XXIX Symposium on Bioinformatics and Computer-Aided Drug Discovery

PROCEEDINGS BOOK

Institute of Biomedical Chemistry
Moscow, Russia (Virtual), September 18-20, 2023

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 XXIX SYMPOSIUM "BIOINFORMATICS AND COMPUTER-AIDED DRUG DISCOVERY" – Moscow: Institute of Biomedical Chemistry, 2023

The materials of the XXIX International Symposium "Bioinformatics and Computer-Aided Drug Discovery" (Virtual, 18-20 September 2023) are presented. This Symposium is dedicated to the emerging challenges and opportunities for *in silico* drug discovery. Contemporary fields of biomedical science devoted to the analysis of normal and pathological states of the organism and revealing the pathological processes at the cellular and molecular levels are discussed.

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

This information will be useful for researchers whose investigations are dedicated to creating computational methods and their application to drug research and development using bio- and chemoinformatics methods based on post-genomic technologies. It can also be useful for undergraduate, graduate, and postgraduate students specializing in the relevant fields.

Responsible editors: Corr. 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 (IBMC), I am very happy to welcome the participants of the XXIX Symposium "Bioinformatics and Computer-Aided Drug Discovery".

The annual holding of the Symposium has become a tradition. Next year we look forward to holding the 30th anniversary Symposium. For the first time this Symposium was held in 1995 in the framework of the II Russian National Congress "Man and Drugs" organized by my teacher, Full Member of the Russian Academy of Sciences (RAS), Professor Alexander I. Archakov. Since then, this meeting has been held annually, chaired by Corresponding Member of RAS Vladimir V. Poroikov, leading scientist in Russia in the field of chemoinformatics and computer design of drugs, co-chaired by Full Member of RAS, Professor Nikolay S. Zefirov and since 2018 – by Professor Roman G. Efremov.

The Symposium provides an opportunity for researchers to exchange information of bioinformatics, chemoinformatics and computer-aided drug design methods according to the latest achievements and discuss the modern trends for the development of this multidisciplinary field of science in the future.

In 2022 the XXVIII Symposium was held online in the framework of the International Year of Basic Sciences for Sustainable Development announced by UNESCO. More than 400 people registered to participate in the Symposium. Among the speakers were well-known experts who have been actively working in the field of computer-aided drug design for many years, as well as young scientists, graduate students and students from Russia, Brazil, Germany, Georgia, Israel, India, Iran, Canada, China, Mexico, Peru, Singapore, Turkey, Philippines, Czech Republic, South Korea and others, totally from 50 countries of the world!

The main topics of the Symposium are especially important due to the active involvement of our Institute in the project "Digital Biodesign and Personalized Health Care". This is a global project on the digitalization of health monitoring and healthcare management. As part of this project, IBMC developing a digital information platform designed to optimize treatment using modern pharmacotherapy and taking into account the individual characteristics of the patient.

During last years, the life of most of us was significantly changed. In that case is extremely important to continue normal work, be patient and confident. We again faced with new challenge and need to mobilize our resources and strength of mind to continue research work and do that do what we need to do. All of us save the hope in hearts to see new opportunities and goals in addition to obstacles.

We hope that each other's support and traditions to hold the Symposium will help us to get through difficult times together, find new partners and friends. In this regard, the organization and holding this International Symposium is an important communicative step, which will allow us to unite, hear and understand each other. I would like to thank each of the participants of the Symposium and wish all of you safety and a fruitful work!

Director of the Institute of Biomedical Chemistry,
Doctor of Biological Sciences

Elena Ponomarenko

Dear Colleagues!

We are pleased to welcome you as participants of the XXIX Symposium "Bioinformatics and Computer-Aided Drug Discovery".

It is worth to remind you the statement of Prof. William Jorgensen in his landmark review published in Science in 2004: *"Is there really a case where a drug that's on the market was designed by a computer?" When asked this, I invoke the professorial mantra ("All questions are good questions."), while sensing that the desired answer is "no". Then, the inquisitor could go back to the lab with the reassurance that his or her choice to avoid learning about computational chemistry remains wise. The reality is that the use of computers and computational methods permeates all aspects of drug discovery today. Those who are most proficient with the computational tools have the advantage for delivering new drug candidates more quickly and at lower cost than their competitors*.

Since computer-aided drug discovery science is developing permanently, we are continuing the execution of 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 Full Member of the Russian Academy of Sciences (RAS) Alexander Archakov and co-chaired by the Full Member of RAS Nikolay Zefirov in 1996-2017. An essential contribution to the organization of the first Symposia was made by Professor Alexis Ivanov.

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), 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), and others.

At the upcoming, XXIX Symposium, plenary/keynote lectures will be presented by the experienced scientists representing both academy and industry from Belarus, Germany, India, Israel, Japan, Mexico, The Netherlands, Russia, Sweden and United States. Their lectures cover wide topics dedicated to the emerging challenges and opportunities in computer-aided drug discovery including assessment of genetic and environmental factors influence on complex human diseases based on the study of very large medical datasets, computational physiology for analysis of pathophysiological processes, in silico analysis of epigenomic alterations in gene regulation, computational proteomics and molecular biophysics for identification and/or structural characterization of the promising targets, development of new ligand-based methods for virtual screening and chemical safety estimations, possibilities and opportunities of molecular docking, rational design of glycomimetic drugs, etc. Several lectures present the results of *in silico* studies on SARS-CoV-2/COVID-19 with a goal to combat this and new biogenic threats in the future.

It is necessary to emphasize that the traditional Young Scientists Contest (YSC) aroused great interest: 65 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 fifteen Members

of the International Scientific Committee (ISC) including distinguished scientists from Brazil, China, Greece, India, Israel, Mexico, Russia and Singapore. Based on the voting of the ISC members and taking into account the geographical diversity of the participants, 18 abstracts have been selected for the flash presentations. The best presentations will be awarded by the Diploma of the First, Second and Third Degrees.

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 discussion platform to exchange original scientific ideas, attractive methodological solutions, and breakthrough multidisciplinary technologies. This is especially important in connection with the recent world events, which complicate international scientific and educational relationships, efficient exchange of information and data. These factors have always been at the heart of scientific creativity, especially in the field of biomedicine.

We believe that holding our Symposium in the current conditions, involving the participation of scientists from many countries, will help to develop scientific diplomacy, preserve and increase professional and human relations of colleagues, establish new creative connections, and, as a result, increase the efficiency of computer technologies for the discovery of new medicines. We hope that our Symposium will also contribute to reducing tension in the world. The online format provides unique opportunities for this, including talks given by our authoritative colleagues from all over the world.

Welcome to the sessions of the XXIX Symposium “Bioinformatics and Computer-Aided Drug Discovery”. We wish you very exciting and fruitful meetings and discussions!

Vladimir Poroikov
Corresponding Member of the Russian Academy of Sciences, Prof. Dr.

Roman Efremov
Prof. Dr.

Scientific Program

Scheduled time - Moscow (UTC+3)

Monday September 18, 2023			
Chairpersons: **Vladimir Poroikov and Roman Efremov**			
8:30	9:00	**Opening of the Symposium**	
Plenary lectures			
9:00	9:30	**Roman Zubarev**, *Karolinska Institutet, Stockholm, Sweden*	CHEMICAL PROTEOMICS IDENTIFIES DRUG TARGETS, RESIDENCE TIMES AND ACTION MECHANISMS
9:30	10:00	**Mikhail Panteleev**, *Center for Theoretical Problems of Physico-Chemical Pharmacology of the Russian Academy of Sciences, Moscow, Russia*	COMPUTATIONAL PHYSIOLOGY AND DRUG DEVELOPMENT
Oral presentations			
10:00	10:20	**Arli Aditya Parikesit,** *Department of Bioinformatics, School of Life Sciences, Indonesia International Institute for Life-Sciences, Jakarta, Indonesia*	DRUG PROPERTIES AND DRUG LIGAND-BINDING COMPARISON ANALYSIS ON TENOFOVIR AND ZIDOVUDINE AS A REVERSE TRANSCRIPTASE INHIBITOR OF HIV-1
10:20	10:40	**Allan Kalueff,** *Almazov National Medical Research Center, Saint Petersburg, Russia*	AI-POWERED IN VIVO SCREENS FOR NEUROACTIVE DRUG DISCOVERY USING ZEBRAFISH (DANIO RERIO)
10:40	11:00	**Bhaskar Ganguly,** *Indian Immunologicals Limited, Hyderabad, India*	FUNCTIONAL PROFILING OF MATURE VERSUS IMMATURE DENDRITIC CELL EXOSOME-SHUTTLE miRNAs
Keynote lectures			
11:00	11:30	**G. Narahari Sastry,** *CSIR-North East Institute of Science and Technology, Jorhat, Assam, India; Academy of Scientific and Innovative Research, Ghaziabad, India*	THE IMPACT OF PANDEMICS, EPIDEMICS, AND THE PROLIFERATION OF ARTIFICIAL INTELLIGENCE ON (COMPUTATIONAL) DRUG DISCOVERY
11:30	12:00	**Maria Khrenova,** *Lomonosov Moscow State University, Moscow, Russia*	MECHANISM OF THE APTAMER RECOGNITION BY SARS-COV-2 SPIKE PROTEIN REVEALED BY NANOPORE SEQUENCING AND MOLECULAR MODELING
Oral presentations			
12:00	12:20	**Natia Samsonidze,** *Ivane Beritashvili Center of Experimental Biomedicine, Tbilisi, Georgia*	DBAASP - A COMPREHENSIVE REPOSITORY OF NATURAL MULTIFUNCTIONAL CYCLIC ANTIMICROBIAL PEPTIDES

12:20	12:40	**Marat Kazanov,** *Skolkovo Institute of Science and Technology, A.A.Kharkevich Institute for Information Transmission Problems Russian Academy of Sciences, Moscow, Russia*	ANALYSIS OF THE THREE-DIMENSIONAL LOCALIZATION OF THE APOBEC-INDUCED MUTATIONS IN THE CELL NUCLEUS USING Hi-C DATA
12:40	13:00	**Prashantha Karunakar,** *Department of Biotechnology, Dayananda Sagar College of Engineering (Affiliated to Visvesvaraya Technological University, Belagavi), Bangalore, India*	VINALIGGEN: A METHOD TO GENERATE LIGPLOTS AND RETRIEVAL OF HYDROGEN AND HYDROPHOBIC INTERACTIONS FROM PROTEIN-LIGAND COMPLEXES
lunch break 13:00-15:00			
Chairpersons: **Alexander Tuzikov and Vladimir Sulimov**			
Plenary lectures			
15:00	15:30	**Alexander Tuzikov,** *United Institute of Informatics Problems, Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Minsk, Belarus*	COMPUTER-AIDED DISCOVERY OF NOVEL DRUG CANDIDATES AGAINST SARS-COV-2 TARGETING THE HEPTAD REPEAT DOMAIN 1 IN S2 PROTEIN
15:30	16:00	**Vladimir Sulimov,** *Dimonta Ltd., Research Computing Center, Lomonosov Moscow State University, Moscow, Russia*	DOCKING PARADIGM IN COMPUTER-AIDED DRUG DISCOVERY
Oral presentations			
16:00	16:20	**Dmitry Osolodkin,** *M.P. Chumakov Federal Scientific Center for Research and Development of Immunobiological Drugs of the Russian Academy of Sciences, Sechenov First Moscow State Medical University, Moscow, Russia*	THE GLAMOUR AND GLOOM OF ENSEMBLE DOCKING
16:20	16:40	**Yaroslav Faletrov,** *Faculty of Chemistry, Research Institute for Physical Chemical Problems Belarusian State University, Minsk, Belarus*	NEW FLUORESCENT ANTIFUNGAL AZOLE DERIVATIVE WITH NBD-PIPERAZINE MOIETY AND ITS DOCKING-REVEALED INTERACTION WITH SOME CYTOCHROMES P450
16:40	17:00	**Dmitry Shulga,** *Department of Chemistry at Moscow State University, Moscow, Russia*	IMPROVING ELECTROSTATICS DESCRIPTION IN SCORING FUNCTIONS - INSIGHTS FOR THEIR ROLE FOR DRUGS

Keynote lectures			
17:00	17:30	**Masha Y. Niv,** *The Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem, Israel*	PROGRESS AND CHALLENGES IN LIGANDS DISCOVERY FOR BITTER TASTE RECEPTORS
17:30	18:00	**Alexander I. Sobolevsky,** *Columbia University, New York, USA*	GATING AND MOLECULAR PHARMACOLOGY OF TRP CHANNELS
Oral presentations			
18:00	18:20	**Rodrigo Costa Zeferino,** *Department of Pharmacy, Federal University of Santa Catarina, Florianópolis, Brazil*	IMMUNOMODULATORY ACTIVITY OF BENZNIDAZOLE IN EHRLICH ASCITES CARCINOMA IN SILICO AND IN VIVO
18:20	18:40	**Ricardo Affeldt,** *Universidade Federal de Santa Catarina, Florianópolis, Santa Catarina, Brazil*	IN SILICO PREDICTIONS OF 2-PHENYL-3-(4-DIMETHYLAMINOPHENYL)QUINOXALINE ACTIVITY AND AKT1 INHIBITION
18:40	19:00	**Maricarmen Hernandez Rodriguez**, *Escuela Superior de Medicina, Mexico city, Mexico*	DRUG REPURPOSING OF HNMT INHIBITORS AND THEIR EVALUATION IN SCOPOLAMINE-INDUCED AMNESIA MODEL

Tuesday September 19, 2023			
Chairpersons: **Alexander Kel and Hanoch Senderowitz**			
Plenary lectures			
09:00	09:30	**Hanoch Senderowitz,** *Department of Chemistry, Bar-Ilan University, Ramat Gan, 5290002, Israel*	OPTIMIZATION OF QSAR MODELS FOR VIRTUAL SCREENING
09:30	10:00	**Derek van Tilborg,** *Eindhoven University of Technology, Eindhoven; Centre for Living Technologies, Utrecht, The Netherlands*	EXPOSING THE LIMITATIONS OF MOLECULAR MACHINE LEARNING WITH ACTIVITY CLIFFS
Oral presentations			
10:00	10:20	**Vincent Villanueva,** *Department of Biochemistry, Faculty of Pharmacy, University of Santo Tomas, Manila, Philippines*	A COMPARATIVE STUDY OF SAFETY AND PHARMACOKINETIC PARAMETERS BETWEEN STATINS, BILE ACID SEQUESTRANTS, AND EZETIMIBE AS DIFFERENT CLASSES OF LOW-DENSITY LIPOPROTEIN (LDL) CHOLESTEROL-LOWERING DRUGS IN SILICO
10:20	10:40	**Maxim Gureev,** *I.M. Sechenov First Moscow State Medical University, Moscow, Russia*	MODELING OF MIF-AIF INTERACTIONS IN FIELD OF ALLOSTERIC INHIBITORS DESIGN
10:40	11:00	**Humayun Wali,** *Department of Chemical Engineering, University of Engineering and Technology, Lahore, Pakistan*	SELECTION PROCESS OF PHYTOCHEMICALS FOR UTILIZATION IN DISINFECTION OF DRINKING WATER
11:00	11:20	**Alexander Serbin,** *Biomodulators & Drugs RC, Health RDF, A.V. Topchiev Institute of Petrochemical Synthesis Russian Academy of Sciences, Moscow, Russia*	FROM BASIC PRINCIPLES TO COMPUTATIONALLY REFINED MODELS FOR A PRACTIC SYNTHESIS OF THE NANO-TARGETABLE POLYMERIC ANTIVIRALS
11:20	11:40	**Nehal Rami,** *Department of Microbiology, Mehsana Urban Institute of Sciences, Faculty of Science, Ganpat University, Gujarat, India*	PLANT EXTRACTS IN CANCER THERAPY A COMPREHENSIVE ANALYSIS OF ANTICANCER ACTIVITY AND MOLECULAR DOCKING PROFILES
11:40	12:00	**Stanislav Ignatov,** *Lobachevsky State University of Nizhny Novgorod, Russia*	CONFORMATIONAL DYNAMICS AND STABILITY OF MYCOLIC ACIDS BILAYERS FROM THE MYCOBACTERIUM TUBERCULOSIS OUTER MEMBRANE

Keynote lectures			
12:00	12:30	**Alexander Kel,** *geneXplain GmbH, Wolfenbüttel, Germany; Institute of Chemical Biology and Fundamental Medicine, Novosibisk, Russia; RCSI, Dublin, Ireland*	LISTEN TO A SYMPHONY OF EPIGENOMICS WHEN SEEKING FOR DRUG TARGETS
12:30	13:00	**Yangyang Chen,** *Department of Computer Science University of Tsukuba, Tsukuba, Japan*	DEEP GENERATIVE MODEL FOR DRUG DESIGN FROM PROTEIN TARGET SEQUENCE
lunch break 13:00-15:00			
Chairpersons: **Athina Geronikaki and Alexey Lagunin**			
Young Scientists flash presentations			
15:00	15:10	**Christian Renz Algenio,** *Department of Biology, College of Science, Polytechnic University of the Philippines, Manila, Philippines*	IN SILICO ANALYSIS OF VARIOUS FUNGAL SECONDARY METABOLITES AND ANTIRETROVIRAL DRUGS ON ITS MOLECULAR BINDING TO NIPAH VIRUS PROTEINS INVOLVED IN CELLULAR ATTACHMENT, FUSION, AND REPLICATION
15:10	15:20	**Ankur Kumar,** *Drug Discovery and Development Laboratory, Department of Pharmaceutical Technology, Jadavpur University, Kolkata, India*	FIRST QSTR REPORT ON RATS CHRONIC AND SUB-CHRONIC TOXICITY OF DIVERSE CLASS OF CHEMICALS
15:20	15:30	**Arkaprava Banerjee,** *Drug Theoretics and Cheminformatics Laboratory, Department of Pharmaceutical Technology, Jadavpur University, Kolkata, India*	DEVELOPMENT OF A GLOBAL Q-RASAR MODEL FOR THE EFFICIENT QUANTITATIVE PREDICTIONS OF SKIN SENSITIZATION POTENTIAL OF DIVERSE ORGANIC CHEMICALS
15:30	15:40	**Upasana Hazarika,** *Department of Molecular Biology and Biotechnology, Tezpur University, Assam, India*	INVESTIGATION OF LEISHMANIA DONOVANIS KEY PATHWAYS BY COMPARATIVE NETWORK ANALYSIS TO UNCOVER NEW THERAPEUTIC TARGETS
15:40	15:50	**Assel Diyar,** *Asfendiyarov Kazakh National Medical University, Almaty, Republic of Kazakhstan*	SPATIAL CHARACTERISTICS AND PREDICTION OF PROBABLE ACTIVITY AND TOXICITY OF STREPTOMYCIN AND ITS DERIVATIVES USING PASS-PROGRAM

