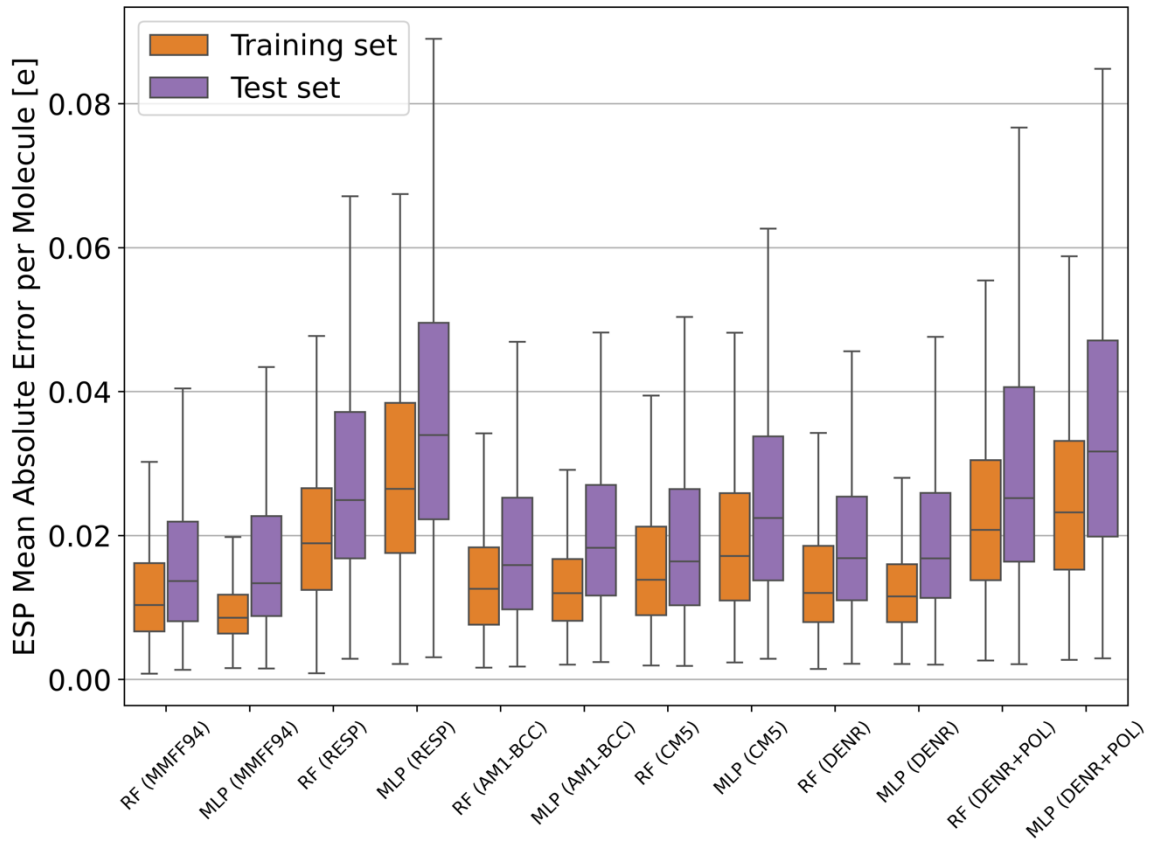

Figure 1. Distributions of cluster-averaged MAE for predicted ESP across all molecules within each cluster. Orange boxes: training set. Purple boxes: test set.

Substantial transferability of investigated RF and MLP models is also confirmed by clustering. Random forest and multilayer perceptron architectures showed appropriate accuracy and transferability in reproducing ESP. The optimal path length for AtomPair fingerprints is 3 that indicates a slight effect of the distant atom environment. These results show significant partial atomic charges locality in machine-learning models.

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QM/MM INVESTIGATION OF THE HYDROLYSIS REACTION IN F1-ATPASE

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Adenosine triphosphate (ATP) hydrolysis, catalyzed by F1-ATPase, is a primary source of energy for cellular processes. This enzyme is a rotary motor protein with three catalytic sites (βTP, βDP, βE) characterized by different nucleotide-binding affinities and catalytic states. The objective of this study was a comparative analysis of the structure and catalytic activity of these three active sites to elucidate the mechanism of ATP hydrolysis. For this purpose, a fully atomistic model of the F1-ATPase enzyme-substrate complex was prepared. Subsequently, hybrid quantum mechanics/molecular mechanics (QM/MM) molecular dynamics (MD) simulations were performed for 20 ns to analyze the structure of the active sites. The QM subsystem, comprising 123 atoms with a total charge of +1, included the side chains of key amino acid residues (Gly159, Lys162, Thr163, Glu188, Arg189, Asn257, Arg260, Gln263, αSer344, αArg373), the ATP phosphate groups, the Mg^{2+} cation, and six water molecules from its coordination sphere. The QM part was treated at the PBE0-D3/6-31G** level of theory, while the MM part was described using the CHARMM force field. The advancement of this study over previous works is the application of extensive QM/MM MD and free energy calculations to all active sites, allowing for a direct comparison of their catalytic competence. From the obtained trajectories, key geometric and electron-density parameters in the active sites were determined. Furthermore, QM/MM MD simulations with an umbrella sampling technique were conducted to obtain the Gibbs free energy profiles for the ATP hydrolysis reaction in each site. The results demonstrate significant differences in the structure and catalytic activity of the sites, providing an atomic-level insight into the reaction mechanism and the rotational cycle of F1-ATPase.

The work was carried out using the equipment of the Shared Research Facility "Supercomputing Resources" of Lomonosov Moscow State University and with financial support from the Russian Science Foundation (project No. 19-73-20032).

VIRAL GENOME COMPLEXITY AND REPEATS' STRUCTURE

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[3]Sechenov First Moscow State Medical University of the Russian Ministry of Health (Sechenov University), Moscow, Russia

We aimed study genome repeats in coronavirus and other prokaryotic genomes to find regions of higher mutability associated with repeated elements and low complexity regions. The measures of compositional complexity coming from statistical physics methods help to find abnormalities in linear genome structure [1]. We extended mathematical measures of complexity estimates for whole prokaryotic genome structure [2].

The measures of compositional complexity help to find abnormalities in linear genome structure (sequences) and make corresponding segmentation [3]. Shannon information (as the first measure of nucleotide frequencies allows delineation of complexity blocks, coding and non-coding regions in a sequence. Shannon information, as well as entropy, could be measured for nucleotides, dinucleotides, and oligonucleotides of any reasonable length (up to 10) in available genome sequences. Despite this measure is easy to count, it can separate real and artificial sequences. We used also new complexity measures and entropy estimates to study graphs structure of gene networks (on the matrix form of network presentation).

The applications of complexity analysis of DNA sequences could be listed by sequence size: Short sequences (transcription factor binding sites, promoters, gene regulatory regions, small domains and microsatellites; Medium size genome regions (genes, patching exon/intron structures, distal gene enhancers); Chromosome arms, and complete prokaryotic genomes [3].

We have analyzed complete viral genome structures. Studying the structure of the genome sequence of the coronavirus causing COVID-19 from the point of view of repeat structure is interest for description of mutability and evolution [1]. New calculations on the available viral genomes using previously developed methods [4] show the predominance of regions of increased complexity encoding the polyprotein, while regions of low complexity are associated with increased mutability. The maximum repeat lengths in the genomes of viruses are direct repeats, which may indicate evolutionarily recent duplications.

We show that the genomes of viruses contain short sections of direct repeats. Viruses represented by single-stranded RNA do not contain extended reverse or complementary repeats (although they could be for random reasons with a low frequency, which is observed when using the appropriate parameters of the LZcomposer program) [4]. In this case, the maximum inverted (in the complementary chain) repeat was found for the African swine fever virus, represented by double-stranded DNA. Thus, the molecular mechanisms of the occurrence of duplications associated with duplications determine the appearance of maximum perfect repeats in the genomes of viruses. The presence of tandem repeats (repeats of text running in a row in two or more copies, determined using the TRF (Tandem Repeat Finder) program) in the genomes of viruses represented by a single-stranded RNA sequence is limited, possibly due to the lack of molecular mechanisms for their occurrence by the mechanism of DNA slippage during replication.

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RATIONAL DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL THIAZOLE/THIAZOLIDINONES MULTITARGET ANTI-HIV MOLECULES

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HIV-1 RT inhibitors were the first drugs approved to treat AIDS and remain key components of highly active antiretroviral therapy (HAART). While HAART effectively suppresses viral replication and slows disease progression, it has limitations, including long-term side effects and the emergence of drug-resistant strains, highlighting the need for new treatments. Based on our previous experience, and insights from existing inhibitors of HIV-1 RT and RNase H, we aim to design and synthesize safer, multifunctional molecules (Figure 1). Using molecular docking studies, these compounds will incorporate pharmacophores targeting multiple stages of the HIV life cycle to enhance efficacy, reduce resistance, and improve pharmacokinetics. Compounds were synthesized by one pot three components reaction. The synthesized compounds were identified using spectroscopy and tested in vitro for activity against key HIV targets, including RNA-dependent DNA polymerase (RDDP) and RNase H. Among the synthesized compounds, several demonstrated strong inhibitory activity, with compound **11** showing IC_{50} values comparable to the reference drug Nevirapine, and compound **4** exhibiting dual inhibition of both RT and RNase H activities. These findings emphasize the importance of a multidisciplinary approach, combining computational modeling with experimental validation, to identify promising leads for therapeutic development.