15:50	16:00	**Maksim Perfilev,** *Research Center for Innovative Medicines, Laboratory for Information Technologies in Pharmacology and Computer Modeling of Drugs, Volgograd State Medical University, Volgograd, Russia*	SEARCH FOR NEW ANXIOLYTIC SUBSTANCES BY NEURAL NETWORK MODELING USING MULTIPLE DOCKING
16:00	16:10	**Aleksandra Sagaidak,** *Laboratory of Molecular Pharmacology, Saint Petersburg State Institute of Technology, Saint Petersburg, Russia*	A NEW TARGET TO OVERCOME ABC TRANSPORTER ACCOSITED CHEMORESISTANCE OF TUMOR CELLS
16:10	16:20	**Ruslan Mallaev,** *M.M. Shemyakin and Yu.A. Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, Moscow, Russia*	ARTEMIS - STUDYING THE COMMUNICATION OF BIOMOLECULES USING INFORMATION THEORY
16:20	16:30	**Dmitrii Shkil,** *Syntelly LLC, Skolkovo Institute of Science and Technology, Skolkovo, Russia*	PREDICTION OF TOXICITY ENDPOINTS AS A PATHWAY TOWARDS MINIMISING RISKS IN DRUG DEVELOPMENT
16:30	16:40	**Daria Frolova,** *Ligand Pro, Skolkovo Institute of Science and Technology, Moscow, Russia*	STRUCTPLM - ENHANCING PROTEIN REPRESENTATIONS WITH STRUCTURAL INFORMATION
16:40	16:50	**Anna Karpenko,** *United Institute of Informatics Problems, National Academy of Sciences of Belarus, Minsk, Belarus*	GENERATIVE HETERO-ENCODER MODEL FOR DE NOVO DESIGN OF SMALL-MOLECULE COMPOUNDS AS POTENTIAL INHIBITORS OF BCR-ABL TYROSINE KINASE
16:50	17:00	**Ivan Kuznetsov,** *Moscow University of Finance and Law, Moscow, Russia*	EDGAR - A DEEP LEARNING-BASED PROGRAM FOR PREDICTION OF FOLDING ENERGY OF NUCLEIC ACIDS
17:00	17:10	**Anton Kolodnitsky,** *Institute of Biomedical Chemistry, Moscow, Russia*	A COMPREHENSIVE DATABASE FOR PREDICTING METABOLISM OF XENOBIOTICS BY HUMAN MICROBIOME
17:10	17:20	**Luis Melo,** *Federal University of Paraiba, João Pessoa, Brazil*	DEVELOPMENT OF A STANDARDIZED APPROACH FOR TRANSFER LEARNING WITH QSAR MODELS
17:20	17:30	**Juan Felipe Avellaneda-Tamayo,** *DIFACQUIM Research Group, Department of Pharmacy, School of Chemistry, Universidad Nacional Autónoma de México, Mexico City, Mexico*	SCHEMICAL MULTIVERSE AND DIVERSITY OF FOOD CHEMICALS
17:30	17:40	**Massyel Martinez,** *National Autonomous University of Mexico, Mexico*	EXPANDING THE EPIGENETIC RELEVANT CHEMICAL SPACE IDENTIFICATION OF DNA METHYLTRANSFERASE I ACTIVATORS

17:40	17:50	**Carlos Daniel Ramirez-Marquez,** *DIFACQUIM research group, Department of Pharmacy, National Autonomous University of Mexico, Mexico City, Mexico*	CHEMOINFORMATIC ANALYSIS OF NATURAL PRODUCTS FROM MEXICO
17:50	18:00	**Mly Huiza,** *Chemical Student Society for Research, Perú*	IN SILICO SCREENING OF COMMERCIAL DRUG-LIKE COMPOUNDS FOR COVALENT INHIBITION OF TC80 INSIGHTS INTO MECHANISM AND PROMISING CANDIDATES FOR THE TREATMENT AGAINST CHAGAS DISEASE
Plenary lectures			
18:00	18:30	**Andrey Rzhetsky,** *University of Chicago, Chicago, IL, USA*	DISSECTING ETIOLOGY OF MALADIES OF THE MIND WITH VERY LARGE MEDICAL DATASETS
18:30	19:00	**Mikhail Pyatnitskiy,** *Institute of Biomedical Chemistry, Moscow, Russia*	IT WAS TWENTY YEARS AGO TODAY: HOW OMICS HAVE SUCCEEDED IN PERSONALIZED MEDICINE

Wednesday September 20, 2023			
Chairpersons: **Sophia Borisevich and Vladimir Palyulin**			
Plenary lectures			
09:00	09:30	**Sophia Borisevich,** *Ufa Institute of Chemistry of the Ufa Federal Research Center of Russian Academy of Sciences, Ufa, Russia*	SEARCH FOR INHIBITORS OF SURFACE VIRAL PROTEINS I TYPE BY MOLECULAR MODELLING
09:30	10:00	**Alexey Lagunin,** *Institute of Biomedical Chemistry, Pirogov Russian National Research Medical University, Moscow, Russia*	IN SILICO PREDICTION OF CELL-LINES CYTOTOXICITY OF DRUG-LIKE COMPOUNDS BASED ON THEIR STRUCTURAL FORMULA
Oral presentations			
10:00	10:20	**Urvashi Tiwari,** *Department of Biosciences, Integral University, Lucknow, Uttar Pradesh, India*	EVALUATION OF SELECTED INDIGENOUS SPICES-AND HERBS-DERIVED SMALL MOLECULES AS POTENTIAL INHIBITORS OF SREBP1 AND ITS IMPLICATIONS FOR BREAST CANCER USING MD SIMULATIONS AND MMPBSA CALCULATIONS
10:20	10:40	**Andrey Markov,** *Institute of Chemical Biology and Fundamental Medicine Siberian Branch of the Russian Academy of Science, Novosibirsk, Russia*	SEMISYNTHETIC TRITERPENOIDS AS PROMISING BLOCKERS OF AGGRESSIVENESS-RELATED TRAITS IN GLIOBLASTOMA MULTIFORME IN SILICO, IN VITRO, AND IN VIVO APPROACHES
10:40	11:00	**Vladimir Ostrovskii,** *Saint Petersburg Federal Research Center of the Russian Academy of Sciences, Saint Petersburg, Russia*	COMPUTER PREDICTION AND IN VITRO STUDY OF ANTIVIRAL ACTIVITY OF HETEROCYCLIC SYSTEMS CONTAINING THIOPYRANO2,3-bQUINOLINE AND TETRAZOLE MOIETIES
Keynote lectures			
11:00	11:30	**Kunal Roy,** *Department of Pharmaceutical Technology, Jadavpur University, Kolkata, India*	Q-RASAR VS. QSAR: EFFICIENT PREDICTIONS OF ACTIVITY/PROPERTY/ TOXICITY ENDPOINTS
11:30	12:00	**Vladimir Palyulin,** *Department of Chemistry, Lomonosov Moscow State University, Moscow, Russia*	MOLECULAR MODELLING AND RECENT EXPERIMENTAL STUDIES OF AMPA RECEPTOR MODULATORS: BINDING MODES AND PHYSIOLOGICAL EFFECTS
Oral presentations			
12:00	12:20	**Grigory Mokrov,** *Zakusov Research Institute of Pharmacology, Russia*	COMPUTER-AIDED DESIGN OF NOVEL TSPO-LIGANDS - POTENTIAL NEUROPSYCHOTROPIC AGENTS
12:20	12:40	**Pavel Vassiliev,** *Volgograd State Medical University, Volgograd, Russia*	CONSENSUS MODELING OF ANXIOLYTIC ACTIVITY OF CHEMICAL COMPOUNDS BY CONVOLUTIONAL NEURAL NETWORKS

12:40	13:00	**Daria Novikova,** *Laboratory of Molecular Pharmacology, Saint Petersburg State Institute of Technology, Saint Petersburg, Russia*	A FRESH ANGLE ON P-GLYCOPROTEIN TO OVERCOME TUMOR CHEMORESISTANCE
lunch break 13:00-16:00			
Chairpersons: **Narahari G. Sastry and Maria Khrenova**			
Oral presentations			
16:00	16:20	**Eugene Radchenko,** *Lomonosov Moscow State University, Russia*	MACHINE LEARNING PREDICTION OF MYCOBACTERIAL CELL WALL PERMEABILITY OF DRUGS AND DRUG-LIKE COMPOUNDS
16:20	16:40	**Alexey Mishin,** Research Center for Molecular Mechanisms of Aging and Age-related Diseases, Moscow Institute of Physics and Technology, Dolgoprudny, Russia	A CASE STUDY OF STRUCTURE-BASED DRUG DESIGN WITH CYSTEINYL LEUKOTRIENE G-PROTEIN COUPLED RECEPTORS
16:40	17:00	**Anna Kulakova,** *Lomonosov Moscow State University, Moscow, Russia*	MOLECULAR MODELING OF GLUTAMATE ACYLATION MECHANISM IN THE ACTIVE SITE OF N-ACETYLGLUTAMATE SYNTHASE
Plenary lectures			
17:00	17:30	**José L. Medina-Franco,** *DIFACQUIM research group, National Autonomous University of Mexico, Mexico City, Mexico*	EXPANDING THE CHEMICAL SPACE AND MULTIVERSE OF NATURAL PRODUCTS AND FOOD CHEMICALS
17:30	18:00	**Robert J. Woods,** *Complex Carbohydrate Research Center, University of Georgia, Athens, USA*	AUTOMATING THE RATIONAL DESIGN OF GLYCOMIMETIC DRUGS
18:00	18:30	**Keykavous Parang,** *Center for Targeted Drug Delivery, Department of Biomedical and Pharmaceutical Sciences, Chapman University School of Pharmacy, Irvine, CA, USA*	AMPHIPHILIC MEMBRANE-ACTIVE PEPTIDES: BROAD-SPECTRUM ANTIBACTERIAL ACTIVITY ALONE AND IN COMBINATION WITH ANTIBIOTICS AND STRUCTURAL INSIGHTS
18:30	19:30	**Closure of the XXIX Symposium on Bioinformatics and Computer-Aided Drug Discovery**	

PLENARY/KEYNOTE LECTURES

SEARCH FOR INHIBITORS OF SURFACE VIRAL PROTEINS I TYPE BY MOLECULAR MODELLING

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Viral surface proteins play a key role in the life cycle of viruses, ensuring the fusion of the viral envelope and the cell membrane. Conformational rearrangements of proteins lead to the unification of the lipid bilayers of the cell membrane and the viral envelope and the formation of a fusion pore through which the viral genome penetrates into the cytoplasm of the cell. On the basis of structural similarity, viral fusion proteins are divided into three main classes. Here, structural features of type I fusion proteins are considered, such as influenza virus haemagglutinin (HA) and the spike protein of SARS-CoV-2 (Fig.). Proteins are homotrimeric formations consisting of three identical subunits. They contain α-helical structures and a fusion peptide located closer to the N-terminus and hidden in the middle of the protein trimer. The fusion mechanisms of these proteins are similar and are mediated by heptad repeats (HR).

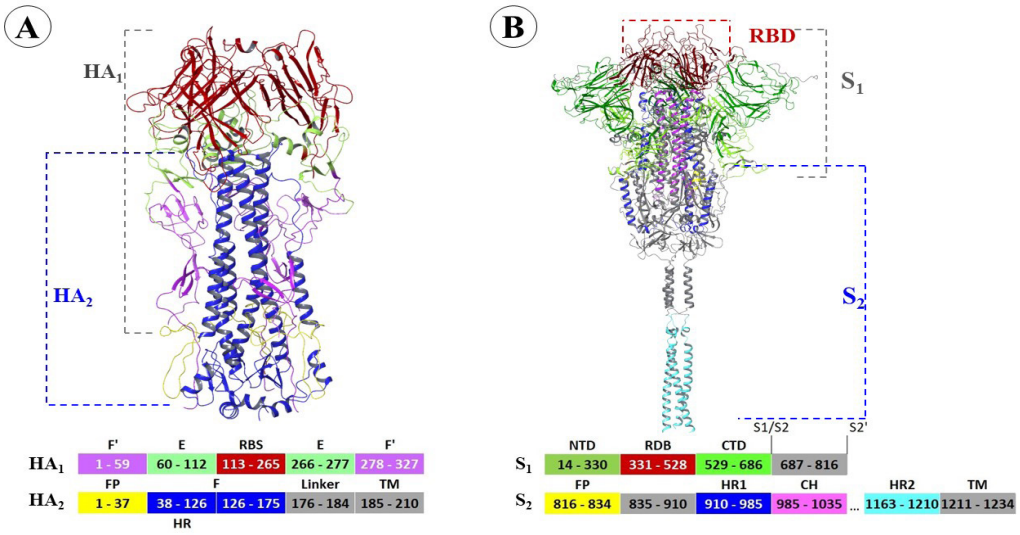

Figure. Structural features of the surface proteins of influenza virus and coronavirus [1].

Pharmacophore profile of potential binding sites of HA and S-protein inhibitors were considered using molecular modelling methods. The described binding sites have a similar pharmacophore profile. Perhaps this explains the antiviral activity of umifenovir and borneol esters against the influenza virus and the S-protein of the coronavirus. According to the results of theoretical calculations in combination with the biological experiments data [1-3], these compounds bind into HA and S-protein, inhibiting protein conformational rearrangements. Perhaps this fact may be a loophole for the search and development of broad-spectrum antiviral drugs.

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DEEP GENERATIVE MODEL FOR DRUG DESIGN FROM PROTEIN TARGET SEQUENCE

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The process of drug discovery for a specific protein target is both tedious and expensive. This process has traditionally entailed complex procedures, which can take years, and cost millions of dollars. Recent advancements in technology have allowed for the application of deep learning (DL) methods to drug discovery. These methods have successfully produced innovative molecular structures, and in doing so, they have greatly minimized both the time required for drug development and the associated costs. However, these DL methodologies, for the most part, hinge heavily on pre-existing knowledge. Some methods utilize known molecular structures and their properties to generate analogous candidate molecules. Others extract data about protein pocket binding sites to create molecules capable of binding to these sites. The dependency on prior knowledge is a limitation since it reduces the diversity and novelty of the generated molecules.

In response to this limitation, this paper introduces an innovative deep learning model, "DeepTarget", designed to generate new molecules based purely on the amino acid sequence of the target protein, thereby decreasing the over-reliance on prior knowledge. DeepTarget is an end-to-end deep learning model, which implies it covers the entire process of drug discovery without needing any human intervention once it has started. DeepTarget is composed of three key modules: Amino Acid Sequence Embedding (AASE), Structural Feature Inference (SFI), and Molecule Generation (MG). The AASE module serves to create embeddings from the amino acid sequence of the target protein. These embeddings are compact representations of the original sequence that retain its essential information. Following this, the SFI module infers potential structural features of the molecule to be synthesized. This module uses the information provided by AASE and predicts the characteristics that the resulting molecule might have. This includes potential binding sites, chemical properties, and other relevant features. The final module, MG, then uses the information from the prior modules to construct the final molecule. The molecule is built bit by bit, with each choice informed by the properties inferred by the SFI module. The authenticity of the molecules generated by DeepTarget was validated through a widely accepted benchmark platform for molecular generation models. Additionally, the interaction between the created molecules and the target proteins was verified, assessed using two critical metrics: drug-target affinity and molecular docking. Drug-target affinity measures how strongly a drug binds to its target protein. A higher affinity implies a stronger bond, leading to a more effective drug. Molecular docking is a method that predicts how and where a molecule will bind to a protein. It allows us to visualize how the generated drug might interact with the target protein.

The experimental outcomes provided strong evidence for the efficacy of the DeepTarget model. It demonstrated that it is entirely possible to generate viable drug molecules based solely on the amino acid sequence of the target protein. This represents a significant leap forward in the field of drug discovery, offering a potential pathway to expedite and economize drug development in the future.

This work was supported in part by the New Energy and Industrial Technology Development Organization (NEDO), the JSPS KAKENHI Grant Number JP22K12144, and the JST Grant Number JPMJPF2017, the National Key Research and Development Program of China (2021YFF1201400), National Natural Science Foundation of China (22173118), Hunan Provincial Science Fund for Distinguished Young Scholars (2021JJ10068), the science and technology innovation Program of Hunan Province (2021RC4011).

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LISTEN TO A SYMPHONY OF EPIGENOMICS WHEN SEEKING FOR DRUG TARGETS

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Accurate identification of therapeutic targets is the first step towards successfully treating intricate conditions like cancer, autoimmune diseases, neurogenerative disorders, and sepsis. Referring to "gene networks" or more precisely, networks governing signal transduction, gene regulation, and protein-protein interactions within cells and organs under normal and pathological conditions, holds key insights for identification of effective drug targets. These molecular networks typically exhibit a hierarchical arrangement where a handful of pivotal molecules, known as master-regulators, occupy the highest level of regulation, exerting control over the activity of hundreds of genes involved in various molecular and physiological processes across cells and the entire organism. In scenarios involving complex diseases, a limited number of master-regulators that have undergone pathological changes often seize control of the gene regulatory networks, steering the system towards a diseased state. Very often such "driver" pathological changes are caused by ***epigenomic*** alterations in gene regulatory regions leading to a dramatic change of gene expression of such master-regulators. Which, in turn often leads to a complete rewiring of the gene regulatory network that is characterized by numerous positive feedback loops that lock the network control on few disease-driving master-regulators [1].

Current genome-wide epigenomic study methods such as ChIP-seq, ATAC-seq as well as DNA methylation kits give an excellent possibility to reveal such disease causing epigenomic alterations in human genome. But often analysis and interpretation of such data focuses only on major events (biggest peaks) and ignores subtle epigenomic changes in regulatory regions of genes that are in fact more important for understanding the disease mechanisms. Researchers are often hear just "loud drum beats" instead of listening to the complex melody of the "symphony of gene regulation". We created an AI-based computational method for integrated analysis of epigenomic and transcriptomics data that carefully analyses composition of transcription factor binding sites (TFBS) in the epigenetically disturbed promoter and enhancer regions of differentially expressed genes in disease. The method reveals repeating sequence of TFBS in such regions ("like symphony motives") that gives clues to understanding the complexity of gene regulation in diseases.

At the current work we analyzed ChIP-seq and RNA-seq data on RunX1 transcription factor whose role in cancer development and metastasis is highly controversial. Depending on the tumor type it can play either a tumor suppressor role or, in contrary, play a pro-oncogenic role. We analyzed data that model loss of RunX1 gene due deletions that happens in many breast cancer cases. We revealed the context dependent compositions of RunX1 binding sites with TF binding sites for several other TFs, such as JUN, PAX2, TCF3 and CTCF in the ChIP-seq peaks located in the promoters of up-regulated genes in such cancers. We show that this repeating "motive" of TF binding sites in the promoters of the breast cancer specific genes plays a very important role during tumor development and growth. We also show that the highest ChIP-seq peaks are flooded by RunX1 binding sites and contain no other TF binding sites and they are located very far away from the differentially expressed genes and most probably play no direct role in transcription regulation but rather used as sort of "parking garage" of the excess transcription factors. This discovery helped us to reveal potent drug targets that can be used in the breast cancer therapy for such subtypes of cancer with the lost RunX1 gene.

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MECHANISM OF THE APTAMER RECOGNITION BY SARS-COV-2 SPIKE PROTEIN REVEALED BY NANOPORE SEQUENCING AND MOLECULAR MODELING

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DNA aptamers are oligonucleotides specifically bound to target molecules that can serve as antibodies of nucleic acid nature. For diagnosing the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), methods using antibodies specific to antigens on the virus are broadly used. We generated by classical SELEX a number of aptamers, interacting with the receptor-binding domain of SARS-CoV-2 spike protein (SARS-CoV-2 Spike RBD) from Wuhan-Hu-1 strain. The sequence identification was performed using a novel methodology based on the nanopore sequencing. For sequence identification of selected aptamers, we created the novel protocol for aptamer identification based on nanopore sequencing. We identified the best aptamer candidate named MEZ. It was chemically synthesized and tested for binding with SARS-CoV-2 Spike RBD domain of the S-protein from different strains. Kd of the complex is 6.5 nM being comparable with known aptamers. Virus neutralization tests demonstrate similar results for already known and MEZ aptamers. We identified differences for aptamers binding to SARS-CoV-2 Spike RBD from Wuhan-Hu-1 and Omicron strains. MD simulations reveal that the number of hydrogen bonds between the protein and aptamer is higher for the more stable complex. Moreover, dynamic network analysis show that the motions of the aptamer and protein are correlated to a higher extent in a more stable complex. Based on the experimental data and computational results we can conclude that the authentic RBD-aptamer complex has two specific points for interaction and the 3'-end of aptamer is responsible for strain identification. Therefore, the selected aptamer based on experimental data can be an alternative biological element for the development of SARS-CoV-2 diagnostic testing with strain specificity and cost efficiency due to the short length of aptamer being 31 nucleotides.

This study was supported by the Scientific School of the Lomonosov Moscow State University (project 23-Sh04-45 "Nanopore sequencing for genetics and synthetic biology: improving the accuracy of the method, genome analysis, metagenomics, selection of aptamers").

IN SILICO PREDICTION OF CELL-LINES CYTOTOXICITY OF DRUG-LIKE COMPOUNDS BASED ON THEIR STRUCTURAL FORMULA

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In vitro cell-line cytotoxicity is widely used in the experimental studies of potential antineoplastic agents and evaluation of drug safety during drug discovery. *In silico* estimation of cytotoxicity against hundreds tumor cell-lines and dozens normal cell-lines considerably reduces the time and costs of drug development and assessment of new pharmaceutical agent perspectives. Here, we represent three new web applications related to the computational assessment of cell-line cytotoxicity: 1) CLC-Pred 2.0 (prediction of cytotoxicity for tumor and non-tumor cell lines, https://way2drug.com/CLC-Pred); 2) CLC-Pred synergy (prediction of cytotoxic synergism for drug pairs against 34 NCI60 cell-lines, https://www.way2drug.com/clc-pred-syn/) and 3) BC CLC-Pred (Breast cancer cell-line cytotoxicity prediction, https://www.way2drug.com/bc/).

CLC-Pred 2.0 [1] is a new version of CLC-Pred web application which was released in 2018. It employs the PASS (Prediction of Activity Spectra for Substance) approach based on substructural atom-centric MNA (Multilevel Neighbourhoods of Atoms) descriptors and Bayesian algorithm. CLC-Pred 2.0 provides three types of qualitative prediction: 1) cytotoxicity against 391 tumor and 47 non-tumor human ("normal") cell-lines based on ChEMBL and PubChem data (128,545 structures) with the mean accuracy of prediction (AUC) calculated by leave-one-out (LOO CV) and the 20-fold cross-validation (20F CV) procedure of 0.925 and 0.923, respectively; 2) cytotoxicity against NCI60 tumor cell-line panel based on Developmental Therapeutics Program NCI60 data (22,726 structures) with the different threshold of IG_{50} data (100, 10 and 1 nM) and the mean accuracy of prediction from 0.870 to 0.945 (LOO CV) and from 0.869 to 0.942 (20F CV), respectively; 3) 2170 molecular mechanisms of actions based on ChEMBL and PubChem data (656,011 structures) with the mean accuracy of prediction 0.979 (LOO CV) and 0.978 (20F CV).

CLC-Pred synergy is a web application which is based on a special version of PASS – PASS DDI. It creates SAR models for estimation of activity for pairs of compounds. PASS DDI uses PoSMNA (Pairs of Substances Multilevel Neighbourhoods of Atoms) for description of structures of pairs of molecules and Bayesian algorithm [2]. The SAR models in CLC-Pred synergy web application were created based on ALMANAC data of cytotoxicity for approximately 5000 drug pairs against NCI60 cell lines [3]. The mean accuracy of prediction for the best SAR models against 34 selected cell lines was 0.85 (LOO CV), 0.79 (5F--CV calculated by "compound out" procedure) and 0.75 (LOO CV calculated by "compound out" procedure).

BC CLC-Pred is a web application which is based on (Q)SAR models created by GUSAR software [4] for 7 breast cancer cell lines based on the data of IC_{50} and IG_{50} values from ChEMBL v. 30 database. The mean accuracy of prediction calculated by 5 fold cross validation procedure was 0.599 (R^2), 0.679 (RMSE) for QSAR models and 0.85 (accuracy) for SAR models.

Thus, the new web applications may be used for computational evaluation of drug cytotoxicity in relation to various cell lines and their rational selection for experimental testing.

This study was supported by Russian Science Foundation grant no. 19-15-00396, https://rscf.ru/project/19-15-00396/.

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EXPANDING THE CHEMICAL SPACE AND MULTIVERSE OF NATURAL PRODUCTS AND FOOD CHEMICALS

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Compound databases provide a rich source of information for a number of practical applications, including drug discovery, compound design, and generation of predictive models. Databases of natural products have increased substantially and there are several compound databases from diverse geographical regions. Latin America is very rich in biodiversity and there are databases that are being assembled or under development. We find it useful and significant to collect, organize and systematize the information available across these compound collections. In a collective effort from eight Latin American countries, we are assembling Latin American Natural Products Database (LANaPD), a public compound collection that gathers the chemical information of natural products contained in diverse databases from this geographical region. The project is trying to gather information from compound databases from Argentina, Brazil, Colombia, Costa Rica, El Salvador, Mexico, Panama and Peru. We anticipate that LANaPD will continue growing and evolving with the update of more compounds from each existing database plus the addition of databases from other Latin American countries. It is also anticipated that LANaPD can be integrated into other large public databases of natural products such as LOTUS or COCONUT [1]. As part of these efforts, we are also including food chemicals [2].

As part of the presentation, we will discuss the concept of Chemical Multiverse as a natural extension of Chemical Space. Indeed, since Chemical Space depends on molecular representation, it is argued that there is no unique Chemical Space. Indeed, in parallel to the continued growth of molecules that are enumerated, there are a plethora of descriptors and sets of properties relevant for different chemical applications, for instance, to represent small organic molecules typically used in drug discovery, metallodrugs, natural products, food chemicals, and peptides, to name a few. Therefore, the Chemical Space of a set of compounds – defined as multidimensional descriptor space – may have alternative versions depending on the descriptors used to determine it giving rise to the Chemical Multiverse [2].

This study is supported by the National Autonomous University of México, Dirección General de Estudios de Posgrado (DGEP), PAPIIT IN201321.

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PROGRESS AND CHALLENGES IN LIGANDS DISCOVERY FOR BITTER TASTE RECEPTORS

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Taste GPCRs are expressed on the tongue and play a key role in food choice and consumption. Ligands of taste GPCRs are numerous, chemically diverse and often have multiple bio-targets. Extraoral expression of taste receptors in multiple tissues, including gut, heart and brain, suggests the existence of yet unknown, endogenous ligands, and diverse physiological roles.

By integrating machine learning and modeling with experimental testing, we aim to expand the bitter chemical space and to explore the roles of ectopic taste receptors.

I will present BitterMatch machine learning approach and its application to computationally matching of molecules to bitter taste receptors in human and mice [1], including prospective discovery of new bitter targets for known odor molecules [2]. I will then illustrate how an iterative data-driven approach lead us to discover antagonists for the most promiscuous and widely expressed bitter taste receptor [3], providing chemical probes for studying this receptor's physiology. Next, I will highlight the advancements in experimental and computational determination of 3D structures of taste receptors and discuss implications for tastants' discovery.

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MOLECULAR MODELLING AND RECENT EXPERIMENTAL STUDIES OF AMPA RECEPTOR MODULATORS: BINDING MODES AND PHYSIOLOGICAL EFFECTS

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L-Glutamic acid is the main excitatory neurotransmitter in the central nervous system (CNS). Glutamate receptors localized on neuronal and non-neuronal cells mediate rapid excitatory synaptic transmission in the CNS and regulate a wide range of processes in the brain, spinal cord, retina, and peripheral nervous system. In particular, the glutamate receptors selective to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) also play an important role in numerous neurological disorders and attract close attention as targets for the creation of new classes of drugs for the treatment or substantial correction of a number of serious neurodegenerative and neuropsychiatric diseases. For this reason, the search for various types of AMPA receptor ligands and studies of their properties are attracting considerable attention both in academic institutions and in pharmaceutical companies around the world. This presentation focuses mainly on the advances in this area obtained in recent years. Particular attention is paid to the structural diversity of new chemotypes of positive and negative allosteric modulators as well as their binding sites. The studies of the mechanisms of action of AMPA receptor ligands that mediate their therapeutic effects are also discussed.

In our works, we have designed new classes of AMPA receptor modulators using pharmacophore models, molecular docking, and molecular dynamics simulations. Efficient approaches to their synthesis have been developed and optimized. Experimental *in vitro* studies have confirmed high modulator activities (subnanomolar or picomolar) of the designed compounds.

This study was supported by Russian Science Foundation, grant no. 22-15-00041.

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COMPUTATIONAL PHYSIOLOGY AND DRUG DEVELOPMENT

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Modern drug development relies heavily on in-depth understanding of physiological and pathological processes. Computational models of these processes, and of their pharmacological modification, are a critical tool able to integrate our understanding of numerous physical and chemical events into a comprehesive quantitative simulation able to capture all aspects that are not feasible to consider other wise. These models can be utilized at different stages of drug development including identification of the targets, planning of the trials and interpretation of their results, minimization of the risks and optimization of the treatment effects, and many others. Choice of the model and approach depend on the stage of drug development and of the goal. Here we discuss some the principles of these applications, as well as problems and prospects in the field.

AMPHIPHILIC MEMBRANE-ACTIVE PEPTIDES: BROAD-SPECTRUM ANTIBACTERIAL ACTIVITY ALONE AND IN COMBINATION WITH ANTIBIOTICS AND STRUCTURAL INSIGHTS

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The main aim of this study was to create and assess a new group of antimicrobial peptides (AMPs) that possess a broad-spectrum activity. These peptides have the potential to be used as standalone antibiotics or in conjunction with other antibiotics. Despite numerous efforts by various research teams to establish AMPs as a viable alternative to traditional antibiotics, only a few have successfully progressed through clinical trials. This can be attributed to challenges such as their relatively large molecular size, toxicity to mammalian cells, and vulnerability to degradation by proteolytic enzymes, which hinder their drugability. To address these clinical limitations, our research group has been dedicated to developing small cationic AMPs that exhibit greater selectivity towards bacterial membranes and increased stability against peptidases. We report the synthesis and antibacterial activities of a library of amphiphilic membrane-active peptides. Lead cyclic peptides showed broad-spectrum activity against drug-resistant Gram-positive (MIC = 1.5-6.2 μg/mL) and Gram-negative (MIC = 12.5-25 μg/mL) bacteria. In combination with commercially available antibiotics, tetracycline, tobramycin, clindamycin, kanamycin, levofloxacin, polymyxin B, metronidazole, and vancomycin, lead peptides showed remarkable synergism against a large panel of resistant pathogens. Cytotoxicity study showed the predominant lethal action of the peptides against bacteria as compared with mammalian cells. A plasma stability study revealed approximately 2-fold higher stability of lead cyclic peptides as compared to their linear counterparts after 24 h incubation. Calcein dye leakage and scanning electron microscopy studies revealed the membranolytic effect of peptides. Nuclear magnetic resonance spectroscopy and molecular dynamics simulations studies of the interaction of the peptides with phospholipid bilayer provided a solid structural basis explaining the membranolytic action of the peptides with atomistic details. *In vivo* animal studies were used to determine the pharmacokinetics and efficacy of the lead peptide utilizing a mouse methicillin-resistant *Staphylococcus aureus* (MRSA) septicemia model. These results highlight the potential of newly designed amphiphilic peptides as the next generation of peptide-based antibiotics.

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IT WAS TWENTY YEARS AGO TODAY: HOW OMICS HAVE SUCCEEDED IN PERSONALIZED MEDICINE

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For over 20 years we have witnessed the rise of omics technologies, which have allowed us to characterize biological processes with significantly greater sensitivity and resolution than ever before. This gave many researchers reason to predict the leading role of omics in the upcoming revolution in medicine, including uncovering numerous new diagnostic and prognostic biomarkers. Furthermore, the simultaneous study of multiple levels of molecular activity should theoretically enable deep phenotyping of individuals, aiding in the search and prediction of health trajectories, laying the foundation to early disease detection and more effective intervention for the treatment of chronic complex diseases. Currently, it is evident that the initial predictions were overly optimistic: we do not see widespread application of omics technologies in clinical practice, as their superiority over existing methods has not yet been fully established.

Among the various omics disciplines, genomics has achieved the greatest success in the field of precision medicine. Despite not accounting for spatial and temporal variation within the organism, genomics enjoys the broadest clinical implementation, with a clinical sequencing market annual growth rate of approximately 20% and forecasted to reach $19 billion worldwide by 2026 [1]. Specific applications include diagnosing monogenic disorders where it was shown to increase overall diagnostic rate. Another well-established example of clinical utility is illustrated by pharmacogenomics: annual proportion of new drug approvals with genomic labeling has increased by nearly threefold for the last 20 years. The most significant efforts in pharmacogenomics have been undertaken in oncology. Over the last 10-15 years, significant progress has been made in understanding the mechanisms of oncogenesis through large-scale tumor sequencing projects. However, the results of clinical trials in precision oncology remain ambiguous. The early successes in breast cancer transcriptomics during the 2000s sparked hope that gene expression tests would be widely embraced in clinical practice. However, ultimately, only a few transcriptomics studies yielded successful laboratory-developed tests, and merely a handful of individual assays obtained FDA clearance. Regarding proteomics, metabolomics, and epigenomics, their integration into clinical practice is even more limited. Furthermore, there is currently no convincing evidence to support the use of the microbiome analysis in making clinical decisions.

There could be several reasons why omics fail to achieve widespread clinical implementation. Acquiring samples through invasive procedures and meeting specific storage requirements (like FFPE processing) poses challenges. There is a significant difference between biomarker discovery and the far more challenging process of biomarker validation. Successful cases of translating research into clinical practice involve extensive validation on independent cohorts and rigorous statistical evaluation [2]. This contradicts the current practice of p-hacking and the bias toward publishing and financially supporting only positive studies. Indeed, it might be necessary to realign the primary focus of omics research. Currently, there is a bias towards oncology, with the majority of clinically approved omics-derived biomarkers targeting cancer, while other critical areas, like neurodegenerative disorders, remain underrepresented. There are high hopes attached to the successes of the last decade in the field of artificial intelligence. However, the challenges encountered by Watson Health as a cancer diagnostics tool demonstrate that there is still a long way to go. Large-scale clinical trials and longitudinal studies are necessary to demonstrate the benefits of omics-based approaches over conventional methods. Moreover, the development of standardized protocols and data analysis pipelines hopefully will facilitate the integration of omics data into clinical decision-making processes.

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Q-RASAR VS. QSAR: EFFICIENT PREDICTIONS OF ACTIVITY/PROPERTY/TOXICITY ENDPOINTS

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Quantitative Structure-activity Relationship (QSAR) models are routinely used for the prediction of various endpoints (activities/properties/toxicities) using chemical structural and/or property information in a supervised learning approach. Read-Across-based predictions on the other hand do not involve statistical model building and are derived based on (chemical or biological) similarity to close congeners. Both the QSAR and Read-Across approaches are extensively used for data gap filling (predicting activity/property/toxicity values for compounds devoid of experimentally measured endpoint values), thus minimizing the need for experimental testing, animal handling, manpower, time, and cost. Recently, QSAR and read-across techniques have been merged into a new emerging field of read-across structure-activity relationship (RASAR) [1] that uses the chemical similarity concepts of read-across (an unsupervised step) and finally develops a supervised learning model (like QSAR) using machine learning algorithms. Recently, our group has developed a q-RASAR approach for quantitative predictions using Euclidean distance, Gaussian kernel, or Laplacian kernel-based similarity for RASAR descriptor calculations followed by data fusion with important physicochemical/structural descriptors and development of a q-RASAR model with the application of an appropriate statistical method or machine learning application. The tools for RASAR descriptor calculations and optimization of hyperparameters have been made available at https://sites.google.com/jadavpuruniversity.in/dtc-lab-software/home. With the applications in modeling of several endpoints like materials properties, toxicity, and ecotoxicity of chemicals, drugs, and mixtures [2-5], we demonstrate that the q-RASAR approach enhances the external predictivity of conventional QSAR models with the same amount of input chemical information. In addition, the models show the importance of several RASAR descriptors like *RA function,* $g_{m,}$ and *average similarity* which are originally computed based on the available structural and physicochemical information. A q-RASAR model also has the advantage over read-across predictions in providing easy interpretation and indicating quantitative contributions of important chemical features. It appears that the q-RASAR approach should be extensively applied for modeling various activity/property/toxicity endpoints for the development of reproducible, transferable, and predictive models.

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DISSECTING ETIOLOGY OF MALADIES OF THE MIND WITH VERY LARGE MEDICAL DATASETS

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I will cover a collection of interrelated topics in dissection of etiology of complex human diseases, as seen through lens of large-scale medical data analysis. Individual studies that I will cover focus on mosaic of genetic, environmental, and genetic-environmental interaction factors. The studies relied on massive medical records from US, Sweden, Denmark, and Japan, and a battery of modeling approaches.

Genetics. Typically, estimating genetic parameters, such as disease heritability and between-disease genetic correlations, demands large datasets containing all relevant phenotypic measures and detailed knowledge of family relationships or, alternatively, genotypic, and phenotypic data for numerous unrelated individuals. Here, we suggest an alternative, efficient estimation approach through the construction of two disease metrics from large health datasets: temporal disease prevalence curves and low-dimensional disease embeddings.

Environment. The search for the genetic factors underlying complex neuropsychiatric disorders has proceeded apace in the past decade. Despite some advances in identifying genetic variants associated with psychiatric disorders, most variants have small individual contributions to risk. By contrast, disease risk increase appears to be less subtle for disease-predisposing environmental insults. In this study, we sought to identify associations between environmental pollution and risk of neuropsychiatric disorders. Our results show that air pollution is significantly associated with increased risk of psychiatric disorders. We hypothesize that pollutants affect the human brain via neuroinflammatory pathways that have also been shown to cause depression-like phenotypes in animal studies.

Genetics and environment. In complex diseases, the phenotypic variability can be explained by genetic variation (G), environmental stimuli (E), and by interaction of genetic and environmental factors (G-by-E effects), where G-by-E contribution remains largely unknown. In this study, we focus on ten major neuropsychiatric disorders using data for 138,383 US families, with 404,475 unique individuals. We show that, while gene-environment interactions account for only a small portion of the total phenotypic variance for a subset of disorders (depression, adjustment disorder, substance abuse), they explain a rather large portion of the phenotypic variation of the remaining disorders: over 20 percent for attention-deficit / hyperactivity disorder, migraine, and anxiety/phobic disorder, and close to 30 percent for recurrent headaches, sleep disorders, and post-traumatic stress disorder. In this study, we have incorporated – in the same analysis – clinical data, family pedigrees, the spatial distribution of individuals, their socioeconomic and demographic confounders, and a collection of environmental measurements.