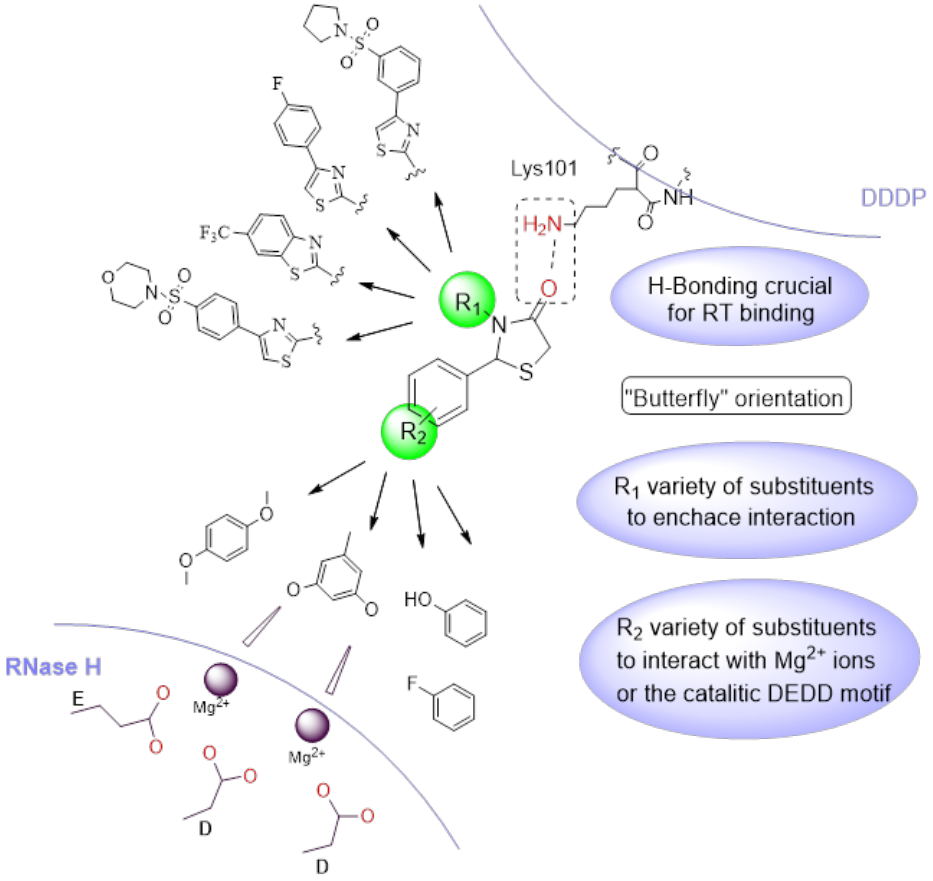

Figure 1. The design of novel RT/ RNase H dual inhibitor.

X-RAY CRYSTALLOGRAPHIC ANALYSIS OF 17-PYRIDIN-2-YL ESTRANE DERIVATIVES: LEAD-LIKE COMPOUNDS AGAINST BREAST AND CERVICAL CANCER

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Abiraterone, used mainly as its prodrug abiraterone acetate, is a leading treatment for castration-resistant prostate cancer through inhibition of CYP17A1 [1]. Ongoing studies also explore its potential in breast cancer therapy. Building on this, we previously synthesized novel 17-pyridinyl estrane derivatives [2]. Among them, 3-methoxy-17α-(pyridin-2-yl)estra-1,3,5(10)-trien-17β-ol (**1**) and 3-methoxy-17-(pyridin-2-yl) estra-1,3,5(10),16-tetraen (**2**) showed notable antiproliferative activity against MCF-7 breast cancer cells. Molecular structures and absolute configurations of compounds of **1** and **2** were confirmed by single X-ray diffraction.

Also detailed structure analysis was performed by Mercury CSD [3] and CrystalExplorer [4]. Aromatic ring interactions between molecules were analyzed using the Aromatics Analyzer tool available in Mercury software. To gain deeper insight into the factors governing crystal packing, it is essential to qualitatively rank specific intermolecular interactions, as relying solely on geometric criteria may fail to identify the most significant or energetically dominant contacts [5, 6]. Consequently, a "whole-of-molecule" approach was employed for the crystal structures of compounds **1** and **2**, in which pairwise intermolecular interaction energies were computed using the CE-B3LYPlevel of theory [7], as implemented in CrystalExplorer, to obtain accurate energy estimations.

The crystal packing of **1** and **2** is dominantly arranged by Van der Waals forces and corresponds to fingerprint plots of computed Hirshfeld surfaces. C–H···π interactions and $\pi\cdots\pi$ stacking can be observed. Intermolecular hydrogen bonding is not present in both compounds. Only intramolecular O–H···N hydrogen bond is observed in **1.** The results of the calculations gives deeper insight to previous statements. The single dominant interaction is dispersion that is stabilizied by energy of –47.6 kJ mol^{-1} in the crystal structure of **1** and –54.6 kJ mol^{-1} in **2**.

This approach provides a detailed analysis of the drug structures and helps to understand the way they interact within the crystal structure, serving as a basis for understanding potential interactions in molecular docking.

The authors gratefully acknowledge the financial support of the Ministry of Science, Technological Development and Innovation of the Republic of Serbia (Grants No. 451-03-66/2024-03/ 200125 & 451-03-65/2024-03/200125) and Provincial Secretariat for Higher Education and Scientific Research of the Autonomous Province of Vojvodina [Project: New steroid derivatives – potential chemotherapeutics, No. 003056514 2024 09418 003 000 000 001/1]

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COCCINIA GRANDIS L, QUERCETIN: A COMPUTATIONAL LOOK AT ITS ANTI-DIABETIC POWER

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Type 2 diabetes mellitus (T2D) is a progressive metabolic disorder characterized by insulin resistance, defective insulin secretion, and chronic hyperglycemia. Accounting for over 90–95% of global diabetes cases, T2D has escalated to epidemic proportions, largely driven by obesity, sedentary lifestyles, and genetic susceptibility. Sustained hyperglycemia is a key factor underlying debilitating complications, including cardiovascular disease, nephropathy, neuropathy, and retinopathy, thereby intensifying its global health and economic burden. Therapeutic strategies frequently aim to attenuate postprandial glucose excursions by targeting digestive enzymes essential for carbohydrate hydrolysis. Human pancreatic α-amylase (HPA; EC 3.2.1.1), a 57 kDa enzyme that cleaves α-1,4 glycosidic bonds in starch and glycogen, plays a central role in glucose release. Although acarbose remains a clinically validated inhibitor of HPA, its undesirable gastrointestinal side effects necessitate the pursuit of safer, naturally derived alternatives.

Flavonoids, a diverse class of plant-derived secondary metabolites, have emerged as promising enzyme inhibitors due to their favorable safety and pharmacological profiles. Quercetin, a predominant phytoconstituent of *Coccinia grandis* L.—a traditionally consumed antidiabetic vegetable in India—has shown significant inhibitory activity in preliminary in-vitro studies (unpublished data). To elucidate its molecular mechanism, we applied an integrative computational framework. Molecular docking revealed that quercetin binds with high affinity at the catalytic site of HPA, while molecular dynamics (MD) simulations conducted over 500 ns demonstrated remarkable stability of the HPA–quercetin complex. Detailed trajectory analyses, including RMSD, RMSF, radius of gyration (Rg), solvent-accessible surface area (SASA), principal component analysis (PCA), and hydrogen bond profiling, confirmed robust ligand–protein interactions under physiological conditions. Importantly, MM-PBSA free energy calculations highlighted the superior binding affinity of quercetin (–22.38 kcal/mol) compared to acarbose (–12.97 kcal/mol).

Collectively, these findings position quercetin as a potent natural inhibitor of HPA, exhibiting stronger binding affinity and structural stability than the standard drug acarbose. This study not only validates the ethnopharmacological relevance of *Coccinia grandis* L. but also advances quercetin as a promising lead compound in the rational design of safer and more effective therapeutics for managing type 2 diabetes through modulation of postprandial hyperglycemia.

EVALUATION OF TWO NAPHTHOPYRANONES ISOLATED FROM *PAEPALANTHUS BROMELIOIDES* AS ANTI-*HELICOBACTER PYLORI*, CHEMOPREVENTIVE AND MMP-9 INHIBITORS

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Helicobacter pylori (Hp) is a carcinogen class I that infects the human stomach and occurs in approximately 45% of the global population. Extended infections may lead to the development of gastric injury, and ultimately, gastric cancer. The release of some virulence factors of Hp, especially CagA, is related to the activation of the inflammatory pathways NF-κB and MAPK, which then lead to the overexpression of MMP-9[1]. The metalloproteinases play an important role in tumor growth and metastasis by remodeling the extracellular matrix. Due to the rise of resistance of actual therapy, the search for novel anti-Hp molecules that also act synergically to prevent the damage caused to the host by inhibiting some of these downstream enzymes directly are necessary. In this way, we isolated two molecules, paepalantine (**1**) and 5-methoxy-3,4-dehydroxanthomegnin (**2**) from *Paepalanthus bromelioides* through maceration of the floral heads in MeOH. Column chromatography (CH_2Cl_2 to obtain **1** and CH_2Cl_2/Ethyl Acetate 1:1 to obtain **2**) was done and the substances were characterized by ^1H NMR and mass spectrometry. We evaluated anti-Hp activity against ATCC 43504 and clinical strain by broth microdilution technique to assed the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC). We also assessed the cytotoxic concentration (CC_{50}) for gastric adenocarcinoma (AGS) and fibroblasts (L-929) cells to determine the selectivity index (SI). **1** and **2** already have antibacterial and cytotoxic activity described. PASS Online was used to search for possible targets and was found MMP-9 with a probability of activity (Pa) around 0.5 among other relevant activities like antineoplastic and antagonist of endothelial growth factor, that suggests a potential for inhibiting cancer progression, and metastasis. Then, molecular docking was performed in GOLD, using GoldScore as primary scoring function and ChemScore for rescore, to trial the potential inhibition of these substances for MMP-9. CASTp 3.0 was used to determine the residues for the active site: Gly186, Leu187, Leu188, Ala189, His190, Leu222, Val223, His226, Gln227, His230, His236, Pro240, Glu241, Ala242, Leu243, Tyr245, Pro246, Met247, Tyr248, Arg249, Thr251, Pro255 added to Zn301. The docking was validated by redocking B9Z, the crystallized ligand, and a RMSD of 1.7487 Å was obtained and the results were compared to marimastat, a well-known MMP inhibitor described in literature. **1** and **2** presented a MIC of 8 and 16 for ATCC and clinical strain respectively. The MBC values were the same for the ATCC but not for the clinical strain. Both naphthopyranones showed activity against both Hp strains in vitro. PASS revealed a reasonable probability of activity for these molecules to inhibit the development of cancer and angiogenesis. The molecules presented similar docking scores compared to marimastat. Further structural modifications can be performed to achieve better results to enhance the interactions, especially with Zn301, which was not observed, probably due to the rigidity of **1** and **2**. The structural improvements may also contribute to the selectivity index and even the antibacterial activity of these molecules.

Table 1. Summarized results for **1** and **2**.

Substance	ATCC 43504		Clinical strain		AGS	L-929	SI	MMP-9 Expression inhibitor (Pa)	Antineoplastic (Pa)	Endothelial growth factor antagonist (Pa)	GoldScore	ChemScore ΔG
	MIC (μg/mL)	MBC (μg/mL)	MIC (μg/mL)	MBC (μg/mL)	CC_{50} (μM)	CC_{50} (μM)						
1	8	16	16	64	137.68 ± 20.61	153.68 ± 13.15	1.12	0.511	0.793	0.766	58.3888	−31.9923
2	8	16	16	32	144.77 ± 0.17	287.62 ± 12.06	1.99	0.476	0.853	0.597	58.4175	−29.2075
amoxicillin	0.063	0.125	0.250	0.250	-	-	-	-	-	-	-	-
cisplatin	-	-	-	-	21.72 ± 2.59	22.19 ± 1.30	1.02	-	-	-	-	-
marimastat	-	-	-	-	-	-	-	-	-	-	60.4606	−24.8263

This study was funded by the Foundation of Support to Research and Innovation of Espírito Santo (FAPES), PROCAP DOUTORADO 2024 nº 14/2023 – grant number 2024-H3X2T.

DESIGN AND SYNTHESIS OF PEPTIDE INHIBITORS TARGETING HER2 AS A THERAPEUTIC STRATEGY IN BREAST CANCER

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Cancer is one of the main pathologies affecting the population worldwide. In this context, breast cancer is considered one of the most frequent causes of death in women. Conventional therapies used for the treatment of this type of cancer cause adverse effects and many of the drugs used have decreased their efficacy due to the generation of cancer cells resistance.

Several research studies have focused on discovering promising therapeutic targets in order to innovate targeted therapies for breast cancer. Within these studies, it has been reported that HER2 is involved in signaling pathways related to carcinogenic processes, participating in the proliferation and survival of cancer cells, therefore, it represents promising pharmacological target to design treatment schemes focused on breast cancer. Consequently, it is essential to use the knowledge and tools offered by the field of medicinal chemistry to promote progress in the creation of new therapeutic alternatives for the treatment of this disease. In this sense, the development of bioactive peptides with anticancer properties has demonstrated clinical applications and therapeutic benefits, which represents an opportunity to explore new strategies based on peptide therapy.

In this project, we used computational methods in order to design 3D pharmacophoric model targeting HER2 receptor based on the structure of the HER2/Trastuzumab complex. Subsequently, a set of peptides were designed based on the structural requirements identified in the pharmacophoric map and their fit to the model was determined by virtual screening. The affinity of the peptides on HER2 receptor was explored by molecular docking studies and were predicted for potential allergenicity and toxicity. The most promising peptide identified in the *in silico* methodology, PHER37, was obtained by solid-phase chemical synthesis and was characterized by spectrometric (UHPLC-ESI-QTOF-MS) and spectroscopic (^{1}H and ^{13}C-NMR) techniques. The different analyses were consistent with the expected mass and molecular structure.

The pharmacophore modeling allowed us to identify and establish the essential chemical-structural characteristics that a molecule must have in order to interact with HER2 and block its activity, which lays the foundation for the possible selection of compounds with potential inhibitory activity on this receptor that can be used as a useful strategy in the treatment of breast cancer. The peptide obtained is a potential candidate for its evaluation on breast cancer cell lines and for possible use in therapies targeting this disease**.**

The present study was conducted at the Escuela Superior de Medicina, Instituto Politécnico Nacional (ESM-IPN), within the framework of the PhD Program in Medical Research.

FROM STRUCTURE TO STRATEGY: CHEMOMETRIC MODELING FOR THE PREDICTION OF TERMINAL HALF-LIFE OF PHARMACEUTICALS AND ITS ROLE IN FUTURE THERAPEUTICS

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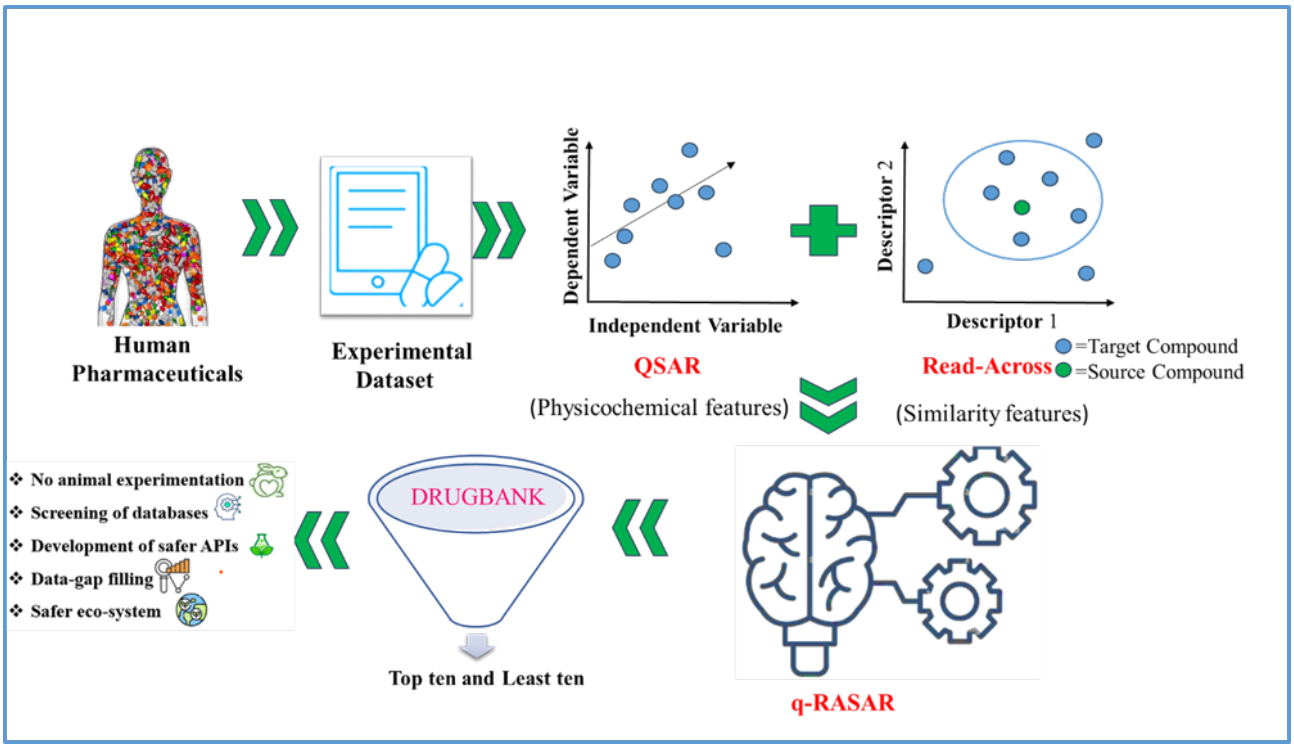
The terminal half-life ($t_{1/2}$) is a crucial pharmacokinetic parameter for estimating the dose regimen and duration of action of a drug. Previously, few research papers have been published on the pharmacokinetic parameters that correlate with the chemical structure of pharmaceuticals, but these are time-consuming and costly. The main goal of the current study is to generate a quantitative read-across structure-activity relationship for terminal half-life estimation of diverse pharmaceuticals. The dataset of 895 pharmaceuticals has been used for 2D descriptor computation and model development. Herein, the combinatorial (q-RASAR) approach of read-across and QSAR has been employed for model generation. Finally, the Partial Least Squares-based q-RASAR model is developed and validated based on the various validation parameters as per the OECD principles. The final q-RASAR model is statistically more significant, reliable, and robust than the corresponding QSAR model based on different statistical parameters ($R^2 = 0.617$, $Q^2_{(Loo)}=0.601$, error-based predictions = 0.221), external parameters (Q^2_{F1} & Q^2_{F2} are 0.635) [1]. It has been concluded that the presence of the RA function and the presence of 6-membered rings are accountable for the long terminal half-life. Similarly, the presence of the phenol/enol/carboxyl OH group, the presence of positively charged N, solubility, and average molecular weight contribute negatively to the terminal half-life. Additionally, the DrugBank database was screened and predicted the terminal half-life of new and untested pharmaceuticals using the model, which further helped in the prediction of the dosing frequency and accumulation profile of new pharmaceuticals. This study further helps to formulate and optimize safe and eco-friendly pharmaceuticals.