THE IMPACT OF PANDEMICS, EPIDEMICS, AND THE PROLIFERATION OF ARTIFICIAL INTELLIGENCE ON (COMPUTATIONAL) DRUG DISCOVERY

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The emergence of pandemics and epidemics presents a formidable challenge to public health and more rapid demand of developing new drugs. In response to infectious disease like COVID-19 pandemic has been a global threat since its first outbreak in 2019, leading to millions of infections and fatalities worldwide. The integration of AI into drug discovery holds great potential for responding effectively to pandemics, epidemics, and emerging infectious diseases. In this study we have considered several categories of viral infections such as: a) respiratory infections, b) digestive infections, c) viral haemorrhagic fevers, d) sexually transmitted infections (STIs), e) neurological infections and f) congenital infections. Efforts have been made to get the druggable protein targets in all these cases, and the drug repurposing strategies will be presented. This is followed by text mining where; the manifestation of these various infections is traced. Immuno-modulation, inflammation and co-morbidities are also considered. Further, a mix of machine learning and molecular modelling techniques were adopted to come up with strategies for preventive, curing and crisis management for the various infections. More emphasis is provided to predict what may be the future pandemics and how do we deal with them.

Conventional drug discovery methods faced challenges in responding rapidly to this novel virus. AI-based approaches have demonstrated promise in expediting drug discovery processes during pandemics and epidemics. The complicated role played by the host immune system and the mechanism of viral entry and its manifestation is interesting in its own right and inclusive approaches are indispensable to have a holistic look at the pathophysiology of the disease. By analysing large datasets and patterns within available data, AI can generate innovative models that have the potential to provide optimal solutions.

OPTIMIZATION OF QSAR MODELS FOR VIRTUAL SCREENING

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QSAR models correlate molecular descriptors for a set of compounds with their activities and could therefore be used for unveiling the factors that govern molecular properties and for designing new compounds with favorable properties. In addition, due to their computational efficiency QSAR models could also be used for the virtual screening (VS) of large collections of commercially available compounds.

Due to the large number of calculate-able descriptors and their combinations, the derivation of QSAR models could be treated as an optimization problem. For continuous responses, typically optimized metrics are related to model performances on a training set, e.g., R^2 and Q_{CV}^2. Similar metrics, calculated on an external test set (e.g., $Q_{(F1/F2/F3)}^2$), are used to evaluate the performances of the final models. A common theme of these metrics is that they are context –"ignorant". In this work we therefore propose that QSAR models should be developed and evaluated based on their intended usage. More specifically, we argue that QSAR models developed for VS should be derived and evaluated using a VS-aware metric, e.g., an enrichment-based metric.

To demonstrate this point, we have developed a new algorithm for the derivation of QSAR models in the form of Multiple Linear Regression (MLR) equations by optimizing an enrichment-based metric, named Enrichment Optimization Algorithm (EOA). Using multiple datasets, we compared the performances of the new algorithm in small-scale VS campaigns with (1) MLR models derived and optimized by "classical" metrics. (2) Support Vector Machine (SVM) and Random Forest (RF) models, and (3) Three common docking tools (Glide-SP, GOLD, AutoDock Vina). We found that the best EOA models showed, in most cases, more consistent results across the training, validation and test sets and outperformed the corresponding MLR, SVM and RF models in most VS tests. Similarly, EOA models consistently outperformed all docking tools, across all datasets, in terms of the area under the ROC curve and $EF_{1\%}$ metrics that measure the overall and initial success of the VS process, respectively.

However, in contrast with docking-based VS, EOA-based VS does not provide ligand binding modes or approximated binding free energies, two factors that are important for hit selection and optimization. In parallel, most docking programs were developed to be as general as possible and consequently their performances on specific targets may be sub-optimal. With this in mind, we have used EOA to develop target-specific scoring functions for six protein targets, by re-deriving the weights associated with the components that make up GOLD's ChemPLP scoring function. We then used the original ChemPLP function in small scale VS experiments on the six targets, and subsequently rescored the resulting poses with the modified functions and also used the modified functions for compounds re-docking. We found that in many cases, either rescoring the original ChemPLP poses or re-docking with the modified functions, yielded better results in terms of AUC and $EF_{1\%}$ metrics and that docking of compounds with the new functions into their respective binding sites provided better results, RMSD-wise, than GOLD's original ChemPLP function.

In summary, we view EOA-based models as efficient tools for VS that can easily handle the currently available large collections of commercial and proprietary screening compounds, thereby increasing the probability of identifying good starting points for drug and material design efforts.

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GATING AND MOLECULAR PHARMACOLOGY OF TRP CHANNELS

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Transient receptor potential (TRP) channel TRPV6 is highly selective to Ca^{2+} and plays vital roles in calcium homeostasis. Dysregulation of TRPV6 is implicated in various diseases, including cancers, making this ion channel an important drug target. To facilitate structure-based drug design, we studied TRPV6 gating and regulation using structural biology (X-ray crystallography and cryo-EM), functional recordings, mutagenesis, and molecular dynamics (MD) simulations. Channel opening during TRPV6 constitutive activity is accompanied by an α-to-π helical transition in the pore-lining S6 transmembrane helices. As a result of this transition, the intracellular halves of the S6 helices bend and rotate by about 100 degrees, exposing different residues to the channel pore in the open and closed states. Ca^{2+} inhibits TRPV6 via binding to calmodulin (CaM), which mediates Ca^{2+}-dependent inactivation. The TRPV6-CaM complex exhibits 1:1 stoichiometry; one TRPV6 tetramer binds both CaM lobes, which adopt a distinct head-to-tail arrangement. The CaM C-terminal lobe plugs the channel through a unique cation-π interaction by inserting the side chain of lysine K115 into a tetra-tryptophan cage at the ion channel pore intracellular entrance and converting the channel into a unique inactivated conformation, distinct from the closed and open states. We discovered that (4-phenylcyclohexyl)piperazine derivatives (PCHPDs), computationally-predicted nanomolar-affinity TRPV6 inhibitors, insert themselves into the intracellular pore entrance and convert the channel into the non-conducting inactivated state, mimicking the action of calmodulin. We found that the inorganic dye ruthenium red (RR) and phytoestrogen genistein, which bind in the selectivity filter and the lower pore of TRPV6, respectively, act not only as ion channel blockers but also as gating modifiers, converting the channel from the open to closed state. We investigated the action of the negative allosteric inhibitors aminoethoxydiphenyl borate (2-APB), antifungal drug econazole, and cannabinoid tetrahydrocannabivarin (THCV) that bind to different sites on the transmembrane domain periphery. All three compounds appear to outcompete annular lipids and stabilize TRPV6 in the closed conformation. Studies of TRPV6 structure and function advance our understanding of the role of this channel in physiology and pathophysiology, uncover new sites and mechanisms of regulation, and inform future therapeutic design.

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DOCKING PARADIGM IN COMPUTER-AIDED DRUG DISCOVERY

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The COVID-19 pandemic has triggered a wave of publications on the application of molecular modeling to the search for inhibitors of coronavirus target proteins [1]. Docking certainly ranks first in the list of applied molecular modeling methods. Due to the sharply increased popularity of docking, this work is devoted to docking. What does docking do? What mathematical and physical methods and approximations are used in docking? What are the disadvantages of docking? Is there currently an alternative to docking at the initial stage of new drug development? What ways of further development of docking are seen now? Docking is a molecular modeling method performing positioning ligands in the active site of the target protein and estimating the free energy of the protein-ligand binding. The greater the calculated protein-ligand binding energy, the lower the concentration of the ligand leads to the desired therapeutic effect, resulting in a more effective drug based on this ligand.

Several dozen docking program exist now. Each docking program is a unique combination of various mathematical, physical, chemical and computational methods, but most of them are explicitly or implicitly based on the docking paradigm [2, 3]. The docking paradigm assumes that the ligand binds to the active site of the target protein at a position corresponding to the global energy minimum of the protein-ligand system. Thanks to this paradigm, the complex physical-chemical problem of docking is reduced to a rigorous mathematical problem of global optimization. However, to solve this mathematical problem, it is necessary to determine the target energy function, the global minimum of which must be found – the energy of the protein-ligand system. Obviously, this energy must be calculated by quantum mechanics (quantum chemistry) methods. However, such methods are too time consuming to be used in solving the global optimization problem. Instead, sets of classical potentials of interatomic interaction are used – the so-called force fields. This is one of the main sources of docking inaccuracies.

To speed up the search for the global energy minimum, the active site of the target protein is covered with a 3D-grid containing at the nodes pre-calculated potentials of the interaction of the probe atoms of the ligand with the entire protein. This is also a source of docking inaccuracies. In most docking programs, the solvent is taken into account too roughly or not taken into account at all. This is the third main source of docking inaccuracies, because water solvent has a high dielectric constant and screens strongly Coulomb interactions resulting in noticeable values of desolvation effect contribution into the protein-ligand binding energy. Finally, global optimization methods should be improved to be able to find the global minimum on the energy surface with a large number of dimensions determined by a number of degrees of freedom of the protein-ligand system. The ligand positioning accuracy of most docking programs is satisfactory, but the accuracy of binding free energy calculation is usually unsatisfactory. The latter can be improved by postprocessing for ligands with best docking scores using ligand docked positions in the protein.

Recently, there has been a clear trend towards moving from laptop docking to supercomputer docking, allowing to screen by docking very large databases containing many millions of ligands, as well as improving docking accuracy by using many computing cores to dock a single ligand. In the coming years, docking programs will evolve towards greater accuracy through the use of quantum mechanics and supercomputers, whose performance will continue to grow exponentially over time.

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EXPOSING THE LIMITATIONS OF MOLECULAR MACHINE LEARNING WITH ACTIVITY CLIFFS

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Machine learning has become a crucial tool in drug discovery and chemistry at large, *e.g.*, to predict molecular properties, such as bioactivity, with high accuracy. However, activity cliffs – pairs of molecules that are highly similar in their structure but exhibit large differences in potency – have received limited attention for their effect on model performance. Not only are these edge cases informative for molecule discovery and optimization but also models that are well equipped to accurately predict the potency of activity cliffs have increased potential for prospective applications. Our work aims to fill the current knowledge gap on best-practice machine learning methods in the presence of activity cliffs. We benchmarked a total of 24 machine and deep learning approaches on curated bioactivity data from 30 macromolecular targets for their performance on activity cliff compounds. While all methods struggled in the presence of activity cliffs, machine learning approaches based on molecular descriptors outperformed more complex deep learning methods. Our findings highlight large case-by-case differences in performance, advocating for (**a**) the inclusion of dedicated "activity-cliff-centered" metrics during model development and evaluation and (**b**) the development of novel algorithms to better predict the properties of activity cliffs. To this end, the methods, metrics, and results of this study have been encapsulated into an open-access benchmarking platform named MoleculeACE (Activity Cliff Estimation). MoleculeACE is designed to steer the community toward addressing the pressing but overlooked limitation of molecular machine learning models posed by activity cliffs.

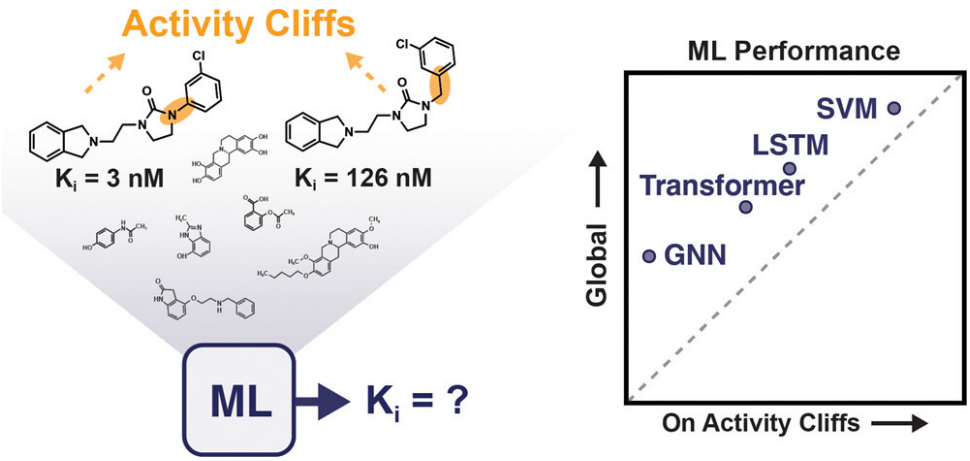

Figure. Graphical abstract. Using 30 different molecular bioactivity datasets, a wide range of molecular machine learning methods are evaluated on their performance on activity cliff molecules.

COMPUTER-AIDED DISCOVERY OF NOVEL DRUG CANDIDATES AGAINST SARS-COV-2 TARGETING THE HEPTAD REPEAT DOMAIN 1 IN S2 PROTEIN

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To date, over 750 million SARS-CoV-2-infected cases had been reported, including more than 6 million deaths (https://covid19.who.int/), causing an unprecedented threat to public health. More importantly, numerous variants of SARS-CoV-2 have continuously emerged, some of which have been defined as variants of concern, such as Delta (B.1.617.2) and Omicron (B.1.1.529) (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/). These facts require the development of potent and broad-spectrum antiviral agents against SARS-CoV-2 infection and COVID-19 disease. In this study, the structure-based virtual screening approach to drug repurposing was used to identify novel small molecules of clinical significance with activity against the heptad repeat domain 1 (HR1) in the S2 subunit of the SARS-CoV-2 spike (S) protein, an ideal conserved target site critically important for mediated membrane fusion and virus infectivity [1]**.** To solve this problem, studies were carried out, including (i) high-throughput docking of the HR1 domain with compounds from the library of bioactive molecules including the FDA-approved drugs and investigational drug candidates, (ii) assessment of the binding affinity for the docked ligand/HR1 complexes using three scoring functions followed by calculations of the exponential consensus rank (ECR) for each compound and ranking the ligands under the ECR values, (iii) molecular dynamics (MD) simulations and binding free energy calculations of the ligand/HR1 complexes for the top-ranked compounds, and (iv) post-modeling analysis aimed at the identification of the most promising drug candidates that can target the HR1 binding site.

Based on the data from molecular modeling, nine top-ranking compounds that showed the low values of binding free energy to HR1 and stability within the MD simulations were selected as the most promising fusion inhibitors able to block this functionally significant domain of the SARS-CoV-2 S protein. These compounds were then assessed for inhibitory efficacy against SARS-CoV-2 infection in the Key Laboratory of Medical Molecular Virology of the Fudan University (School of Basic Medical Sciences, Shanghai, China). As a result, three compounds, namely Itraconazole, Bemcentinib, and Navitoclax, revealed potent in vitro activity towards SARS-CoV-2. Among these compounds, Bemcentinib and Itraconazole were recently reported to show effective inhibitory activity against SARS-CoV-2, whereas Navitoclax had not reported before to have anti-HCoV activity. Navitoclax, an orally active anticancer drug inhibiting Bcl-2, could bind HR1 and block six-helix bundle formation, efficiently inhibiting fusion and infection of all SARS-CoV-2 variants tested, as well as SARS-CoV and MERS-CoV, with IC_{50} values ranging from 0.5 to 3.7 μM. Navitoclax, as a developing small-molecule drug, has many unique advantages, including low-cost, good oral bioavailability, mature production technology and well-characterized *in vivo* safety. These findings suggest that Navitoclax is a promising repurposed drug candidate for development as a safe and orally available broad-spectrum antiviral drug to combat the current SARS-CoV-2 and its variants, as well as others HCoVs.

This work was financed by grant of the Belarusian Republican Foundation for Fundamental Research (project X21COVID-003) with the support of the Alliance of International Organizations (ANSO-CR-PP-2021-04).

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AUTOMATING THE RATIONAL DESIGN OF GLYCOMIMETIC DRUGS

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There are now many examples of promising therapeutics developed by converting carbohydrates into drug-like molecules that inhibit disease-related carbohydrate-protein interactions [1, 2]. However, the process of such a conversion is complex and far-too-often driven by trial and error. In this era of advanced computing, sophisticated computer modeling, and high-resolution experimental data, the potential exists to combine these data and tools to create an automated, suite of online tools that facilitates the objective creation and virtual screening of glycomimetic molecules as inhibitors of the cognate interactions.

We illustrate this pipeline and performance on a series of sialosides of potential interest in inhibiting diseases, such as viral and bacterial infections. The benefits of an online service are numerous; including enhancing efficiency and repeatability, consistency and democratization of access.

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CHEMICAL PROTEOMICS IN DRUG DESIGN

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Drug discovery is usually performed either by targeted approach when the key protein is known, or by phenotypic screening which is agnostic in respect to drug target. In both cases, it is important to find or verify the intended drug target, as well as discover off-targets, as the latter are the main culprits of potential drug toxicity. Drug target identification can be performed by modern methods of chemical proteomics that don't require the drug modification and/or a prior knowledge of the target or its properties. One such method is Functional Identification of Target by Expression Proteomics (FITExP) that utilizes the empirical fact that, in late apoptosis, the target protein significantly changes its abundance [1]. FITExP is thus well-suited for designing anti-cancer treatments and other situations when the drug intends to kill cells, and as a byproduct reveals the cell death modality [2]. FITExP however is not related directly to drug binding and thus produces no information on drug-protein interaction.

Such information is available in a complementary method of target identification known as Proteome-wide Integral Solubility Alteration (PISA) assay [3]. PISA analysis relates to previous approaches, such as CETSA MS and TPP, but offers dramatically higher throughput and better proteome coverage. PISA doesn't require cell death or even phenotype change and is applicable to both living cells as well as cell lysate. Combination of the two complementary approaches PISA and FITExP offer unprecedented sensitivity and specificity of drug target identification; such combination is extremely useful in other biological studies as well [4].

Furthermore, as drugs only perform the desired action so long as they stay bound to the target, the residence time of drugs on their target is an extremely valuable parameter for predicting drug efficacy *in vivo*. PISA analysis offers such a possibility [5].

Many novel drugs act via modulation of the redox state of the cells, which can be probed by redox proteomics [6]. Novel approach to redox proteomics that dramatically increases the depth of analysis will be described.

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ORAL PRESENTATIONS

IN SILICO PREDICTIONS OF 2-PHENYL-3-(4-DIMETHYLAMINOPHENYL) QUINOXALINE ACTIVITY AND AKT1 INHIBITION

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Cancer is a global public health problem of major concern being responsible for the death of 10 million people in the last decade. In this context, the PI3K/Akt/mTOR phosphatidylinositol-3-kinase signaling pathway plays a key role in the growth, survival, and metastasis of tumor cells, being controlled by Akt1. Therefore, Akt1 protein kinase is a promising therapeutic target in the fight against cancer [1]. Computer-Aided Drug Design emerges as a powerful tool for prediction and simulation of the interactions of small molecules and receptors, reducing cost and time of production of new drugs [2-4].