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ADVERSE OUTCOME PATHWAY (AOP)-INFORMED QSTR MODELLING FOR MECHANISTIC SCREENING OF PER- AND POLYFLUOROALKYL SUBSTANCES (PFAS)

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Conducting experimental studies on PFAS is challenging due to their vast chemical diversity, and the requirement for time- and resource-intensive investigation for each compound across all potential diseases and adverse effects. To address this issue, a quantitative structure-toxicity relationship (QSTR) workflow based on an adverse outcome pathway (AOP) was developed, relating the PFAS molecular structures to molecular initiating events (MIEs), as inferred from three PubChem bioassays (AID-1030, AID-504444, AID-588855) [1]. The AID-1030 assay, which measures inhibition of ALDH1A1, gives mechanistic insight into reproductive toxicity from PFAS. AID-54444 is linked to pathways relevant to pulmonary fibrosis, indicating PFAS' perturbations in oxidative and pro-fibrotic signalling. AID-588855 captures signalling perturbations linked to lung cancer. The investigation was limited strictly to compounds that met the current Organisation for Economic Co-Operation and Development (OECD) definition of PFAS [2]. As the dataset contained fewer active compounds compared to inactive ones, data balancing techniques were applied to address class imbalance. The training data sets were balanced by 5 different types of oversampling methods (ADASYN, random oversampling, Borderline SMote, SMote, and SVM-SMote). Fourteen classifiers were trained using a machine learning algorithm for each of the balanced training sets, resulting in seventy models per dataset. Champion models were objectively chosen using the Sum-of-Ranking-Differences (SRD) analysis. The resulting models exhibit good predictive power and interpretability. SRD found that Gradient Boost, using random sampling, is the champion for AID-1030, Random Forest, using SVMsmote, for AID-504444, and Support Vector Classification, using Random oversampling, for AID-588855. SHAP analysis yielded the descriptor contributions that suggest plausible mechanistic links between PFAS structural motifs and AOP progression. Substructure analysis was also performed to identify the key substructures that contributed to toxicity. The pipeline supports the prospective virtual screening of extensive PFAS inventories. It enables integration with AOP-Wiki entries for prioritising compounds to focus on for in vitro testing and mechanistic follow-up, thereby supporting regulatory decision-making and prioritisation across jurisdictions. Collectively, this validated computational pipeline works as an AOP-aware screening and prioritisation instrument for emerging PFAS.

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NEURAL NETWORK APPROACH FOR STRUCTURAL PATTERN RECOGNITION OF HUMAN CYP17A1 DUAL ACTIVITY

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In drug discovery, identification of interactions between drugs (or drug candidates) and target proteins is an important issue. Machine and deep learning are fundamental artificial intelligence technologies of the 21st century and accurate methods of extracting structural patterns and building predictive models [1]. CYP17A1 is a dual function enzyme that catalyzes both 17α-hydroxylase and 17,20lyase reaction in steroid hormones biosynthesis. The disorders of this enzyme are accompanied with hormone-dependent tumors, especially prostate cancer. The lyase inhibition is preferred over hydroxylase because this leads to a better control of circulating C19 androgen precursors without decreasing the cortisol level. Both reactions share the same active site, making selective inhibition of a single reaction extremely challenging [2]. Our work aims to develop multiclassification neural network to identify non-inhibitors, inhibitors of predominately 17α-hydroxylase reaction, inhibitors of predominately 17,20lyase reaction and determine structural patterns, which are significant for inhibition of these two reactions separately.

The strategic workflow of the study includes five steps. The first step is data collection (ChEMBL, PubChem, BindingDB, and PatentScope databases), followed by preprocessing, standardization, and labeling: non-inhibitors of CYP17A1 (class 0) predominately 17,20 lyase inhibitors (class 1, Hydroxylase/Lyase IC_{50} ratio > 5), predominately 17α-hydroxylase inhibitors (class 2, Hydroxylase/Lyase IC_{50} ratio < 5). The second step is the calculation of molecular fingerprints and descriptors (PADEL 1D and 2D descriptors; E-state, PubChem, Substructure, Klekota-Roth, 2D atom pairs fingerprints), which were used separately for multiclass classification model construction. The third step involves training fully connected neural networks with optimized hyperparameters and evaluating the obtained models. The fourth step is identifying the model with the best performance and decoding the top 10 molecular fingerprints using feature selection technique based on random forest and variance threshold algorithms. The fifth step is the determination of the chemical space of non-inhibitors, 17α-hydroxylase inhibitors, and 17,20-lyase inhibitors separately. The best performance model, trained on Klekota-Roth fingerprints (KRFP), achieved accuracy of 0.87 and an F1score of 0.86. We analyzed the distribution of top-20 significant Klekota-Roth fingerprints, responsible for 17α-hydroxylase and 17,20lyase inhibition manifestation. It was revealed that the key patterns for inhibitors of 17,20-lyase activity of CYP17A1, in contrast to inhibitors of 17α-hydroxylase activity: the presence of structures with conjugated double bonds (KRFP297), fragments of the secondary alkyl center (KRFP1), fragments with carboxylic-amide structural elements (KRFP4237). However, for inhibitors of 17α-hydroxylase activity, patterns corresponding to 1H-imidazole (KRFP2393) and 4- substituted pyridine (KRFP3616), as well as a trisubstituted benzene structural fragment (KRFP1592) are more remarkable.

The obtained model acts as a molecular ‘pattern detector’, highlighting the structural fingerprints that tip CYP17A1 dual activity. The performed framework provides a promising tool for drug design and discovery of selective 17,20lyase inhibitors – novel active pharmaceutical ingredients for treatment castration-resistance prostate cancer.

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THE ROLE OF ELECTROSTATIC INTERACTIONS IN AUTODOCK4 SCORING FUNCTION

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The goal of the study was to investigate the role of electrostatic interactions within the AutoDock4[1] scoring function and to estimate the influence of the quality of atomic charges (q) on the overall performance of the scoring function. For that purpose, we rigorously studied/tested AutoDock4 using CASF-2016 benchmark[2] to perform scoring power test (capability to predict correct ΔG_{bind}) docking power test (capability to predict correct pose) and ranking power test (capability to correctly rank known ligands for a certain target on a set of various targets).

$$\Delta G_{bind}^{AD4} = w_{vdw}\sum_i\sum_j\left(\frac{A_{ij}}{r_{ij}^{12}}-\frac{B_{ij}}{r_{ij}^{6}}\right)+w_{hbond}\sum_i\sum_j E(t)\left(\frac{C_{ij}}{r_{ij}^{12}}-\frac{D_{ij}}{r_{ij}^{10}}\right)+w_{estat}\sum_i\sum_j\frac{q_i q_j}{\epsilon(r)r_{ij}}+w_{desolv}\sum_i\left[S_i\sum_j V_j e^{-r_{ij}^2/2\sigma^2}\right]+w_{tors}N_{tors}$$

In case of scoring power test, the influence of different electrostatics is estimated via use of a number of charge schemes both for ligand (Gasteiger, 6-31G* ESP, MMFF94, PM7, Mulliken, Lowdin, DENR, Formal charges and zero charges) and receptor (Gaisteier, Kollman, MMFF94, PM7, DENR, Formal charges and zero charges) parts, followed by fitting *w* parameters of AutoDock4 equation to reproduce the experimental affinities. The importance of different contributions for docking power and ranking power test was estimated by switching off the specific contributions within the scoring function, without readjusting the regression weights for the rest of them.

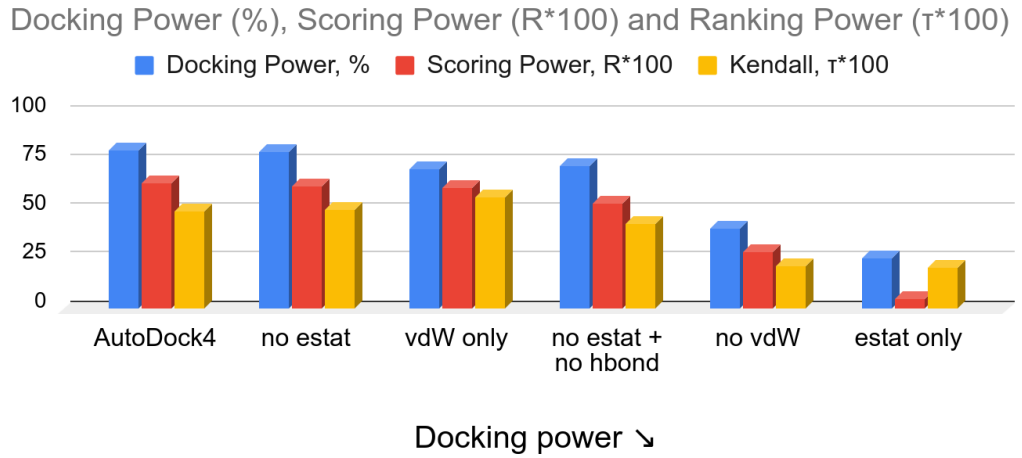

Figure 1. Performance of the AutoDock4 in CASF-2016 tests.

Surprisingly, the study shows that the AutoDock4 is generally insensitive to the quality of atomic charges used. Moreover, it was discovered that the complete exclusion of the electrostatic interactions from the equation does not lead to any significant performance change in any of the aforementioned tests.

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IN SILICO CLICK CHEMISTRY-DRIVEN DESIGN OF BLOOD-BRAIN BARRIER-PERMEABLE DOPAMINE D3 RECEPTOR LIGANDS

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The dopamine D3 receptor (D3R) is a pivotal therapeutic target for neurological and psychiatric disorders. In this study, we developed an innovative *in silico* click chemistry approach to design D3R ligands with intrinsic blood-brain barrier (BBB) permeability. Using 1-phenyl-4-[4-(1H-1,2,3-triazol-5-yl)butyl]piperazine as a core scaffold, we systematically modified the 1,2,3-triazole moiety and screened candidates based on their predicted brain-to-blood concentration ratio (logBB). Among the generated compounds, 1-{4-[1-(decahydronaphthalen-1-yl)-1H-1,2,3-triazol-5-yl]butyl}-4-phenylpiperazine emerged as the most promising, exhibiting superior predicted D3R binding affinity and BBB permeability compared to the reference antagonist eticlopride. Molecular dynamics simulations further validated its stable receptor interactions. This work introduces a novel lead compound for D3R-targeted therapies and establishes a streamlined workflow combining *in silico* click chemistry with BBB permeability assessment to expedite antipsychotic drug discovery.

MOLECULAR DYNAMICS INSIGHTS INTO SERM-INDUCED ENDOMETRIAL SAFETY FOR BREAST CANCER THERAPY

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Adjuvant hormone therapy with selective estrogen receptor modulators (SERMs), such as tamoxifen, remains the standard treatment for premenopausal breast cancer patients [1]. While SERMs effectively reduce recurrence risk and exert beneficial effects on bone and cholesterol metabolism, their agonistic activity in the endometrium limits their use in postmenopausal women due to the risk of uterine cancer. Current adjuvant strategies rely on aromatase inhibitors, which, however, induce secondary osteoporosis—an opposite effect to that of SERMs [2].

The objective of this study was to explore molecular determinants underlying the endometrial safety of SERMs. We applied molecular dynamics simulations to investigate the estrogen receptor (ER) ligand-binding domain (LBD) in complexes with clinically relevant SERMs. Both Asp351 and Phe404 emerged as key residues, as their interactions with SERM side chains are clinically associated with uterotropic effects and endometrial cancer risk. Asp351 in particular has been implicated in tamoxifen resistance, with mutations such as Asp351Tyr leading to altered receptor activation, while Phe404 mutations have been recently linked to poor clinical outcomes in patients resistant to selective estrogen receptor degraders.

Our results show that reduced interactions between the antiestrogenic side chains of SERMs and Asp351/Phe404 strongly correlate with clinical observations of endometrial safety. The data indicate that hydrogen bonding, charge neutralization by cyclic amines, and π–π stacking are crucial for stabilizing antiestrogenic conformations. These features may explain why raloxifene-like SERMs, with their ability to neutralize the Asp351 charge via cyclic amines, demonstrate safer gynecological profiles compared with tamoxifen analogues.

Taken together, these findings establish a mechanistic link between ER side chain interactions and SERM pharmacology in different tissues. Optimizing side chain length, rigidity, and orientation could enable the rational design of next-generation SERMs that preserve efficacy in breast cancer treatment and chemoprevention, while minimizing adverse outcomes such as deep vein thrombosis, cataracts, and, critically, endometrial cancer. This approach provides a conceptual framework for achieving the “ideal SERM profile” for postmenopausal breast cancer therapy and prevention.

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SEQUENCE DIVERSITY OF NUCLEOTIDE AND PROTEIN SEQUENCES OF ALLATOSTATIN A FROM *APIS MELLIFERA* AND OTHER SOCIAL ORGANISMS USING *IN SILICO* APPROACH

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Despite ecological and evolutionary differences, eusocial insects, especially *Apis mellifera*, share key social behavioural traits like foraging, defensive, and mite grooming. Among the various behavioural genes considered so far, allatostatin A (*ast -A*) is a well-studied insect neuropeptide crucial for regulating feeding, development, activity / sleep, and learning, with its effects mediated by gut neuroendocrine cells that express *ast-A* gene. However, this gene is restricted to Insect's Order and its homologs such as galanin and somatostatin is reported in mammalian orders. This gene has diverse interacting partners in neuropeptide (NPF) pathways. Consequently, this study rigorously investigates the sequence diversity of allatostatin A (*ast A*) in *Apis mellifera* and other social organisms, with a keen focus on neuropeptide (NPF) pathway. The remarkable diversity indices, elevated dN / dS ratios, and a wide array of interacting partners within this pathway suggest a significant correlation between these factors and the evolution of social behaviour in both insects and mammals.

Multiple sequence alignment (MSA) of *ast-A* reveals a plethora of nucleotide positions that demonstrate substantial divergence across taxa. In contrast, several conserved nucleotide positions, denoted by asterisks (*) are posited to play a critical role in maintaining essential amino acid residues in the ast-A protein sequence. To elucidate these findings, MSA of AST-A protein from *Apis mellifera*, alongside its homologs in various social organisms, showcases a compelling mix of conserved and variable residues across these pivotal protein families. The high occurrence of identical or similar aligned amino acid residues among other orthologs underscores an impressive level of conservation. These highly conserved residues are instrumental in forming active-site pockets and consensus motifs that are vital for understanding the protein's functional capabilities. Conversely, the variable residues correspond to structurally diverse regions composing the loop areas of these proteins. Leveraging the data on conserved residues, the phylogenetic tree constructed using maximum likelihood (ML) method for AST-A reveals robust branches with compelling bootstrap support. These tree topologies imply a shared evolutionary pathway among the selected social organisms. Notably, the average dN / dS ratio being less than 1 indicates that AST-A protein is likely under negative selection, reflecting stringent functional constraints that have shaped its establishment within these evolving populations. Specifically, these constraints on certain amino acid residues are intricately linked to the regulation of behaviour in social organisms, underscoring the importance of allatostatin A in the evolutionary narrative of social behaviour.

MOLECULAR MODELING STUDY OF CRUZAIN ENZYME INHIBITION BY 2-ACETAMIDOTIOPHENE-3-CARBOXAMIDE DERIVATIVES

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Chagas disease is a neglected tropical disease caused by the protozoan *Trypanosoma cruzi* (*T. cruzi*), responsible for approximately 12,000 deaths annually. Current therapies, such as nifurtimox and benznidazole, have limited effectiveness during the chronic phase and cause significant adverse effects, underscoring the urgent demand for safer and more effective therapeutic alternatives [1].

In this context, cruzain (CRZ) emerges as a promising therapeutic target due to its expression in all life forms of *T. cruzi* metacyclogenesis and its essential role in parasite survival. Non-covalent inhibitors derived from the 2-acetamidothiophene-3-carboxamide class have already demonstrated potent trypanocidal activity with low mammalian toxicity [2] . The present study aims to investigate the inhibition mechanism of CRZ by five selected derivatives of this class using Molecular Modeling techniques.

The docking protocol was validated by the redocking method using a cristallographic structure retrieved from the Protein Data Bank (PDB ID: 4KLB), consisting of the ligand AC1 bound to the cruzain enzyme. The softwares employed were the AutoDock Vina 1.2.0, AutoDock-GPU and DOCK6, and the top scored poses of 100 replicates for each program were evaluated. These validated protocols achieved pose accuracies (RMSD $\leq$ 2.0Å compared to the reference crystallographic pose) of 86%, 90% and 88%, respectively.

Subsequently, additional CRZ-ligand complexes were obtained through molecular docking of the remaining four compounds (AC2-5) selected from the work of Wiggers et al. (2013). The dockings were performed in decaplicates using the previously validated parameters. The ligands AC2-5 showed different hydrogen bonds when compared with the co-cristallyzed ligang AC1, interacting mostly with residues Ser61, Gly66 and Asn70. Ligand AC2 generally formed more hydrogen bonds than the other ligands. By using three different programs it was obtained a variety of possible ligand-enzyme complexes. After a group similarity analysis the best poses were selected.

The most promising complexes for each ligand were then subjected to Molecular Dynamics (MD) simulations using GROMACS 2024.1, performed in triplicate for a duration of 500 ns. System preparation for MD consisted of exclusion of water molecules from the tridimensional enzymatic structure, residue protonation adjustments (pH 5.5) and charge equilibration. Preliminary analysis suggest that the interaction with this class of ligands do not change significatively cruzain secondary structure or radius of gyration, and hydrogen bonds seem to be critical for ligand binding to the enzyme active site. Subsequent analyses will focus on enzyme structural dynamics and detailed enzyme-ligand interaction profiles.

The MD simulations are expected to provide detailed insights into the inhibition profile of the evaluated compounds, elucidating the molecular mechanism underlying CRZ inhibition. These findings may significantly enhance our understanding of CRZ inhibition mechanism and aid the rational design of novel inhibitors with improved anti-Chagasic activity.

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EXPLORATION OF NOVEL HETEROCYCLES AS POTENTIAL POLY (ADP-RIBOSE) POLYMERASES INHIBITORS VIA STRUCTURE BASED DRUG DESIGN AND MOLECULAR MODELLING: A COMPUTATIONAL STUDY