We have designed a drug prototype based on diphenylquinoxaline heterocycle by virtual screening of different phenyl-substituted compounds which lead us to dimethylamino promising structure (Fig. A). The structure of this compound was submitted to the PASS Online software (www.way2drug.com/PASSOnline), to predict the interaction with molecular targets, cytotoxicity in tumor cell lines (CLCPred) and chances of expression of genes (DIGEP-Pred). Most of the targets are ascribed to kinases and activity was found for different cancer cell lines (Fig. B). Other interesting targets associated with gene ontology are related to signal transduction, response to stress and metabolic process due to the presence of the methylamino groups (www.way2drug.com/SOMP). ADME parameters were also predicted for bioavailability and druglikeness (Fig. C) and the compound was found BBB permeant, gastrointestinal absorpted and inhibitor of the main P450 cytocrhomes (www.swissadme.ch). With this results, we have performed molecular docking with modified autoinhibited Akt1 structure (PDB:4ejn) with AutoDockVina 4.2 [5] (Fig. D) resulting in a lingand-receptor binding energy of -11.2 kcal mol^{-1}. The binding of the ligand on the active site was mainly from hydrophobic interactions where Trp80 plays a key role on the enzyme activity, showing that the compound has promising activity. The prototype compound was succesfully synthesized and in *in vitro* experiments are being carried out.

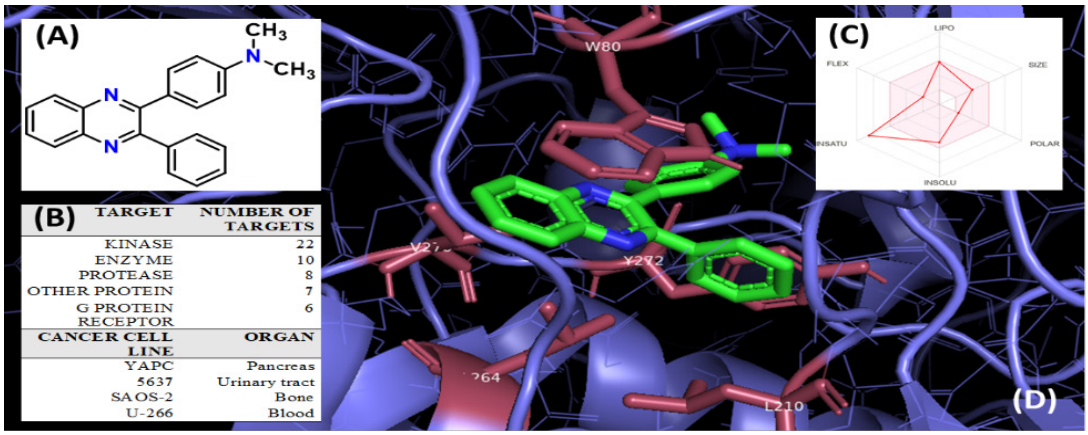

Figure. (A) Structure of prototype compound, (B) predicted representative targets and cancer cell line results, (C) bioavailability radar (D) active site from molecular docking with Akt1.

This study was supported by Portugal-Brazil cooperation FCT-CAPES edital (grant no. 22/2019).

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NEW FLUORESCENT ANTIFUNGAL AZOLE DERIVATIVE WITH NBD-PIPERAZINE MOIETY AND ITS DOCKING-REVEALED INTERACTION WITH SOME CYTOCHROMES P450

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Fungal infections have retained their status as big human health treat resulting in publication of the first fungal priority pathogens list by the World Health Organization (WHO) [1]. Thus, development of new antifungals will survive in drug design mainstreams to fight back. Computer-aided calculations have become a necessary part of works devoted new drug design. Namely, protein-ligand docking allows *in silico* evaluation of the interactions in terms of geometric details (poses) and binding energies (E_{bind}). We have design and then synthesized new fluorescent ketoconazole derivative based on the substance itself being consequently deacetylated and conjugated with 7-nitrobenzofurazan-4-yl chloride (NBD-Cl) resulted in N-deacetyl-N-NBD-ketoconazole (KDN). The product was characterized using mass-spectrometry, ^{1}H-NMR and spectrofluorimetry. It was shown the its fluorescence increase in acidic medium, likely, due to its NBD-piperazine moiety. It was shown that KDN save fungistatic activity at the level of its parent compound doing KDN a perspective prototype of a new drug or fluorescent molecular probe similar to those described [2]. To evaluate KDN in more details we docked its structure against vast majority of 3D structures of cytochromes P450 using Autodock Vina engine and FYTdock helper programs [3, 4]. We have found that KDN can realize the most affine interactions with CYP51 of *Tripanasoma brucei* (pdb 2x2n; energy of binding -12.5 kcal/mol) among others.

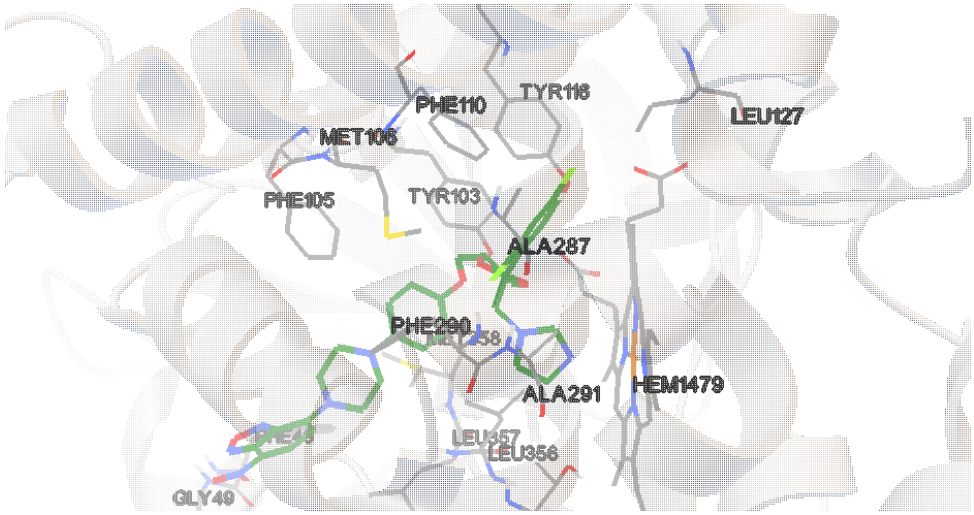

Figure. Docking pose of KDN close to the heme of CYP51 of *Tripanasoma* (pbd 2x2n)

Thus, we have designed, synthesized and preliminarily evaluated both *in silico* and *in vitro* a novel fluorescent antifungal azole with a great potential to be further evaluated as new antifungal drug and/or fluorescent molecular probe for P450s.

This study was supported by GSPSR grant (no. g.r. 20210560).

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FUNCTIONAL PROFILING OF MATURE VERSUS IMMATURE DENDRITIC CELL EXOSOME-SHUTTLE miRNAs

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Dendritic cells (DCs) are the most professional antigen-presenting cells, which undergo a hallmark transition from an immature to a mature state. DCs release high levels of exosomes (DCEs), containing miRNAs, which orchestrate their tolerogenic or immunogenic functions. This study aimed to identify the exosomes-shuttle miRNAs that are differentially expressed between the mature and immature states of DCs, and to assign functional enrichments to the targets of these miRNAs.

The GEO data series GSE33179 [1] was analyzed with GEO2R [2] and all miRNAs significantly dysregulated between mature and immature DCEs were selected for downstream targetome analysis. The interactions and targets were mapped separately for the upregulated and the down-regulated miRNAs [3, 4]; interaction networks and functional enrichments of the targets were generated [5] and visualized [6].

24 miRNAs were found upregulated and 19 miRNAs were found down-regulated in the exosomes of mature DCs over exosomes of immature DCs with 1949 and 1186 targets involved in 131 and 32 pathways, respectively. Based on the findings, functional association of targets of dysregulated DCE miRNAs with key maturation-dependent processes such as migration and energy metabolism were uncovered. Further, the results present miRNA signatures for identifying DC maturation state and uncover miRNA targets that may possibly serve as therapeutic options in the treatment of various immune dysfunctions.

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MODELING OF MIF/AIF INTERACTIONS IN FIELD OF ALLOSTERIC INHIBITORS DESIGN

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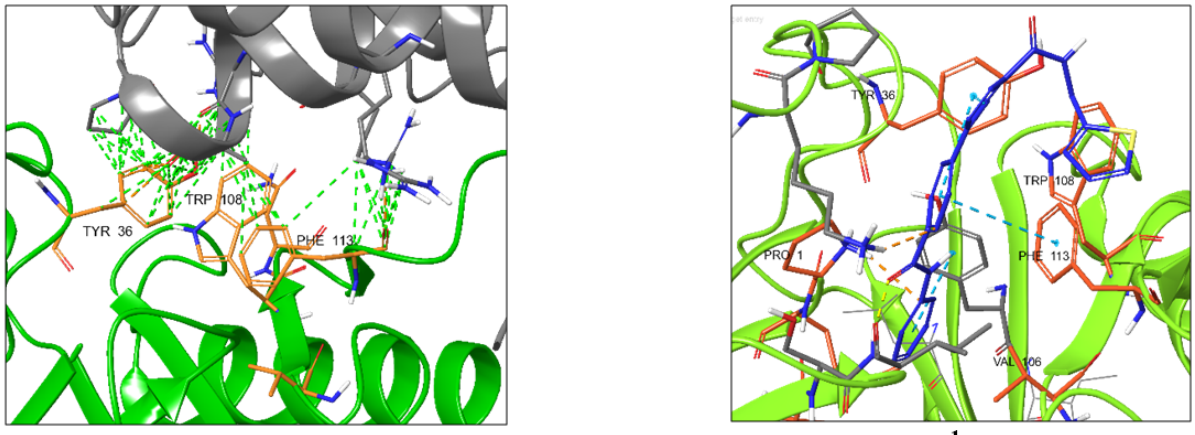
Parthanatos is a sort of caspase-independent programmed cell death caused by the buildup of poly (ADP-ribose) (PAR) polymers, and it is distinguished by a different route from apoptosis, necroptosis, and any other type of cell death. Parthanatos is linked to a variety of illnesses, including ischemic stroke, glutamate excitotoxicity, inflammation, reactive oxygen species (ROS)-related damage, and cancer. In 2016, it was shown that macrophage migration inhibitory factor (MIF) plays a critical role in the induction of parthanatos by generating a MIF/AIF complex that translocates from the cytosol to the nucleus, causing DNA breakage and cell death. MIF (macrophage migration inhibitory factor) is a multifunctional cytokine and key signaling molecule that has been linked to inflammation and cancer. One of MIF's recently discovered functions is to attach to apoptosis-inducing factor (AIF), which "brings" cells to death under pathological situations. The interaction between MIF and AIF, as well as their nuclear translocation, is a key event in parthanatos. However, traditional competitive MIF tautomerase inhibitors have little effect on MIF functions in parthanatos. We investigated the putative binding mechanism of MIF/AIF proteins in this work using surface analysis and protein-protein docking.

The surface of the trimeric MIF protein revealed four notable cavities for protein-ligand or protein-protein interactions: 1 – Trimer center section, central solvent channel. 2 – Cavities on the exterior of the MIF protein between trimer subunits. They are described as allosteric and CD74-binding sites in several papers. 3 – Each monomer's sides between the -helices produced by Phe18-Ala29 and Ser74-Arg86. This segment contains a lot of leucine and is responsible for the lipophilic leucine zipper-like structure. 4 – "Pseudo-(E)LR" motif, since the glutamate (Glu/E) was replaced with aspartic acid (Asp/D), allowing interaction with CXCR2 due to structural similarities with its ligand CXCL8. We used the PIPER program to do protein-protein docking to better understand the MIF/AIF interaction. During the computations, 70,000 protein orientations were created, from which 50 best-fitting poses were improved and assessed. As a result, we discovered an energy-favorable cluster of docking solutions in which MIF interacts with AIF at the allosteric site area, which includes residues Tyr36, Trp108, and Phe113. Based on the results obtained, was developed a novel non-competitive 1,2,3-triazole-based MIF inhibitor 6y that blocks protein-protein interaction between MIF nuclease and AIF protein by steric blocking of critical hydrophobic regions [1].



a b

Figure. (a) – protein-protein interactions between MIF (green) and AIF (grey); (b) – compound 6y considered as MIF/AIF interaction inhibitor bound to MIF protein

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DRUG REPURPOSING OF HNMT INHIBITORS AND THEIR EVALUATION IN SCOPOLAMINE-INDUCED AMNESIA MODEL

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Lower activity of the histaminergic system is associated with neurological disorders, including Alzheimer's disease (AD). Thus, the enhancement of histaminergic neurotransmission by inhibition of histamine N-methyl transferase (HNMT), which degrades histamine, appears as an important approach. Although several molecules have been identified as HNMT inhibitors, its effects in increasing the histamine levels are poor mainly by their low blood-brain penetration. Thus, the repositioning of drugs has a great impact on the development of new therapeutics since it allows to identify new uses for an already approved drug, which significantly reduces costs and research time, allowing to develop new treatments for relevant diseases.

For this purpose, rigid and flexible molecular docking studies of 185 FDA approved drugs with the HNMT enzyme were carried out to select two compounds to perform molecular dynamics (MD) simulations to evaluate the binding free energies and stability of the enzyme-drug complexes. After that, an HNMT inhibition assay was performed to corroborate their effect towards HNMT. Finally, the effect of the mentioned drugs on the hippocampal histamine levels and Novel Object Recognition (NOR) paradigm in a scopolamine-induced amnesia model was evaluated.

Molecular docking studies with HNMT allowed the selection of dihydroergotamine and vilazodone since these molecules showed the lowest Gibbs free energy values. Analysis of the binding mode of vilazodone showed interactions with the binding pocket of HNMT with Glu28, Gln143, and Asn283. In contrast, dihydroergotamine binds to the HNMT active site in a different location, apparently because it is overall the more rigid ligand compared to flexible vilazodone. HNMT inhibitory activity for dihydroergotamine and vilazodone was corroborated (IC_{50} = 72.89 μM and 45.01 μM, respectively) by *in vitro* assays. After that, male Wistar rats administered intraperitoneally (*ip*) with vilazodone (4 mg/kg) and dihydroergotamine (1 mg/kg) showing increased histamine levels in the hippocampus after 3 h, being the highest for the vilazodone group. In behavioral assays, male Wistar rats treated daily *ip* with vilazodone (4 mg/kg), and dihydroergotamine (1 mg/kg), subjected to memory impairment with scopolamine (1 mg/kg, *ip*) showed memory enhancing in scopolamine-induced memory deficits in the NOR performance as indicated by an increase in the recognition index. In conclusion, drug repurposing of HNMT was achieved by employing computational studies and their effects on histamine levels and memory were demonstrated.

This research was funded by Consejo Nacional de Ciencia y Tecnologia (CONACyT) grant no. 320862; PAPIIT-UNAM grant no. IN212421; Instituto Politécnico Nacional grant no. 20227029, 20231144, and 20230708.

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CONFORMATIONAL DYNAMICS AND STABILITY OF MYCOLIC ACIDS BILAYERS FROM THE *MYCOBACTERIUM TUBERCULOSIS* OUTER MEMBRANE

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Bilayers of mycolic acids (MAs), the lipid-like 2-alkyl-3-hydroxy long-chain fatty acids with 60-90 carbon atoms, form the outer membrane of *Mycobacterium tuberculosis* that has high strength and extremely low permeability for external molecules including antibiotics. The MA molecules can obtain a variety of conformations traditionally classified into several major types. For the first time, we were able to study them using the all-atom long-term molecular dynamics simulations (from 300 ns up to 1.2 μs) in order to investigate the conformational changes and most favorable structures of the mycolic acid molecules inside the mycobacterial membranes [1]. It was found that the membrane structure and properties are crucially dependent on the initial packing of the α-mycolic acid (AMA) molecules, as well as on the presence of the secondary membrane components, keto- and methoxy mycolic acids (KMAs and MMAs). Membranes with different initial structures can retain their thickness, density distribution and, in some cases, conformational composition for a long time. For the AMA-based membranes, the most labile conformation was W, which changes significantly within 300 ns, turning into other types of conformations. In contrast to the W structure, the other types of initial packing studied (sZ and eU, as well as their mixture) turn out to be much more stable. The conformational transitions that occurred in the AMA membranes based on the W conformation were described by the first-order kinetics, with the decay of the W structure leading mainly to the sU, eU, sZ structures with noticeably higher amount of sU (Fig. 1). The characteristic time of the W decay and the accumulation of product conformations was 160–220 ns. In the multicomponent membranes, the presence of the KMA and MMA components, which tend to be in the W conformation, additionally stabilized both the W and eU conformations of AMA, and this effect depended on the KMA/MMA concentration. The typical density profile for such a membrane is shown in Fig. 2. The membrane where AMA mostly has the eU conformation is much thicker and, at the same time, much denser. It can be said with certainty that such a packing of MA molecules in the membrane promotes the formation of a much stronger outer mycobacterial membrane that should be much more resistant to the threatening external factors.

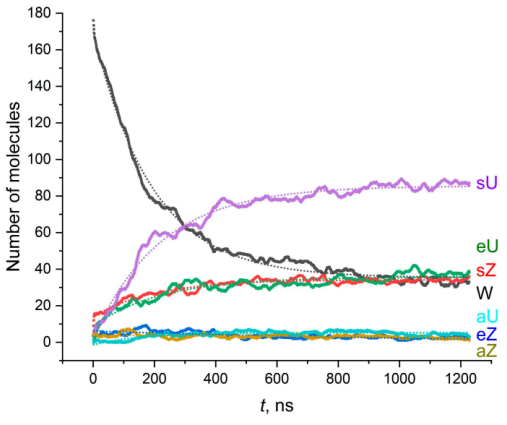

Figure 1.

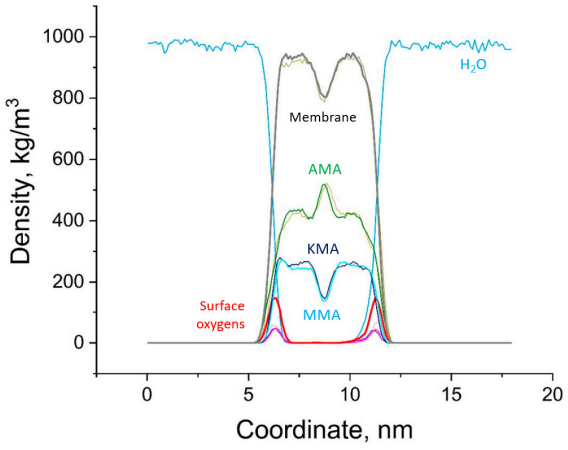

Figure 2.

This study was supported in the framework of the Strategic Academic Leadership Program "Priority 2030" of the Lobachevsky State University of Nizhny Novgorod (project N-473-99). Authors thank the research HPC facility of UNN for supercomputer time at SC "Lobachevsky".

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AI-POWERED *IN VIVO* SCREENS FOR NEUROACTIVE DRUG DISCOVERY USING ZEBRAFISH (*DANIO RERIO*)

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The zebrafish (*Danio rerio*) is rapidly emerging in modern biomedicine as a promising translational tool for disease modelling and innovative drug discovery. Capitalizing on high genetic, physiological and pharmacological homology with mammals, several drugs originally developed in zebrafish are now entering clinical trials. Biomedical research has also benefitted recently from a wide range of artificial intelligence (AI) applications that enable precise and objective extraction of biomedical data in both clinical and pre-clinical assays. The use of zebrafish, small freshwater teleost fish, for neuroscience and neuropharmacology research is also growing rapidly, due to their sensitivity to major classes of common CNS drugs, low cost, easy maintenance, and availability of both larval- and adult fish-based drug screens with medium-to-high throughput capabilities. The latter line of research necessitates novel reliable and unbiased methods for collecting neurophenotypic data and their analyses. Our laboratory has developed first AI neural network-based algorithms for zebrafish drug screening assays, and validated them using a large dataset of adult zebrafish locomotor tracks collected in a series of in vivo experiments with multiple established psychotropic drugs. Specifically, we trained AI to recognize various drugs from a wide range of psychotropic agents tested, and then confirmed prediction accuracy of trained AI by comparing several agents with known similar behavioral and pharmacological profiles. We next corroborated the use of this approach to distinguish between control and dopamine-depleted fish treated with a Parkinsonism-inducing neurotoxin, as well as to assess neurotropic potential of a battery of novel NBOMe compounds, revealing anxiogenic/anxiolytic and potent hallucinogenic properties for some of these agents. Overall, presenting a framework for an innovative CNS drug discovery based on AI-driven movement pattern classification in zebrafish, this approach may foster further drug development and in vivo screening utilizing this key model organism.

This study was supported by funds from St. Petersburg State University, Granov Russian Research Center for Radiology and Surgical Technologies, Sirius University of Science and Technology, as well as by Almazov National Medical Research Center.

VinaLigGen: A METHOD TO GENERATE LIGPLOTS AND RETRIEVAL OF HYDROGEN AND HYDROPHOBIC INTERACTIONS FROM PROTEIN-LIGAND COMPLEXES

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Developments in the field of computational structural biology and with increasing computing speeds have encouraged researchers in studying large compound libraries during the virtual screening. After performing molecular docking, the consideration of vina score in filtering the compounds without collecting the hydrogen bond or hydrophobic interaction between protein and ligand complex leads to missing multiple potential lead molecules. The tools used for virtual screening in drug design and discovery studies were previously designed and developed for small datasets. LigPlots were used to generate 2-dimensional (2D) interaction maps of protein-ligand complexes. These maps depict diverse bonds like hydrogen and hydrophobic interactions in varied colors for all ligand conformations within the library. However, handling large numbers of protein-ligand complexes can make this process quite laborious. The development of a tool is strongly required or an implementation of automation to generate all the interaction details has a strong demand. This paper describes an implementation of an automation technique on the executable programs like ligplot.exe, hbplus.exe and hbadd.exe to obtain the 2D interaction map (LigPlots) of the protein and ligand complex (*.ps) and hydrogen bonds and hydrophobic interactions in *.csv format for molecules to be considered for virtual screening by using some sorting & searching algorithms and python's file handling functions, and it also mentions the program's limitations and availability of the program.

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ANALYSIS OF THE THREE-DIMENSIONAL LOCALIZATION OF THE APOBEC-INDUCED MUTATIONS IN THE CELL NUCLEUS USING Hi-C DATA

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Mutations are a commonly acceptable cause of human cancer. Known sources of mutations can have both exogenous and endogenous natures. Examples of endogenous mutagens are ultraviolet light, ionizing radiation, and tobacco smoke. Known endogenous mutagens are DNA repair deficiency, free radical species, and deamination, which is mainly caused, as was recently discovered, by the activity of components of the human immune system – APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like) family cytidine deaminases. Recent advances in the sequencing of cancer genomes allow tracking mutagen activity of APOBEC enzymes based on the so-called mutational signature, which describes a nucleotide context of mutations being unique for many mutational processes. This makes it possible to investigate the heterogeneity of the rate of mutations induced by APOBEC enzymes along the genome and recognize the possible link of mutation rate with the various cellular processes such as transcription, replication timing, as well as with chromatin organization. The understanding of mutational heterogeneity along the genome is important for implication in statistical methods aiming for the identification of the exhaustive catalog of cancer-driving genes.

Hi-C is a comprehensive technique for the detection of chromatin interactions in the cell nucleus. This method allows exploring the biophysical properties of chromatin as well as the implications of chromatin structure for the biological functions of the nucleus. Among the main insights from the analysis of Hi-C data is the recognition of the topologically-associated domains (TADs) and transcriptionally active and inactive regions (A and B compartments). Hi-C data provide the opportunity to model and understand three-dimensional architecture of the human genome.

In many cases in the sequenced cancer genomes, the APOBEC-induced mutations were found positionally clustered and located on one of two DNA strands [1]. In addition, these genomes usually contained APOBEC-induced mutations distributed positionally along the genome. We suggest that these mutations could actually be clustered in 3D space in the cell nucleus, and this hypothesis could be analyzed using Hi-C data. The performed analysis revealed distinct patterns of mutation clustering in 3D space for cancer samples with APOBEC activity, as compared to the control samples.

This study was supported by Russian Science Foundation (grant no. 22-14-00132).

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MOLECULAR MODELING OF GLUTAMATE ACYLATION MECHANISM IN THE ACTIVE SITE OF N-ACETYLGLUTAMATE SYNTHASE

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N-acetylglutamate synthases (NAGS) are a family of enzymes that catalyze the reaction of N-acylation of glutamate, where acetyl coenzyme A is a donor of the acetyl group. There are two large groups of N-acetylglutamate synthases identified on the basis of phylogenetic and structural analysis: hexameric bacterial NAGS and tetrameric animal NAGS; these two subclasses include apparently related enzymes, but their active sites are strongly different. The catalytic mechanism has not been reliably established for any N-acetylglutamate synthase [1]. In this work the glutamate acylation mechanism in the active site of bacterial N-acetylglutamate synthase from Neisseria gonorrhoeae (PDB ID 3B8G) was calculated by modern modelling methods.

First step of glutamate acylation mechanism in bacterial NAGS is binding of reactants – glutamate and acetyl-CoA. On the basis of crystallographic data and classical molecular dynamics, the canonical recognition motif for acetyl-CoA in NAGS from Neisseria gonorrhoeae (Gln364-Glu365-Gly366-Gly367-Tyr368-Gly369) was found. Additional binding of acetyl-CoA by the kinase domain of another monomer unit through hydrogen bonding of the terminal phosphate group of acetyl-CoA with Arg134, Arg151, and Lys152 is non-characteristic for the NAGS family. A reactive conformation of glutamate is fixed by hydrogen bonds between the α-carboxyl group of the molecule and the guanidine group of Arg316 and its γ-carboxyl group and the guanidine group of Arg416 or Arg425.

Next step of glutamate acylation mechanism is deprotonation of glutamate. According to umbrella sampling molecular dynamics, this step is carried out before glutamate enters the active site of the enzyme, since there are no suitable proton acceptor residues in the active site. Glu353 stabilize the protein tertiary structure through the formation of a salt bridge with Arg416 and cannot participate in the role of a proton acceptor, as it proposed in the literature [2].

The reaction mechanism was established using a combined method of quantum mechanics/molecular mechanics (QM/MM) and molecular dynamics with QM/MM potentials (QM/MM-MD) with the addition of a bias potential by the umbrella sampling method. The quantum part was calculated using the unrestricted density functional theory method: the PBE0 functional with D3 dispersion correction and the 6-31G** basis. The molecular mechanical part was described using the CHARMM force field. The free energy profile of the reaction was constructed using weighted histogram analysis (WHAM). According to these methods, N-acylation of glutamate by acetyl-CoA occurs through a direct nucleophilic attack of the glutamate nitrogen atom on the carbonyl carbon atom of acetyl-CoA; transition states are stabilized through the formation of hydrogen bonds with the amino acid residues of the oxyanion hole. For the loop on which the discovered oxyanion center is located, a canonical structural motif was found among bacterial NAGS, which suggests the unity of the established mechanism for all enzymes of the subgroup.

This research was funded by the Russian Science Foundation (grant no. 23-13-00011).

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SEMISYNTHETIC TRITERPENOIDS AS PROMISING BLOCKERS OF AGGRESSIVENESS-RELATED TRAITS IN GLIOBLASTOMA MULTIFORME: *IN SILICO*, *IN VITRO*, AND *IN VIVO* APPROACHES

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Glioblastoma multiforme (GBM) is one of the most aggressive malignancies, accounting for 49% of malignant central nervous system tumors, with a median overall survival of approximately 15 months. Despite extensive efforts to develop new treatments, outcomes for GBM patients remain exceptionally poor due to the diffuse growth pattern of GBM and its resistance to radio- and chemotherapy. These malignant traits of GBM can be associated with its glial-mesenchymal transition (GMT), a process endowing glioblastoma cells with highly invasive and stem-like phenotype. Considering the current focus of drug discovery strategies mainly on finding effective inducers of glioblastoma cell death, the development of anti-GMT agents can be considered as a novel promising approach in anti-GBM therapy.

In this study, we explored the inhibitory potential of a series of amide derivatives of soloxolone in relation to a range of malignant characteristics of GBM cells. Using AlzPlatform and PreADMET tools, we predicted the ability of explored compounds to penetrate the blood-brain barrier (BBB), which was further verified in murine model using HPLC-MS/MS. Screening of soloxolone derivatives for their anti-GBM potency identified hit compounds, which effectively inhibited (a) TGFβ-stimulated GMT in U87 cells, including overexpression of mesenchymal markers, the loss of cell adhesiveness, and changes in cell morphology, (b) the motility and invasiveness of GMB cells, as well as their stem-like traits, (c) the proliferation of GBM cells by inducing mitochondrial stress, and (d) the three-dimensional growth of U87 cells in spheroid culture. Moreover, the hit compounds were found to exhibit a high synergistic effect with temozolomide *in vitro*. Using a network pharmacology approach accompanied by molecular docking simulations, we identified four potential protein targets of hit compounds associated with their anti-GBM potency, including EGFR, HER2, AKT1, and LonP1. Revealed anti-GBM activity of hit compounds was finally verified in a U87 glioblastoma xenograft model *in vivo*. Additionally, given the crucial role of P-glycoprotein (P-gp) overexpressed at the BBB in the effectiveness of anti-GBM drugs, the potential of the evaluated triterpenoids to inhibit P-gp efflux activity was predicted using ADMETlab, SwissADME, and LiverTox tools. Obtained results were further verified using a molecular modeling approach followed by the detailed confirmation of P-gp inhibitory activity of the hit compounds in rhodamine-123 and doxorubicin efflux assays in KB-8-5 and RLS40 cells, which exhibit a multi-drug resistant phenotype.

Taken together, our findings provide valuable insights into the anti-GBM and anti-GMT potencies of semisynthetic triterpenoids and highlight the blockage of GMT as a novel and promising strategy for GBM treatment.

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A CASE STUDY OF STRUCTURE-BASED DRUG DESIGN WITH CYSTEINYL LEUKOTRIENE G PROTEIN COUPLED RECEPTORS

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CysLT1R and CysLT2R, two G Protein Coupled receptors (GPCRs) activated by cysteinyl leukotrienes, play pivotal roles in inflammation-related disorders and certain cancers. The constitutively active state resulting from the L129Q mutation in CysLT2R has been identified as a driving oncogenic mutation in various melanocytic tumors [1-3]. Although numerous antagonist families exist for CysLT1-2Rs, the development of inverse agonists targeting CysLT2R L129Q remains a formidable challenge.

Implementing the X-Ray crystallography at the synchrotron and x-ray free-electron sources, we determined the high-resolution crystal structures of CysLT1 and CysLT2 receptors in complex with anti-inflammatory compounds, offering insights into the structural basis of ligand interactions [4, 5]. By these structures, we pursued structure-activity relationship studies, performed structure-based drug design and analyzed cell-based functional assays to experimentally characterize drug candidates. Our rigorous virtual ligand screening, employing the ENAMINE database, yielded five novel antagonist chemotypes with desirable molecular weight (~400 Da) and cLogP (~3.5), providing scope for further optimization. Notably, two chemotypes demonstrated inverse agonism against CysLT2R L129Q, as validated through functional assays [6]. Our ongoing efforts involve securing international patents for these novel compounds, with plans to advance to lead optimization, co-crystallization studies, and subsequent stages of drug development.

This work was supported by the Russian Science Foundation (project no. 22-24-00454, https://rscf.ru/project/22-24-00454/).

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COMPUTER-AIDED DESIGN OF NOVEL TSPO-LIGANDS – POTENTIAL NEUROPSYCHOTROPIC AGENTS

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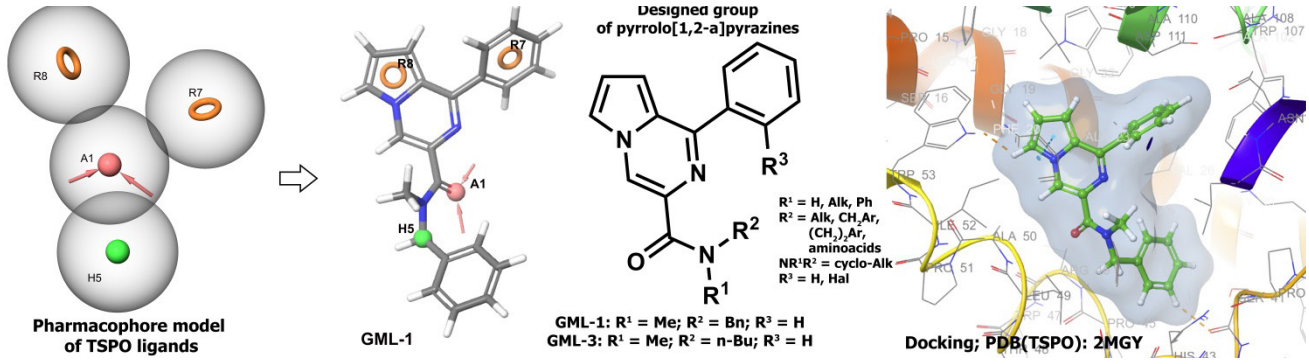
Translocator protein 18 kDa (TSPO) is considered as a promising target for creating safe fast anxiolytics, antidepressants and other neuropsychotropic agents [1]. The ligands of TSPO activate the transport of cholesterol into mitochondria by this transporter that is the rate-limiting step of neurosteroids biosynthesis. Neurosteroids are potent positive allosteric modulators of $GABA_A$ receptor, which plays an important role in the pathophysiology of neuropsychotropic disorders.

To design the new potential TSPO ligands on the first stage we generated the refined pharmacophore model based on a library of the most promising known TSPO ligands, having both the best receptor binding characteristics and the most attractive spectrum of biological activity (Figure), using Schrödinger's Phase software. According to calculations, the resulting optimal model of TSPO ligands has the following components: 1. Two aromatic groups, one of which is usually heterocyclic (R7 and R8); 2. Aliphatic or aromatic hydrophobic group (H5); 3. Electron acceptor group (A1). In most molecules, it is between the H5 and R7/R8 groups. Based on this model we designed the group of 1-arylpyrrolo[1,2-*a*]pyrazine-3-carboxamides which is fully consistent with the identified model.

Further selection of molecules for synthesis within the proposed group was carried out on the basis of the following selection criteria: 1. High values of theoretical affinity of compounds calculated using the molecular docking method; 2. Favorable profile of calculated ADMET-characteristics of compounds. Molecular docking was performed using the TSPO structure in complex with the selective ligand PK-11195 (PDB ID: 2MGY) using the Glide v8.1 Schrödinger program. ADMET parameters were calculated using the QikProp v6.8 Schrödinger and ADMETlab 2.0 programs. The selected molecules had a high theoretical affinity for the TSPO active site. The docking score, which determines the energy of the ligand-receptor interaction, was below -8 for all substances. Among the key ligand-receptor interactions, a π-π stacking interaction of the pyrrole or phenyl ring with TRP143 and a hydrophobic interaction with the LEY49-TRP53 sequence were observed.



The most promising molecules according to the methods of molecular modeling were synthesized (Fig.). These compounds were analyzed using *in vivo* models of neuropsychotropic activities [2, 3]. Compounds with an anxiolytic, antidepressant, nootropic and neuroprotective properties were found. The lead compounds had 10^{-8}-10^{-7} M TSPO-affinity measured in radioligand assay. The lead compounds GML-1 and GML-3 were chosen for full preclinical studies as fast anxiolytic and antidepressant, respectively. These compounds showed excellent efficiency and safety profiles and good pharmacokinetics.

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A FRESH ANGLE ON P-GLYCOPROTEIN TO OVERCOME TUMOR CHEMORESISTANCE

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In recent years, clinicians have succeeded in the treatment of primary tumors, which has led to a significant increase in the life expectancy of patients. However, a new problem associated with the emergence of secondary tumors, which are chemoresistant in most cases, has arisen. P-glycoprotein (MDR1) is considered to be one of the major players in tumor chemoresistance due to efflux of a wide range of anticancer drugs, including doxorubicin, paclitaxel, and many others.

As a way to combat chemoresistant tumors, the combined use of drugs with P-glycoprotein inhibitors has been proposed. Despite intensive research on this transmembrane protein in recent decades, no clear understanding of small molecule characteristics required to inhibit P-glycoprotein function has yet been achieved. There are no data on specific sites, binding to which can inhibit the activity of this transport protein. All P-glycoprotein inhibitors known to date were obtained by optimizing molecules that are active towards other targets. In fact, these are competitive substrates of the considered transporter, which only partly retract its activity, allowing one to increase the bioavailability of antitumor drugs when used together. However, the results of clinical trials clearly indicate an insufficient efficiency of this approach.

PROTAC (proteolysis targeting chimera) is one of the successful strategies for fighting tumors; it is based on targeted protein degradation due to the spatial approximation of ubiquitin ligase and target protein. At the same time, it is proposed that P-glycoprotein ubiquitination, although does not lead to proteasomal degradation of the transporter, causes its removal from the membrane, after which it no longer performs the transport function. Thus, we hypothesized that the development of a PROTAC-like molecule targeting P-glycoprotein would allow us to overcome tumor chemoresistance caused by overexpression of this transport protein.

In this work, we studied the surface of P-glycoprotein in terms of sites suitable for ubiquitination by a E3 ligase using both the algorithm for binding site identification and protein-protein docking. Structures differing in conformational state were used as P-glycoprotein models. As a result, we identified 8 putative sites for the binding of small molecule ligands, and two of them seem to be the most promising. According to the latest data, small molecule compounds with high affinity to these sites can not only serve as structural fragments for proteolysis targeting chimera, but also exhibit their own inhibitory effect on P-glycoprotein-mediated efflux of anticancer drugs.

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THE GLAMOUR AND GLOOM OF ENSEMBLE DOCKING

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Ensemble docking is an advanced technique of molecular modelling applied to drug discovery, allowing the user to sample conformational space of the target protein via careful selection of protein structures to improve the performance of docking-based virtual screening. Two main approaches may be used for the structure selection procedure, one based on molecular dynamics simulations and another on the analysis of the protein structures available in the Protein Data Bank (PDB). The latter approach becomes especially appealing when numerous structures of the same protein are available, and crystallographic fragment screening campaigns became one of established sources of such large sets of experimental data.

We have applied ensemble docking to different kinds of proteins, including enzymes, in the virtual screening workflows. Since a retrospective enrichment analysis could be possible due to presence of information on actives and inactives, we have attempted to quantify the performance of ensemble docking and compare it to the docking against individual protein structures. A few examples will be given in the presentation.

An especially elaborated analysis will be provided for SARS-CoV-2 main protease, which is one of the most thoroughly studied enzymes of the last three years. This *débutante* had a few hundred structures in the PDB by the end of its first year thanks to relative ease of its crystallisation and validated druggability in the course of COVID-19 pandemic. Numerous screening campaigns also provided large sets of experimentally assessed active and inactive inhibitors. We have applied different approaches to ensemble selection and several sets of actives and inactives, as well as a reference diverse library, to study a virtual screening performance with the aim to establish a workflow for selection of compounds for experimental assessment. Observed metrics revealed a mixed quality of enrichment, attributable to the validation dataset composition. Nevertheless, overall performance of the crystallograhic ensemble docking confirmed the improvement achievable by the teamwork over the single-model approach.