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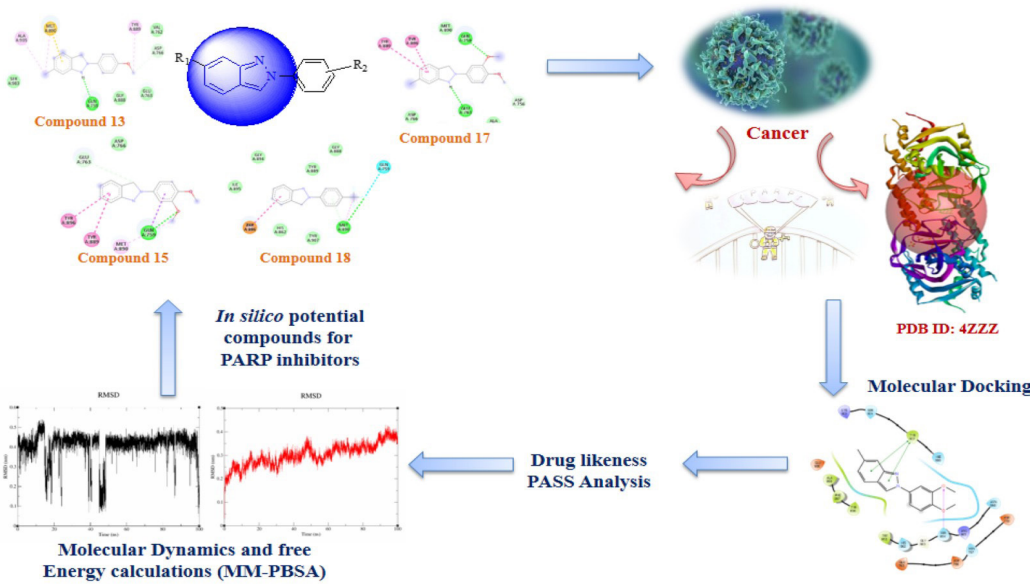
Cancer would be the major risk factor for mortality globally, with approximately 10 million deaths and injuries expected in 2030, representing for roughly about one in six deaths. Breast, colon, lung, prostate, and rectum cancers seem to be the most frequent malignancies. Cancer develops when normal cells become mutated into tumour cells together in multi-stage approach which further usually evolves among a pre-cancerous tumour to a malignant cancer. It's interesting to note that the target protein PARP-1 plays a well-known role in DNA signalling and repair and is a preferred cancer target. PARP-1 is also implicated in a variety of certain other cellular processes, such as apoptosis, cell division, transcriptional control, as diversification, and chromosome stability [1]. PARP inhibition has emerged as a significant therapeutic strategy for treating various tumor types. This study evaluates a series of previously synthesized 2H-indazole derivatives as potential poly(ADP-ribose) polymerase (PARP) inhibitors using computational approaches. Multiple scoring methods including AutoDock Vina, Glide, and MM/GBSA analysis demonstrated the inhibitory efficacy of these derivatives compared to the reference inhibitor NU1025. Compound **17**, featuring a methyl substituent at the C-6 position and dimethoxyphenyl moiety at the N-2 position of the indazole ring, emerged as the most potent candidate. Molecular dynamics simulations over 100ns confirmed enhanced binding interactions between PARP1 and compound **17**. The derivatives demonstrated strong interactions with key residues including Asp766, Gly888, Glu763, Ala755, and Ala935. PASS algorithm predictions further supported the antineoplastic potential of these compounds. This investigation establishes compound **17** as a promising PARP inhibitor candidate for cancer treatment, highlighting the therapeutic potential of novel 2H-indazole derivatives in affecting cancer cell cytotoxicity through PARP inhibition.



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IMPLEMENTATION OF HIGH-THROUGHPUT SCREENING DATA FOR DRUG SYNERGY PREDICTION IN ONCOLOGY

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The development of synergistic anticancer combinations is of considerable interest in modern oncology. The combined application of drugs can provide an effect that exceeds the sum of their individual actions, leading to deeper tumor suppression and regression[1]. Combinations can block alternative survival pathways, reduce the likelihood of drug resistance, and allow dose reduction of individual components while maintaining therapeutic efficacy and lowering toxicity [2]. An additional advantage is the sensitization of tumors resistant to monotherapy, as well as the combination of short-term response (targeted or cytotoxic agents) with long-term immune control (immunotherapy)[3].

The search for effective combinations is carried out on cell models using the dose-response matrix approach, which makes it possible to evaluate the combined action of compounds. Various synergy models are applied for analysis, including Bliss, Loewe, ZIP, and HSA.

At the same time, the development of such therapeutic regimens is a labor-intensive and costly process. High-throughput screenings require significant resources, while multifactorial experiments generate large data volumes that demand complex bioinformatics processing.

Under these conditions, computational approaches become especially relevant, as they narrow the search space for promising combinations and reduce the experimental burden. Machine learning enables the creation of predictive synergy models, optimization of candidate selection for validation, and improved reproducibility of results.

In this study, synergy prediction was performed based on drug combination data from the NCI-ALMANAC and MERCK studies. Preliminary data evaluation, threshold optimization, model construction was carried out.

We employed the PASS DDI software for drug–drug interaction prediction. The method is based on PoSMNA descriptors[4], which are used to establish structure-activity relationships (SAR) for drug pairs. SAR models were built and validated using a specifically designed cross-validation procedure which excludes intersections on individual compounds between drug pairs in training and test data sets. This procedure provides an objective and unbiased estimation of drug–drug interaction data.

The resulting models enable the assessment of potential drug synergy and can serve as a basis for the rational selection of candidates for further preclinical and clinical studies, with prediction accuracy exceeding 70%.

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7-DAY-LONG BLOOD PLASMA PROTEOME ANALYSIS FROM CRITICALLY ILL PATIENTS

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The possibility of using proteomics to replace the standard set of biochemical analyses has long been considered attractive. However, label-free mass spectrometry of blood plasma has not yet yielded the expected results, since in terms of accuracy and speed of measurements it is significantly inferior to both ELISA and targeted proteomics. Previously, Philipp Geyer et al. [1] have shown that the plasma proteome of healthy individuals is stable. Therefore, in the present study, we hypothesized that there is a sub-proteome of plasma that destabilizes in ICU patients as their condition worsens and stabilizes as their condition improves. To test this hypothesis, we examined 8 groups of 7 ICU patients plasma samples collected over 7 consecutive days of ICU stay. Four groups showed improvement in overall condition ("Positive group", PG), while four groups showed downgrade in overall condition ("Negative group", NG) over time. The 7 patients selected for the study, were 4 men (age 66.8+/-4.3, height 173+/-2.7 cm, body weight 76.3+/-6 kg) and 3 women (age 59.7+/-7.3, height 160.7+/-5.2 cm, body weight 68.8+/-10.7 kg). The ICU subjects were monitored with the recording of basic vital signs and the calculation dysfunction scores (SOFA), on mechanical ventilation and continuous infusion therapy.

Frozen plasma samples were assigned random positions on a 96-well plate and prepared with a Tecan liquid handling station. Preparation included reduction of disulfide bonds, protein peptization, carbamidomethylation, «trypsinolysis», solid-phase extraction, drying and reconstitution. Tryptic peptide samples were subjected to LCMS and panoramic DDA analysis on an Orbitrap Exploris 480 Mass Spectrometer was performed. Samples were analyzed in a random order. Data were analyzed with MaxQuant software against reference proteome (UP5640). Obtained intensities were further processed with in-house R scripts.

In total 253 proteins were identified, from them 12 demonstrated 7-day CV (iBAQ) > 1 at least for one patient. Comparison of reliably identified proteins between different groups and days demonstrated that only 66 proteins appeared in all samples. Appearance of four proteins (apolipoproteins A-L1 and D, kininogen-1 and an immunoglobulin) could be associated with better patient's condition (NG in early days and PG in late days), while appearance of complement component C6 could be associated with worsening. Analysis of protein representation between the PG and NG showed that only complement factor D and Cystatin-C were significantly upregulated and complement C4A was downregulated in the PG in all days. Between-days comparisons revealed that five proteins including complement C3 significantly decreased with time in the NG, while complement C2 increased. For the PG five other proteins including apolipoproteins A-IV and D increased with time, while serum amyloid A-1 decreased. Analysis of 7-day CV of protein iBAQ values showed that for 19 proteins the CV within the patient was significantly smaller than the CV of the same protein in the total dataset, thus indicating that these proteins could be considered as patient-specific. These proteins included hemoglobin and related proteins, complement components, apolipoproteins and immunoglobulins. Hierarchical clustering analysis of protein and clinical tests z-scores revealed that for all patients protein expression allowed clustering of adjacent days.

Altogether we conclude that the stability of the proteome obtained by panoramic mass spectrometry is preserved even in intensive care unit conditions.

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BIOINFORMATICS MODELING OF S100B GENE CLONING INTO THE VECTOR (pComb3XSS) FOR SUBSEQUENT PROTEIN EXPRESSION

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This study aimed to perform an in silico verification of cloning the S100B gene cDNA [1] into the pComb3XSS vector using the Benchling platform (benchling.com), to ensure successful subsequent protein expression. It demonstrates how modern bioinformatics tools can simulate and optimize critical molecular cloning steps before laboratory work begins, thereby reducing risks and costs.

Traditional cloning approaches often proceed without preliminary in silico analysis or rely on fragmented manual calculations, which can lead to unsatisfactory outcomes at the stages of restriction, ligation, transformation, or target protein expression. This study introduces comprehensive computer modeling using the Benchling platform, integrated into the standard laboratory workflow. This approach not only predicts experimental success but also enables the early identification of potential issues (e.g., the emergence of unintended stop codons, reading frame shifts, or incorrect placement of restriction sites).

The complete cloning procedure was successfully simulated in this study. Key achievements include:

1. Construct Design. The recombinant plasmid pComb3XSS-S100B was designed and visualized using Benchling.

2. Cloning Step Verification. Computer modeling of the restriction digestion with the selected enzymes SacI and XceI and subsequent ligation of the linear S100B insert into the plasmid vector pComb3XSS was performed. The analysis confirmed the correct reading frame and preservation of the vector's key functional elements.

The computer simulation of S100B cDNA insertion into the pComb3XSS vector conducted in this study represents the first and critical stage in developing a recombinant system for the investigation of this protein. The successful in silico construction using the Benchling platform confirms the feasibility of this approach. The resulting recombinant construct enables the subsequent expression and purification of the S100B protein, providing a foundation for fundamental research into its functions and for the development of novel diagnostic tools in medicine and pharmaceutics. Furthermore, the described method significantly reduces the time, consumable costs, and number of unsuccessful attempts in genetic engineering workflows, thereby enhancing the overall efficiency of scientific research in the fields of protein engineering and biotechnology.