This study was partially supported by the Ministry of Science and Higher Education of the Russian Federation (project no. FNZG-2021-0001).

COMPUTER PREDICTION AND IN VITRO STUDY OF ANTIVIRAL ACTIVITY OF HETEROCYCLIC SYSTEMS CONTAINING THIOPYRANO[2,3-*b*]QUINOLINE AND TETRAZOLE MOIETIES

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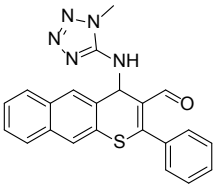
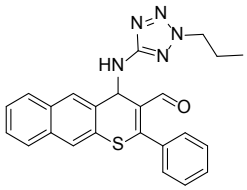
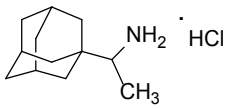
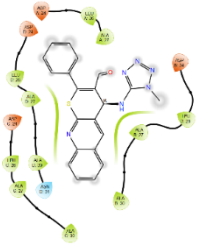
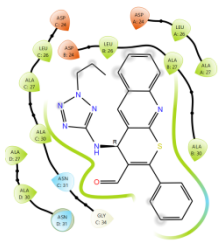
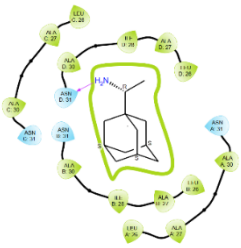
In recent decades, the search for new active components of antiviral drugs has become particularly relevant [1]. We conducted a computer prediction and *in vitro* study of the antiviral activity of two compounds **1** and **2**, containing pharmacophore fragments such as thiopyrano[2,3-*b*]quinoline and tetrazole. The cytotoxic and antiviral properties of the synthesized compounds were tested *in vitro* against influenza A/Puerto Rico/8/34 virus in MDCK cells. The studies revealed low cytotoxicity of these compounds. The antiviral activity of the compounds was found to be higher than that of rimantadine **3**. The calculations conducted for the investigated compounds have shown that the most preferable targets are the M2 channel and polymerase basic protein 2 (PB2). The interaction with the first target is energetically favorable due to the significant contribution of lipophilic interactions, which ensures binding specificity. On the other hand, for PB2, the compounds bind primarily through electro-static interactions provided by the aromatic structure of the scaffold, as well as the electron density of the tetrazole fragments.

Table. The results of *in vitro* study and computer modeling using the Schrödinger Suite 2022-4 software package.

Compound No.		**1**	**2**	**3**
Structure				
CC_{50}, μM		>750	>700	312.3±22.8
IC_{50}, μM		46±5	18.4±2,7	64.1±7.2
SI		>16	>38	5
GlideScore, kcal/mol	**M2**	-8.34	-5.08	-6.6
	PB2	-5.08	-5.33	-6.05
Ligand interactions diagrams with M2 channel				

In conclusion, our study emphasized the significance of searching for new active components of antiviral drugs among tetrazole derivatives of the 4*H*-thiopyrano[2,3-*b*]quinolines.

This study was supported by the Russian Science Foundation (grant No 23-13-00224).

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DRUG PROPERTIES AND DRUG LIGAND-BINDING COMPARISON ANALYSIS ON TENOFOVIR AND ZIDOVUDINE AS A REVERSE TRANSCRIPTASE INHIBITOR OF HIV-1

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The human immunodeficiency virus (HIV) infection has been a public health concern with no available cure. It is recommended for HIV patients to be supplied with antiretroviral therapy (ART) as their lifelong treatment to help reduce the course of this disease. Hence, there are two types of commonly used ARTs, namely tenofovir and zidovudine. Up to this point, it is unknown how both drugs perform in the *in silico* settings of both pharmacodynamics and pharmacokinetics manner. This research utilized bioinformatics approaches to examine tenofovir and zidovudine as an inhibitor of reverse transcriptase (RT) enzyme in HIV-1. Pertaining, the methodology, the 3D Model of the RT enzyme was generated using Swiss-Model Expasy from the FASTA amino acid sequence obtained from Protein Data Bank (PDB). The enzyme then went through several modifications using PyMOL before inserting them into CASTp: Computed Atlas of Surface Topography of Proteins active site prediction software, as well as PyRx (Python Prescription Virtual Screening Tool) and BIOVIA Discovery Studio 2021 for molecular docking. PreADMET analysis was used to determine the absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of the two drugs.

The results from molecular docking revealed that tenofovir possessed higher binding affinity towards HIV-1 RT rather than zidovudine. ADMET analysis showed that tenofovir have better Pgp-inhibitor absorption and blood brain barrier (BBB) distribution than zidovudine. Meanwhile, zidovudine possessed higher carcinogenic properties. Both drugs exhibited poor at Caco-2 absorption with high passive MDCK permeability, tested positive for human intestinal absorption (HIA), have up to 30% bioavailability, proper plasma protein binding (PPB) and volume distribution (VD), may act as both CYP substrate and inhibitor, have moderate clearance (CL), long half-life ($T_{½}$), and possessed different toxicity and allergic properties.

MACHINE LEARNING PREDICTION OF MYCOBACTERIAL CELL WALL PERMEABILITY OF DRUGS AND DRUG-LIKE COMPOUNDS

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The cell wall of *Mycobacterium tuberculosis* and related organisms has a very complex and unusual organization that makes it much less permeable to nutrients and antibiotics, leading to the low activity of many potential antimycobacterial drugs against whole-cell mycobacteria compared to their isolated molecular biotargets. The ability to predict and optimize the cell wall permeability could greatly enhance the development of novel antitubercular agents. Employing the QSAR/QSPR methods to achieve this goal, one of the key challenges is the lack of direct measurements of permeability. Thus, it is usually indirectly estimated from comparison of the target and whole-cell activities. Using an extensive structure–permeability dataset for organic compounds derived from published experimental big data covering multiple enzyme and cell assays (5371 compounds including 2671 penetrating and 2700 non-penetrating compounds), we have created a predictive classification model [1] based on fragmental descriptors and an artificial neural network of a novel architecture that provides better accuracy (cross-validated balanced accuracy 0.768, sensitivity 0.768, specificity 0.769, area under ROC curve 0.911) and applicability domain compared with the previously published results.

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PLANT EXTRACTS IN CANCER THERAPY: A COMPREHENSIVE ANALYSIS OF ANTICANCER ACTIVITY AND MOLECULAR DOCKING PROFILES

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Breast cancer remains the most prevalent cancer in women and one of the leading causes of cancer-related fatalities globally. However, overcoming the continuous resistance posed by the disease, developing effective prevention and treatment strategies, and ensuring affordability are significant challenges in mitigating its impact. This research aims to identify potential phytochemicals with anticancer properties in extracts of *Aegle marmelos* L. using an in silico approach that targets multiple pathways. Hexane, methanol, and aqueous extracts of *Aegle marmelos* L. were analysed to determine their phytochemical composition, revealing the presence of various beneficial compounds such as alkaloids, flavonoids, phenols, oils, phytosterols, coumarins, and saponins. Antioxidant activity was measured using the DPPH assay, and the extracts exhibited remarkable antioxidant potential, as indicated by their low IC50 values. The MTT assay was employed to evaluate their anticancer properties. Cell viability was assessed for each extract by comparing them to a negative control and a positive control (Cisplatin). The *Aegle marmelos* L. (leaves) extracts demonstrated significant efficacy against the MCF-7 breast cancer cell line in this study. Furthermore, GC-MS and LC-MS analysis confirmed the presence of specific phytochemicals in the selected plant extract. The identified compound from GC-MS and LC-MS analysis was further examined for its anticancer activity through molecular docking, comparing the binding affinity of the phytochemical with the target protein. Caryophyllene oxide emerged as the most promising anti-cancer compound, exhibiting the highest binding affinity for Human estrogen Alpha receptor (PDB id: 3ERT) and Epidermal growth factor receptor (PDB id:2J5F).Some compounds having higher affinity for targeted proteins further analysed for drug likeness by Swiss ADME tool. These findings suggest that extracts of *Aegle marmelos* L. (leaves) could serve as a natural remedy for breast cancer treatment.

DBAASP - A COMPREHENSIVE REPOSITORY OF NATURAL MULTIFUNCTIONAL CYCLIC ANTIMICROBIAL PEPTIDES

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In recent years, there has been a growing concern over the increasing prevalence of drug-resistant and multidrug-resistant bacterial strains, primarily due to the improper use of antibiotics. Antimicrobial peptides (AMPs) offer potential alternatives to conventional antibiotics due to their multifaceted activities and reduced risk of inducing bacterial resistance. Nonetheless, the development of AMP-based drugs is hindered by several challenges, such as toxicity and metabolic instability. One promising strategy to address metabolic instability is the macrocyclization of peptides.

Information regarding natural small cyclic peptides are scattered throughout literature and various databases. We aimed to consolidate data on cyclic peptides within the DBAASP (Database of Antimicrobial Activity and Structure of Peptides), transforming it into a comprehensive repository of cyclic AMP information. Analysing ribosomal and non-ribosomal cyclic peptides according to their amino acid compositions, cyclization bonds, targets they act on, and mechanisms of action enhances our understanding of cyclic peptides that nature has provided to defend living organisms.

DBAASP houses around 21 000 AMPs, including 3 519 natural peptides. Nature employs two types of synthesis for peptides: ribosomal and non-ribosomal. In DBAASP, there are 537 non-ribosomally synthesized peptides, 438 of which are small cyclic peptides (SCP – length < 25 AA). Notably, over a third of small cyclic non-ribosomal peptides fall under the ultra-short category (USCPs – length ≤ 5 AA). Nature also employs an alternative approach to create cyclic peptides through post-translational modifications referred to as post-ribosomal peptide synthesis (PRPS). DBAASP contains 2 983 ribosomally synthesized peptides, including 423 SCPs. Of note, small macrocyclic peptides represent more valuable drug candidates, driving the exploration of small cyclic peptides within DBAASP.

Analysing DBAASP data allows us to visually perceive the diversity of cyclic structures and intrachain bonds involved in cyclization. Both non-ribosomal and post-ribosomal synthesis contribute to the exceptional structural diversity observed in natural AMPs. However, the number of bond types contributing to cyclic structure diversity is limited. Cyclization bonds utilized in post-ribosomal and non-ribosomal synthesis encompass amide, ether, ester, thioether, and imine. Disulfide bonds exclusively form during post-ribosomal synthesis, while amine bonds occur in non-ribosomal AMPs. Consequently, many ribosomally synthesized and post-translationally modified peptides (RiPPs) and non-ribosomally synthesized cyclic AMPs share common types of rings formed post-cyclization. For example, both synthesis types give rise to five-member rings like thiazoline, thiazolidine, and oxazoline. Cyclic esters and amides (lactones and lactams) are ring structures found in both RiPPs and non-ribosomally synthesized AMPs. However, cystines and lanthionines, amino acids pivotal for cycle formation, occur exclusively in RiPPs. It is worth noting that despite different synthesis methods yielding similar rings, the proteins engaged in these systems are non-homologous, suggesting they emerged via convergent evolution.

This work was supported by Shota Rustaveli National Science Foundation of Georgia (SRNSFG) (grant no. FR-21-3368).

FROM BASIC PRINCIPLES TO COMPUTATIONALLY REFINED MODELS FOR A PRACTIC SYNTHESIS OF THE NANO-TARGETABLE POLYMERIC ANTIVIRALS

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Viruses, the cells' genome-targeting parasites, become now globally-increasing threat, coursing severe illness, incl. ones of high mortality. Key molecular root of biological life is based on the polymeric chains: oligomeric motifs of lipids (membranes), polysaccharides, polypeptides → proteins, nucleic acids (NA), etc. Exclusively the covalently linked backbone of biopolymeric chains is capable of accumulating energy to resist thermal (≈300 ±50 ^{o}K) chaos in motion-dissociation of small molecules, and to provide evolution towards the stable macro- and supra- molecular bio-life systems. Being smallest among biologic objects, infectious viral particles, the virions, represent themselves the most concentrated inter-bio-polymeric nanocomplexes: NA (genome), covered by proteins (capsid), enveloped frequently by lipid membrane over that the glycoprotein spikes are exposed, as sensors for search of permissive cells' receptors. Thus, viruses are, fundamentally, the polymeric based constructs, and within the nano-scale gradations, mainly: 5-20 nm (external spikes and cells' mediators for entry) up to 30-300 (rarely→1000) nm – virions. At the same time, currently applied arsenal of antiviral drugs, consists generally of small molecules (≤1 nm). Such, too great inadequacy between geometrical (energy and functional) scale of virus-specific macromolecular targets and small molecule antivirals is crucial fact, but it is out of modern Drug Design and Modeling focus so far. Of cause, the small molecules level could be seemingly profitable, but it, nevertheless, limits an antiviral effectiveness dramatically, if upgrading toward adequate generations of the "*Polyantivirals*" not follows timely.

In this report the *Polyantivirals* conception is formulated with some basic principles for design and synthesis, arising from accumulated knowledge (incl. our oven 40 years empiric background) of virus–specific (macro/supra) molecular structures' properties, behavior, and neutralization, within: (I) extracellular virions, their preorientation toward cells, (II) connection with cellular membranes, recognition the permissive cells and entry (adsorption +/- fusion), (III) intracellular replication, and (IV) self-assembly, maturation, and release of new virions. It is very important that only step III, involved multiple metabolites, and enzymatic active centers of small size, may be objective priority for a traditional design, QSAR modeling and application of small molecule antivirals. Opposite, the steps I, II and IV of viral life cycle are naturally more vulnerable to the nano-competent therapeutic intervention, namely, by means of the *Polyantivirals*. A computer-aided simulation of interactions between "synthetic" (Polyantiviral ligands) and biological (target) polymers has required some adaptations of processing/analysis for docking and MD, as more complex case comparing with a traditional modeling the small molecule ligands. Suitable solutions were implemented in collaboration with V. Tsvetkov, regarding *Polyantivirals* inhibition of fusion mediators of HIV [1], influenza and other viruses. These allowed clarifying details of the target-blocking mechanisms and structural parameters to optimize antiviral effectiveness and to select directions for purposed synthesis. For this goal, different polymeric backbones, side-modifying and linker groups as well varied degrees of modification were taken into account. In addition, some synthetically-specific groups, inserted into polymeric chain via controlled RAFT-copolymerization, were modeled as factors capable of influence on binding the viral targets. Finally, a computer-aided quantum-chemical–co–kinetic investigation, performed with Boris Bolshchikov [2], elucidating fine mechanisms of the alternating radical cyclocopolymerization, allows us to regulate precisely the chain's composition-structure and isomerism, that are very relevant for practice synthesis of *Polyantivirals* with a required bioactivity.

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IMPROVING ELECTROSTATICS DESCRIPTION IN SCORING FUNCTIONS: INSIGHTS FOR THEIR ROLE FOR DRUGS

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Electrostatic interactions are undoubtedly the cornerstone of intermolecular interactions. Being the major contributor of interactions between the drug like molecules in vacuo, electrostatic interactions define both orientation and long range attraction between molecules in the specified conditions. Such importance of electrostatic contribution is reflected in omnipresence and significance of electrostatic terms in classical force fields of molecular mechanics.

The electrostatic interpretations are also being widely used in the realm of drug discovery, where the affinity and selectivity of drug-like molecules against different targets are studied in macroscopic conditions and in water media. Both quantitative AI/ML/QSAR models as well as qualitative explanations are being successfully used.

Several works [1,2] were aimed at improving the accuracy of electrostatic interactions in the force field (physics) based scoring functions, in particular in AutoDock4, which has long been used in both academic and industry drug discovery studies. It was shown that, the RESP and AM1-BCC charge models which are fitted to the molecular electrostatic potential (MEP) of organic molecules calculated at RHF/6-31G* level give the best results. Since our empirical charge calculation approach DENR [3] is fast and was calibrated to reproduce MEP at the same level, our initial aim was to study how DENR is suitable for the combined use with AutoDock4 to hopefully provide more accurate results than Gasteiger charges used in AutoDock4 by default. To that end we studied the change in statistics of AutoDock4 scoring funct62ion accuracy in going from Gasteiger to DENR charges on a representative set of ligand-receptor complexes with high quality data – the coreset of CASF2016 Update study (a subset of PDBBind database).

The performed analysis surprisingly revealed that AutoDock4 scoring function is rather insensitive to atomic charges model. Moreover the contribution of electrostatic interactions into the overall score is small. The subsequent in detail analysis led us to two main conclusions. First, at technical level the physics-based electrostatic interactions are significantly duplicated by the the empirical-based hydrogen bond term in AutoDock4. Second, at conceptual level, we have inspected the role of electrostatic interactions for enhancing ligand-receptor affinity (hence scoring) and arrived at a conclusion that generally in drug discovery one should distinguish between the goal of enhancing the affinity and the goal of producing a new successful drug. The latter assumes, in particular, better off-target selectivity and good ADMET properties, which partially contradict to purely affinity maximization goals. Therefore the proper account of electrostatic interactions are more crucial at a higher level of drug discovery process and perhaps surprisingly not so important for affinity maximization.

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EVALUATION OF SELECTED INDIGENOUS SPICES-AND HERBS-DERIVED SMALL MOLECULES AS POTENTIAL INHIBITORS OF SREBP1 AND ITS IMPLICATIONS FOR BREAST CANCER USING MD SIMULATIONS AND MMPBSA CALCULATIONS

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High death rates and a poor prognosis are the results of localized breast cancer spreading to distant metastasis. Research showed that Abnormal sterol regulatory elementary binding protein 1 has been demonstrated (SREBP), which regulates lipid and cholesterol synthesis, may lead to breast cancer proliferation [1]. Therefore, it can be used as a target against breast cancer. Even though a lot of research and technological advances have been made in the field of cancer treatment, there is still room for improvement in the side effects of treatments and the associated costs. Towards this direction, we aim to develop such drug candidates against the aberrant SREBP1a using simulations of molecular dynamics and docking, which would reduce the side effects, associated with cancer treatment and be cost-effective and within reach of the common populace. The anticancer properties of natural bioactive compounds derived from plants are intensely interesting. Natural plant-based bioactive substances have been demonstrated to improve the efficacy of chemotherapy in several trials. A set of 20 indigenous spices and herbs was identified for molecular docking. The top two ligands, Diosgenin and Smilagenin, and known inhibitor Betulin were chosen for MD simulation to determine the steadiness of their docked complexes. Analysis of post-MD research, and PCA all provided evidence in support of the interaction potential of diosgenin and smilagenin.

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CONSENSUS MODELING OF ANXIOLYTIC ACTIVITY OF CHEMICAL COMPOUNDS BY CONVOLUTIONAL NEURAL NETWORKS

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According to WHO [1], approximately 635 million people in the world suffer from depression and anxiety disorders, their number continues to increase, and therefore the search for new anxiolytic drugs is being intensively conducted. The use of artificial intelligence methods to search for new anxiolytic substances is one of the most relevant areas of modern pharmacology and bioinformatics.

The purpose of this work is to construct a classification consensus ensemble model of the dependence of the anxiolytic activity of chemical compounds on their structural QL-descriptors by the method of convolutional artificial neural networks.