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MOLECULAR MODELING OF GES β-LACTAMASES

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The most important mechanism underlying the antibiotic resistance in Gram-negative bacteria is the production of β-lactamases — enzymes capable of hydrolyzing β-lactam antibiotics. The GES family represents a distinct group among extended-spectrum serine β-lactamases (ESBLs). Their catalytic mechanism involves a nucleophilic attack by the serine residue (Ser64) on the β-lactam ring of the substrate, resulting in the formation of the acyl-enzyme complex. Deacylation of this complex and subsequent release of the hydrolyzed antibiotic occur via activation of a water molecule by the Glu166 residue, located on a critical structural element — the flexible Ω-loop. A distinctive feature of GES enzymes is their capacity to acquire point amino acid substitutions that broaden their activity spectrum, and the majority of functionally significant substitutions occur within the Ω-loop. For instance, the Gly170Ser substitution enhances carbapenemase activity (increasing 100-fold Kcat of imipenem hydrolysis) while simultaneously reducing activity against monobactams (80-fold decrease for aztreonam).

In this study, we investigate the impact of point amino acid substitutions on the flexibility of the Ω-loop and, consequently, on the activity of GES-family proteins. The 1 μs classical molecular dynamics (MD) trajectories were computed for the apo forms of nine proteins: GES-1, 2, 5, 6, 11, 12, 13, 14, 18. Correlated residue motions were examined using dynamic network analysis. For a more comprehensive analysis, the EnGens software package was employed to abstract the features of the active site and Ω-loop, reduce dimensionality of the feature space with the PCA and UMAP techniques followed by clustering procedures, enabling effective analysis of the MD data. We demonstrate that mutations induce changes in the mobility and accessible conformations of the Ω-loop. Alas, these calculations were not sufficient to establish a clear correlation between the dynamic behavior of the loop and the enzymatic activity of the protein. The described procedure should be re-implemented for the enzyme-substrate complexes, not the apo forms, and the cefotaxime ligand was chosen for subsequent consideration. Initially generated force field parameters of cefotaxime by Charm General Force Field (CGenFF) had high penalty values, requiring additional verification and correction. Re-parametrization was carried out with the VMD Force Field Tool Kit plugin and ORCA QM software. All calculations were carried out at the MP2/6-31G* theory level. To validate the obtained parameter values, we compared the structures obtained by QM and MM energy minimization. RMSD between the QM and MM structures decreased from 1.02 to 0.65 Å for the old and the new values respectively.

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DESIGN, DOCKING, ADMET, PASS, SYNTHESIS & BIO-EVALUATION OF NOVEL 7-O-SUBSTITUTED CHRYSIN AS AN ANTICANCER AGENT TARGETING VEGFR-2

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Background. VEGFR-2 is a critical target in cancer therapy, facilitating tumor angiogenesis, yet existing inhibitors face toxicity and resistance issues. Chrysin, a flavonoid with anticancer properties, has VEGFR-2 characteristics but suffers from poor pharmacokinetics. A series of 7-O-substituted chrysin derivatives was designed to enhance binding and drug-like properties by incorporating key hydrogen-bonding groups and hydrophobic elements, informed by VEGFR-2 structural analysis.

Objective. To design and assess novel chrysin derivatives through computational predictions and molecular docking; synthesize and characterize selected derivatives; and evaluate their antioxidant and anticancer activities in vitro, to identify effective candidates that exhibit favorable pharmacokinetics and safety.

Methods. Chrysin derivatives featuring alkylamino and ester substituents were designed using molecular docking against VEGFR-2. ADMET profiling was conducted to anticipate pharmacokinetics and toxicity. In-silico cytotoxicity of chrysin and its hybrids was assessed using CLC-Pred and further analyzed on nine breast cancer cell lines via BC CLC-Pred. Selected derivatives were synthesized via alkylation and esterification, and characterized using UV, IR, NMR, and mass spectrometry. Antioxidant activity was evaluated using the DPPH assay, while anticancer efficacy against MCF-7 cells was assessed through cell viability assays, comparing IC50 values with those of ascorbic acid and sorafenib.

Results. Docking studies indicated strong binding affinities, particularly for ester derivatives. ADMET predictions suggested favorable drug-like characteristics. Compound C7 demonstrated remarkable antioxidant activity (IC50 = 0.6 μM), exceeding both chrysin and ascorbic acid. In anticancer tests, C7 and C8 displayed significant cytotoxicity (IC50 = 1.0 and 1.5 μM, respectively), outperforming chrysin and nearing sorafenib efficacy.

Discussion. The improved bioactivity and predicted safety of C7 and C8 highlight the efficacy of rational structural modifications in optimizing natural products. Their dual antioxidant and anticancer properties underscore their potential as lead compounds for VEGFR-2-targeted breast cancer treatments.

Conclusion. Ester-substituted chrysin derivatives, specifically C7 and C8, demonstrate promising VEGFR-2 inhibition and therapeutic potential, warranting further exploration as multifunctional anticancer agents.

CHEMECAL PROFILE EVALUATION AND ACTIVITY OF *TAMARINDUS INDICA* L. SEEDS ON *HELICOBACTER PYLORI* AND UREASE

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Helicobacter pylori is a bacterium with a high global prevalence (43.9%), which colonizes the stomach and is associated with the leading cause of gastritis, peptic ulcers, and gastric cancer. The current scenario indicates high rates of *H. pylori* resistance to established treatments, highlighting the need for new therapeutic alternatives. A valuable pathway lies in the ethnopharmacological investigation of plants that typically exhibit gastroprotective and antiulcer properties, a potential observed in traditional medicine in *Tamarindus indica* L. (Fabaceae), associated with the presence of phenolic compounds. *H. pylori* are highly adapted to the gastric environment and possesses several virulence factors that enable infection, most notably urease, an enzyme responsible for hydrolyzing urea into ammonia and carbon dioxide, creating a neutral microenvironment around the bacterium that allows it colonization in the host and is considered a promising target for new therapeutic alternatives. Seeking to expand knowledge about this plant species, coupled with the need to find therapeutic alternatives for the eradication of this bacterium, this study aimed to evaluate the chemical profile of *T. indica* L. seeds, their anti-*H. pylori* activity, and urease enzyme inhibition. The chemical profile was evaluated through liquid chromatography combined with mass spectrometry (LC-MS), from the identified compounds, a search for targets was carried out in the PASS Online server, identifying urease as a possible target of action. The urease inhibition was evaluated *in silico* molecular docking with the crystal structure of *H. pylori* urease (PDB: 1E9Y) in the GOLD 2024 software (X: 127.8063, Y: 129.2873, Z: 86.3672, 25Å radius) using GoldScore as primary score and ChemScore for rescore, and *in vitro* by inhibition of the *Jack bean* urease. The anti-*H. pylori* activity was assessed through the broth microdilution technique with ATCC and clinical strains. LC-MS analysis suggested the presence of interesting substances, such as trans-cinnamic acid (ATC), dicyclohexylurea, and 2,2'-(tetradecylamino)diethanol (2,2TD), associated with anti-*H. pylori*, with a minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of 512 µg/mL for the clinical strain. And at the concentration of 256 **µg**/mL, the inhibition of urease was 93.0% ± 2.34 and 93.6% ± 1.32 for the methanolic extract and the 25% methanolic fraction, respectively. The docking was validated by redocking the cocrystallized ligand and obtained a RMSD of 1.3967 **Å.** The best docking scores were observed for 2.2'-TD and ATC, 64.66 and 51.33, respectively, higher than acetohydroxamic acid (standard substance), with a score of 45.72. The literature has already described cinnamic acid and its derivatives as having urease inhibitory potential, and its possibly due to the carboxylate interaction with nickel atoms through electrostatic forces. However, no association was found in the literature with the activity observed for 2.2'-TD, which was able to interact at the binding site, and the long carbon chain may sterically impede urease activity, even with unfavorable interactions. Therefore, the substances noted in the seeds of *T. indica* L. demonstrated potential urease inhibitory activity, possibly presenting a synergistic effect between them, which can complement the treatment of *H. pylori*, although further studies are needed to understand the activity and mechanism of action of the isolated compounds.

OPTIMIZED HPLC APPROACH FOR SIMULTANEOUS ANALYSIS OF CEFOPERAZONE AND ITS DEGRADATION PRODUCTS

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The insight into the chromatographic methods revealed a limited number of highly sensitive procedures providing the selective determination of both cefoperazone and its degradation products with straightforward isocratic elution. The wide variety of existing techniques offers multiple approaches for the development of a well-performing method that addresses the simultaneous separation of the parent compound and its degradation products. Most optimized HPLC (*High Pressure Liquid Chromatography*) methods use gradient elution with different mobile phases and compositions, resulting in retention times often over 15 min [1]. Therefore, the optimization of an isocratic procedure for the determination of cefoperazone and its degradation products would be beneficial in routine pharmaceutical analysis.

This research is focused on the optimization and determination of cefoperazone and its degradation products using HPLC–DAD (*High Pressure Liquid Chromatography Diode Array Detection*). Samples of 0.5 cm³ were taken, filtered through 0.22 μm membrane filters, and analyzed using an HPLC–DAD with an Eclipse XDB-C18 column (150 × 4.6 mm, 5 μm). The column was kept at 30°C. An isocratic elution of acetonitrile (ACN): 0.1% H_3PO_4 of different compositions at a different flow rate was used, and cefoperazone was monitored at 205 nm, an appropriate wavelength of absorption of cefoperazone. During the HPLC method optimization, the mobile phase composition as well as the flow rate were adjusted. Maximum separation was achieved using ACN: H_3PO_4 (30:70, v/v) at a flow rate of 0.8 cm³/min, which resulted in sharp and well-resolved peaks. The retention time was 6.7 ± 0.1 min. The hydrolysis of cefoperazone was performed at 25 ± 1 °C and 4 ± 1 °C for 7 days. At 25 °C, cefoperazone was hydrolyzed to its P1–P4 intermediates. At lower temperatures, hydrolysis was much slower, leading to the formation of mainly P1 and P4 intermediates. From these observations, it can be concluded that hydrolysis is a factor in the environmental degradation of cefoperazone. This study illustrates the capability of optimizing the HPLC method for precise monitoring of cefoperazone and its degradation products with a suitable analysis time.

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STUDY OF SUBSTANCES USING QUANTUM CHEMISTRY IN THE ANHARMONIC APPROXIMATION

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Quantum chemical calculations provide an efficient approach for studying substances. The conformational space of polyatomic "soft" molecules contains numerous structures in shallow potential energy wells, each containing a large number of low-lying vibrational states characterized by small transition energies. The thermodynamic functions of such substances are ensemble averages that account for the concentration of conformers in the equilibrium mixture—their molar fractions. The main sources of error in determining thermodynamic functions include neglecting low-lying conformers (and their associated molar fractions, the mixing contribution, and mirror isomerism), inaccurate treatment of electron correlation (within a single-electron representation), and the use of the harmonic approximation.

Although the free energy and enthalpy obtained by molecular mechanics do not include the total electronic energy, this method is effective for generating a set of structures that includes the global minimum and all low-lying conformers. Optimization using quantum chemistry ranks the conformers in ascending order of energy and identifies the global minimum conformer.

The selection of conformers that contribute to the ensemble-averaged properties is based on molar fractions calculated from the Gibbs free energy. The main contribution to the Gibbs free energy is the electronic component (not accounted for by molecular mechanics methods).

The vibrational contribution to the properties of substances is determined by modeling torsional, deformation, and valence vibrations using second-order vibrational perturbation theory with the Dunham series. Molar fractions, mixing entropies, and free energies of mixing are derived from the temperature dependence of the Gibbs free energy for each conformer in the "rigid rotator-anharmonic oscillator" model.

The procedure for determining the properties of a substance comprises the following steps:

– Conformational space analysis (generation of a set of hypothetical structures optimized by molecular mechanics, which includes the global minimum and all low-energy conformers);

– Selection of the most suitable quantum chemical model based on the experimental properties of reference molecules - a specific "method/basis" combination;

– A preliminary quantum chemical calculation at a low level of theory, involving sorting conformers by increasing total electronic energy and selecting significant conformers that contribute to the properties;

– Determination of molar fractions and mixing contributions to entropy and free energy;

– Solution of the torsion Schrödinger equation for all internal rotations in each selected conformer;

– Calculation of the properties of individual conformers (structure, total electronic energy, harmonic and anharmonic frequencies);

– Refinement of molar fractions (statistical weights);

– Averaging of substance properties over all significant conformers, taking into account symmetry, statistical weights, and mixing contributions.

The calculations were performed using the resources of the Siberian Supercomputing Center, Institute of Physics and Mathematics, Siberian Branch of the Russian Academy of Sciences.

COMPARATIVE EVALUATION OF LSTM AND GRAPH NEURAL NETWORKS FOR ADVERSE DRUG REACTION PREDICTION

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Drug discovery and development is an expensive process in which time and human resources are heavily invested, yet adverse drug reactions (ADRs) remain a major cause of post-approval safety concerns, leading to restricted use or market withdrawal. Conventional approaches such as clinical trials and voluntary reporting are constrained by duration, cost, under-reporting, and limited capacity to capture rare or long-term toxicities [1]. In recent times, machine learning has been increasingly applied to address this gap, but model accuracy is hindered by noisy training data, preprocessing challenges, and chemical structure representation [2]. In particular, the comparative effectiveness of sequence-based versus graph-based modeling, especially with pre-trained embeddings remains underexplored.

In this study, we compared Long Short-Term Memory (LSTM) networks and Graph Neural Networks (GNNs) for ADR prediction using drug-ADR associations from the SIDER database [3]. ADR terms were denoised with cosine similarity, and Positive and Unlabeled learning method was used as a second preprocessing step. Three models were developed; 1) an LSTM with ChemBERTa for drugs and SapBERT for ADRs embeddings; 2) a GNN with the same embeddings; and 3) a GNN using Deep Graph Library (DGL) derived structural embeddings of MOL files with SapBERT for ADRs. The GNN with DGL embeddings achieved the best performance (AUC-ROC = 0.9189), while also reducing training time dramatically (≈3 minutes/epoch vs. ≈8 hours for transformer embeddings).

External validation with the ADReCS [4] database confirmed predictive capability on novel drug-ADR pairs, yielding high-confidence scores for both known and unseen associations. Our findings showed successful prediction of potential associations for compounds and ADRs that were not present in the training set. This result adds to evidence that the model successfully learnt structural and semantic patterns relevant to ADR prediction. Our model could be applied to screen novel compounds during early drug discovery to identify potential safety concerns to streamline clinical testing, thereby reducing waste, enhancing patient confidence and safety during drug development.

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MAGNESIUM BINDING TO TRPV6 ION CHANNEL: INSIGHTS FROM MOLECULAR MODELING

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TRPV6 is a calcium-selective ion channel belonging to the vanilloid subfamily of transient receptor potential (TRP) channels. It functions as a principal regulator of calcium homeostasis in epithelial tissues of intestine, kidney, and placenta, playing an essential role in dietary calcium absorption, bone development and male fertility. Mutations in TRPV6 have been linked to several human diseases such as neonatal hyperparathyroidism, skeletal dysplasia and various kidney disorders. The overexpression of TRPV6 has been shown to promote excessive calcium influx, which can contribute to tumor progression, thus making TRPV6 a potential oncochannel. TRPV6 is inherently active, although modulated by a variety of endogenous factors, such as membrane lipids, calmodulin and divalent cations [1]. Among the latter, intracellular magnesium (Mg^{2+}) was shown as a critical channel inhibitor. However, the molecular basis of magnesium-mediated TRPV6 inhibition remains to be fully elucidated.

In this work, a new intracellular Mg^{2+} binding site of TRPV6 was discovered using a combination of cryo-electron microscopy (cryo-EM), electrophysiology, mutagenesis, and molecular modeling [2]. According to novel cryo-EM structure of TRPV6 in complex with Mg^{2+}, this site is located at the intracellular entrance to the channel pore and is formed by two negatively charged aspartate residues, D489 and D580 on the S5 and S6 transmembrane pore-forming helices. The magnesium binding at this site appears to stabilize the closed state of the pore, thereby effectively blocking ionic conductivity.

To quantitatively characterize this regulatory site, a novel MD simulation protocol was developed. Due to high energy barriers and strong interactions associated with highly charged ions such as Mg^{2+}, direct observation of binding events in conventional MD simulations is challenging, necessitating enhanced sampling techniques. The presented protocol integrates well-tempered metadynamics (WTMetaD) employing a "multiple walkers" setup [3] and electronic continuum correction (ECC) that scales atomic charges to better model solvent polarization effects [4]. Collective variables used in WTMetaD include distances from the cation to the carboxyl carbon atoms of D489 and D580 and the number of water molecules in the ion's first hydration shell. In these simulations, the modified Amber-99sd-ildn force field [5] was employed.

The protocol was first validated on cation–acetate binding and demonstrated good agreement with experimental data. Being applied to the TRPV6 site, Mg^{2+} exhibited strong binding affinity with $\Delta G^0 = -12.9 \pm 0.4$ kJ/mol, whereas Ca^{2+} binding was significantly weaker ($\Delta G^0 = -3.7 \pm 0.6$ kJ/mol). The obtained selectivity aligns with the structural findings from cryo-EM and electrophysiological experiments, supporting the model whereby magnesium binding at the D489-D580 site stabilizes the channel in a closed, nonconducting state.

The integrated WTMetaD and ECC approach provides a robust framework for studying ion-protein interactions and binding energies. It offers a transferable computational tool applicable to other ion-binding sites in proteins.

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DECIPHERING CURCUMIN'S MULTI-TARGET ACTIONS IN METABOLIC SYNDROME USING NETWORK PHARMACOLOGY AND MOLECULAR DOCKING

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Metabolic syndrome (MetS) is a multifactorial disorder characterized by obesity, insulin resistance, dyslipidemia, and hypertension, necessitating multi-targeted therapeutic approaches. Curcumin, the principal bioactive compound of Curcuma longa, exhibits antioxidant, anti-inflammatory, and metabolic regulatory activities; however, its molecular mechanisms in MetS remain incompletely understood. Network pharmacology and molecular docking provide integrative platforms for identifying therapeutic targets and pathways, thereby elucidating multi-targeted mechanisms of action. Curcumin has been reported to inhibit carbohydrate-hydrolyzing enzymes such as α-glucosidase, α-amylase, and lipase. In this study, network pharmacology and molecular docking were employed to elucidate the molecular targets and signaling pathways of curcumin in MetS. Curcumin-associated genes were retrieved from HERB, SwissTargetPrediction, PharmMapper, and SEA databases, while MetS-associated genes were obtained from the Open Targets Platform. Overlapping targets were integrated into protein–protein interaction (PPI) networks constructed via STRING, and hub genes were identified through network topology analysis using Cytoscape 3.10.3. Functional enrichment, including Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses, was performed using the DAVID database. Molecular docking was conducted with AutoDock Vina (PyRx) and visualized in Biovia Discovery Studio. A total of 356 curcumin-related targets and 4046 MetS-related targets were identified, with 242 overlapping targets. Network analysis revealed ten hub genes, including TP53, JUN, AKT1, STAT3, and SRC. These genes were significantly enriched in the lipid and atherosclerosis pathway, AGE–RAGE signaling in diabetic complications, and endocrine resistance pathways, which are central to dyslipidemia, hyperglycemia, oxidative stress, and insulin resistance. Molecular docking demonstrated strong binding affinities of curcumin to TP53, JUN and AKT1 key targets with binding energies below –5 kcal/mol. Collectively, these findings suggest that curcumin exerts therapeutic effects on MetS through multi-target, multi-pathway mechanisms, supporting its potential as a complementary therapeutic strategy for the management of metabolic syndrome.

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AUTHOR INDEX OF ABSTRACTS


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