The training set was formed on the basis of the original verified database [2] on the structures of 537 known experimentally studied substances, of which 273 compounds had pronounced anxiolytic activity, and 264 compounds were low active or inactive. The chemical structure of these compounds was translated using the IT Microcosm system [3] into 8686 species of fragmental QL-descriptors of 11 different types. Linear convolution of the obtained structural parameters was performed using pairs of vectors of 11 types of QL-descriptors using the original ConvDesc program. The obtained 66 convolutional variables served as input neurons for neural network modeling, which was performed in the Statistica program [4]. A two-layer perceptron with "bottleneck" was chosen as the architecture of the neural network. 7 sampling variables were included in the training set, which determined the options for the formation of training, test and validation subsets. With their use, 7 series of neural network training were carried out, ~4 thousand neural networks in the series, about 30 thousand neural networks were trained in total. In each series, one of the most accurate neural networks was selected based on the results of random cross-validation, and a consensus ensemble model was formed from them.

The accuracy indicators of the consensus model on the pooled training set were: total accuracy F_0=77.5%, prediction accuracy of active compounds (sensitivity) F_a=85.0%, prediction accuracy of inactive compounds (specificity) F_n=69.7%.

The obtained model was used to search in silico for substances with anxiolytic activity among 97 new condensed benzimidazole derivatives, the accuracy was F_a=55.0%.

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A COMPARATIVE STUDY OF SAFETY AND PHARMACOKINETIC PARAMETERS BETWEEN STATINS, BILE ACID SEQUESTRANTS, AND EZETIMIBE AS DIFFERENT CLASSES OF LOW-DENSITY LIPOPROTEIN (LDL) CHOLESTEROL-LOWERING DRUGS IN SILICO

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Cholesterol is a nonpolar substance and lipophilic constituent of bile salt used in digestion to facilitate the absorption of fat-soluble vitamins A, D, E, and K and were utilized throughout the body by lipoproteins. The type of lipoprotein is Low-density Lipoprotein (LDL), also called bad cholesterol. LDL-cholesterol-lowering drugs significantly inhibit the production of VLDL, ceasing the production of LDL-C. Our work aims to differentiate three distinct types of drugs in each class of LDL cholesterol-lowering drugs – Statins, Bile Acid sequestrants, and Ezetimibe, *in silico* regarding their safeness and pharmacokinetic parameters.

In silico ADMET tools were utilized in this study to distinguish and predict the pharmacokinetic parameters of each LDL-cholesterol-lowering drug which include SwissADME, SwissTargetPrediction, ADMETlab 2.0, and Way2Drug PASS. The association of these tools enabled the correlation of the pharmacokinetic data generated from each instrument. Apart from providing an understanding of the ADME of the LDL-C-lowering drugs, the generated data allowed the analysis of the chemical properties such as toxicity which gives rise to the risk factors concerning patients with comorbidities and compromised immune systems. It also provided important information on preventing health risks and misusing these drugs, along with informing concerned individuals with updated details on which LDL cholesterol-lowering drug/s are preferred for consumption. Finally, it contributed significantly to the existing literature by comparing and correlating the evaluated drugs.

The pharmacokinetic analysis revealed that Statins inhibit the enzyme HMG-CoA reductase, which lowers LDL-Cholesterol levels, and increases HDL-Cholesterol levels. Atorvastatin, in particular, is metabolized by the CYP3A4 isoenzyme, leading to increased plasma concentration and an increased risk of myopathy and rhabdomyolysis. Bile Acid Sequestrants performed at a similar level with stimulation to the liver to produce more bile acids from cholesterol, leading to a decrease in LDL-Cholesterol levels. Bile acid sequestrants are not systemically absorbed and metabolized by the cytochrome P450 enzyme system, making them safe during pregnancy. On the other hand, Ezetimibe reduces the amount of cholesterol that enters the bloodstream, decreasing LDL-Cholesterol levels, and is the best option for patients with Heterozygous familial hypercholesterolemia. Given the remarkable pharmacokinetic parameters and safety protocols of the LDL-cholesterol-lowering drugs, these significantly inhibit the production of VLDL, ceasing LDL-Cholesterol production and cardiovascular events for those with aortic stenosis, myocardial infarction or coronary revascularization, and acute coronary syndrome lower the LDL-cholesterol of patients regardless of their demographics.

SELECTION PROCESS OF PHYTOCHEMICALS FOR UTILIZATION IN DISINFECTION OF DRINKING WATER

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Objective. Select suitable phytochemicals for water disinfection purposes.
PASS Online and GUSAR Online Predictions. In this research work, about 150 plant species including those which are indigenous to Pakistan were critically examined. According to literature about 100 of these species possessed phytochemicals with antimicrobial tendencies. These phytochemicals need to be ranked based on their tendency to function as antimicrobial agent, their relative toxicity to humans and the environment and their cost.
For this purpose, the structures of the phytochemical molecules were drawn in Marvin Sketch and checked with its structure checker function. These structures or the SMILES of the molecules were fed to PASS Online and GUSAR Online Acute Rat Toxicity Prediction. As a result, a list of about 4000 predicted biological activities, and toxicity data for each phytochemical molecule was obtained. The GUSAR Online software was utilized for the 'prediction' of toxicity values for the remaining phytochemicals.
Selection Methodology. The main criterion of selection is the antimicrobial tendency of any kind in the phytochemical molecule. As the objective here is to inactivate or kill water borne microorganisms, so the procedure of selection will be such to include those phytochemicals which have exhibited some antimicrobial tendency in this regard. In addition to this, another important factor is purchasing cost (because many phytochemicals are rarely available and so costly). Toxicity is yet another important factor as the phytochemical will be consumed along with the food or water into which it is added. Another factor of concern is the solubility in water. If the phytochemical molecule is more soluble, it means more is available for attacking the microorganisms in water. Another important inclusion in the selection of a suitable phytochemical can be molecular mass. Low molecular mass phytochemical being a positive factor from antimicrobial point of view because more molecules are available in given mass. Finally factors like decomposition in water, volatility, and absorption or adsorption into the sediments in water are also important to understand the fate of the phytochemicals in water. The procedure of selection is inclusive of all these factors.
Results. Based on the above criterion of the selection, thymol, eugenol, ferulic acid, menthyl salicylate, carvacrol and menthol were selected.

Immunomodulatory activity of Benznidazole in Ehrlich ascites carcinoma *in silico* and *in vivo*

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Cancer is a major global public health problem represented by about 10 million people dying in the year 2020. In Brazil, the estimate for the three-year period 2023-2025 points to 704,000 new cases of cancer, that is, 483,000. In this context, some innovative treatments such as immunotherapy achieve results against certain types of tumors, but they are not economically viable for a large part of the Brazilian and world population. In this context, Benznidazole (BZN), an antiparasitic drug used for more than 50 years for the treatment of Chagas disease. It is proposed that BZN contributes to the complete elimination of the parasite by modulating the immune response. This ability to modulate the immune response is important because it reduces human morbidity in the acute and chronic phase of the parasitoses [1]. We used PASS software to predict the interaction of BZN with molecular target groups, and to predict possible biological activities [2,3]. The in silico results predicted targets associated with biological processes Signal transduction (55), response to stress (40), metabolic process (35), immune system process (27), whereas the results of prediction of biological activity were Chemosensitizer (Pa=0.888), radiosensitizer (Pa=0.827), oxidizing agent (Pa)0.633, Antineoplastic enhancer (Pa= 0.409), Antioplastic (Pancreatic cancer) Pa=0.409), Calcium channel (voltage-sensitive)activator (Pa=0.482), Antineoplastic (solid Tumors) (Pa=0.404). The *in silico* results demonstrated the full capacity of BZN to act with antitumor activity and also act in the imune system. Knowing this, we performed *in vivo* assays with BZN with isogenic male BALB/c mice, approximately 60 days old, and divided into 3 groups (control, methotrexate, BZN), with Erlich Ascitic Carcinoma. After 9 days of treatments, cell suspensions and a panoptic procedure using the rapid panoptic kit, as well as measurement of myeloperoxidase (MPO)activity. BZN treatment increased the number os cells segmented when compared to control mice (69%). Furthermore, there was a increase in rods (Bad) (86%) and neutrophils (77%) after BZN treatment. Segmented cells have cytotoxic, pro-apoptotic and anti-angiogenic properties, unlike immature neutrophils, which are characterized by potentiation of carcinogenesis, anti-apoptotic and pro-angiogenic [4]. Myeloperoxidase (MPO) activity reduced by 59% after treatments with BZN demonstrating modulation of MPO activity while MTX causes immunosuppression. BZN treatment increased by 69%. increase in rods (Bad) 86% and segmented neutrophils 77%. Myeloperoxidase (MPO) activity reduced by 59% after treatments with BZN demonstrating modulation of MPO activity while MTX causes immunosuppression. Our results corroborate Silva, E.L. et al. 1990 [5], in which he proposes that BZN can act by modulating the immune system. Our data also demonstrated the ability of BZN to modulate the cytotoxic potential of leukocytes in the EAC environment. In this scenario, the results obtained suggest that BZN has an importante ability to inhibit tumor progression in addition to modulating the immune response, which generates a new perspective for future cancer therapies.

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YOUNG SCIENTISTS CONTEST

IN SILICO ANALYSIS OF VARIOUS FUNGAL SECONDARY METABOLITES AND ANTIRETROVIRAL DRUGS ON ITS MOLECULAR BINDING TO NIPAH VIRUS PROTEINS INVOLVED IN CELLULAR ATTACHMENT, FUSION, AND REPLICATION

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Nipah Virus (NiV) is a non-segmented, single-stranded, negative-sense RNA virus responsible for NiV infection, causing outbreaks in several South and Southeast Asian countries. Vaccines as effective pharmaceutical interventions are yet to be discovered, while drug treatments were only given emergency use authorization with limited data on their effectiveness. Due to the pandemic potential of NiV, pharmaceutical intervention must be explored aside from current preventive measures. Using in silico techniques, 49 fungal-derived secondary metabolites with reported antiviral activities and 14 antiretroviral drugs were constructed as ligands using canonical SMILES from PubChem. They were docked using UCSF Chimera, Amber's Antechamber, and AutoDock Vina on the DEPTH-predicted binding site of the constructed target proteins of NiV, involved in cellular attachment, fusion, and replication, from its amino acid sequences retrieved in NCBI. Results revealed that three alkaloids, norquinadoline A, quinadoline B, and scedapin C, the anthraquinone aspergilol G, the quinazoline (14S)-oxoglyantrypine, the cytochalasin Z8, the fumiquinozaline scequinadoline A, and the polyketide isochaetochromin D1 showed high binding affinity on the glycoprotein G, fusion protein F, and phosphoprotein P, respectively. Among the top-scoring metabolites, quinadoline B showed multi-target characteristics due to its favorable binding scores with proteins F and P. Predominant binding interactions found in the complexes are charged and hydrophobic interactions conferring potent complexes. The identified top fungal metabolites provide preliminary knowledge on potential drug development against NiV. In conclusion, the top-scoring metabolites exhibited significant binding scores that established favorable binding interactions with the target proteins of NiV.

CHEMICAL MULTIVERSE AND DIVERSITY OF FOOD CHEMICALS

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Food chemicals have a fundamental role in our daily lives with an extended impact on nutrition and disease prevention, not to mention the economic implications in the food industry. The number of food chemical compounds in public databases has substantially increased in the last few years. There is a broad range of well-established chemoinformatics tools to analyze the contents of such chemical libraries systematically. So far, our and other research groups have analyzed public food chemical libraries containing up to 26,500 compounds. This study aimed to analyze the chemical contents, diversity, and coverage in the chemical space of food chemicals in a large public database of food chemicals with more than 70,000 compounds. It was concluded that food chemicals have distinctive physicochemical properties and constitutional descriptors despite sharing many chemical structures with natural products, and FDA-approved drugs. Food chemicals, on average, have large molecular weights and several apolar structures with saturated hydrocarbons. As compared to reference databases, food chemical structures have low scaffold and fingerprint-based diversity and high structural complexity as measured by the fraction of sp^3 carbons. These structural features are associated with the large abundance of macronutrients as lipids. The chemical multiverse representation of food chemicals (Fig.) showed that food chemicals cover a larger portion of chemical space than natural products and FDA-approved drugs, with overlapping compounds. The results support the need to systematically look for bioactive structures in food chemicals data sets, and follow-up studies addressing key features such as enzymatic processing, or unsaturation enrichment, by chemoinformatics and computational approaches on the large.

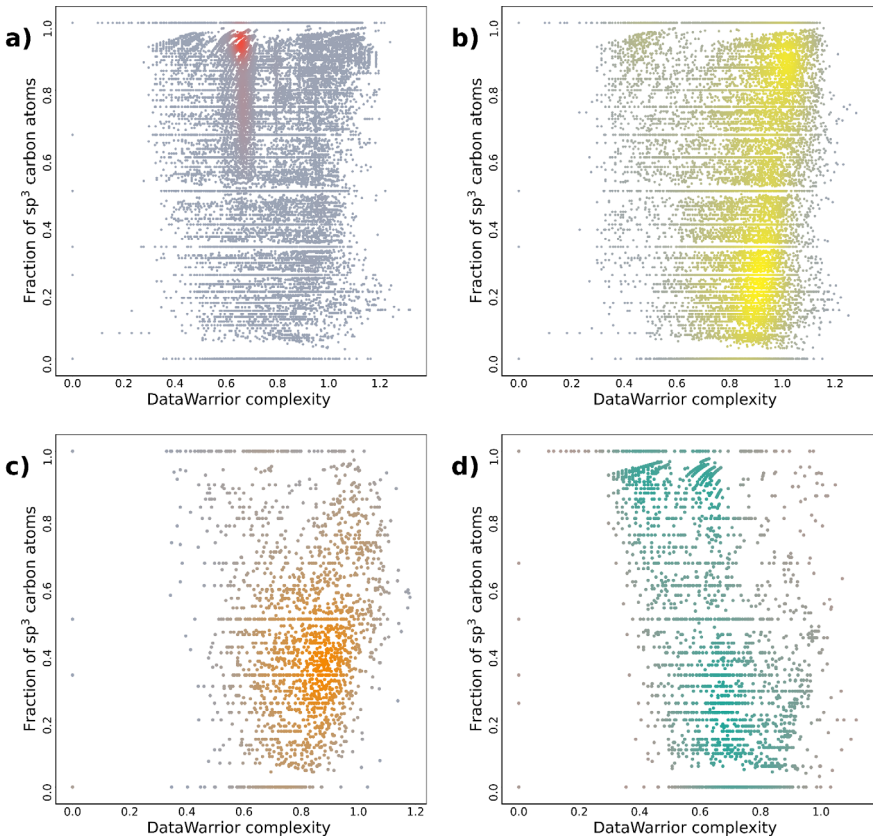

Figure. Density plot of CSP3 vs. DataWarrior complexity index pairwise comparison, computed for a) food chemicals (FooDB, gray-red), b) natural products (UNPD-A, gray-yellow), b) FDA-approved drugs (gray-orange), and d) commercially available compounds from FooDB (gray-green). The density of data points is represented in a continuous scale from denser (colored), to less dense (gray).

DEVELOPMENT OF A GLOBAL Q-RASAR MODEL FOR THE EFFICIENT QUANTITATIVE PREDICTIONS OF SKIN SENSITIZATION POTENTIAL OF DIVERSE ORGANIC CHEMICALS

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Environmental chemicals and contaminants cause a wide array of harmful implications to terrestrial and aquatic life which range from skin sensitization to acute oral toxicity. Most of the previously developed computational models to predict the skin sensitization potential of organic chemicals have the main drawbacks of small data set size and/or individual classes of compounds showing identical skin sensitizing mechanisms. The current study aims to assess the quantitative skin sensitization potential of a large set of industrial and environmental chemicals that act through different mechanisms using the novel quantitative Read-Across Structure-Activity Relationship (q-RASAR) approach. The computed and pretreated structural and physicochemical descriptors of the curated data set were used for the preparation of the data set, which was rationally divided into training and test sets for model development and external validation, respectively. Feature selection was performed to identify the important set of features and a QSAR model was generated. Using the set of important features, Read-Across-based hyperparameters were optimized using the training set compounds and this optimized setting was then used to calculate the similarity and error-based RASAR descriptors. Data fusion, further feature selection, and removal of prediction confidence outliers were performed to generate a partial least squares (PLS) q-RASAR model. This was followed by the application of various Machine Learning (ML) tools to check the quality of predictions. The PLS model was found to be the best based on the quality of external predictions. A simple user-friendly Java-based software tool was developed based on the PLS model which efficiently predicts the toxicity value(s) of query compound(s) along with their AD status in terms of leverages. This model has been developed using structurally diverse compounds and is expected to predict efficiently and quantitatively the skin sensitization potential of environmental chemicals to estimate their occupational and health hazards.

SPATIAL CHARACTERISTICS AND PREDICTION OF PROBABLE ACTIVITY AND TOXICITY OF STREPTOMYCIN AND ITS DERIVATIVES USING PASS-PROGRAM

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The objective of the study. Molecular model analysis of streptomycin derivative compounds and virtual screening of their pharmacological properties and toxicity.

The advancement over previous studies. In recent years, computer methods have been used in solving the problem of establishing the relationship between chemical structure and prediction of biological and toxic properties of new models. Comparison of compound parameters obtained from quantum-chemical calculations and PASS-programs allows to estimate the contribution of this or that physicochemical characteristic to the developed model and to better understand the mechanism of pharmacological and toxic action of the drug.

The results and accomplishments and their significance. Eight models of chemical structures of streptomycin derivatives were created and their spatial characteristics were calculated using the GAUSSIAN 09W program: #1)streptomycin (O-2-Deoxy-2-(methylamino)-alpha-L-glucopyranosyl-(1»2)-O-5-deoxy-3-C-formyl-alpha-L-lyxofuranosyl-(1»4)-N,N'-bis(aminoiminomethyl)-D-streptamine); #2)D-galactose-6-phosphate(1»2)-O-5-deoxy-3-C-formyl-alpha-L-lyxofuranosyl-(1»4)-N,N'-bis(aminoiminomethyl)-D-streptamine); #3)D-galactose-6-phosphate(1»2)-O-5-deoxy-3-C-formyl-alpha-L-lyxofuranosyl-(1»4)-N,N'-D-streptamine); #4)(O-2-Deoxy-2-(methylamino)-alpha-L-glucopyranosyl-(1»2)-O-5-deoxy-3-C-formyl-alpha-L-lixofuranosyl-(1»4)-N,N'-D-streptamine); #5)(O-2-Deoxy-2-(methylamino)-alpha-L-glucopyranosyl-(1»2)-O-5-deoxy-3-C-formyl-alpha-L-lyxofuranosyl-(1»4)-L-1-O-methyl-myo-inositol); #6)O-2-Deoxy-2-(amino)-alpha-L-glucopyranosyl (1»2)-O-5-deoxy-3-C-formyl-alpha-L-lyxofuranosyl-(1»4)-N,N'-bis(carbamyl)-D-streptamine; #7)O-2-Deoxy-2-(amino)-alpha-L-glucopyranosyl-(1»2)-O-5-deoxy-3-C-formyl-alpha-L-lyxofuranosyl-(1»4)-D-1-O-methyl-myo-inositol); #8)O-2-Deoxy-2-(methylamino)-alpha-L-glucopyranosyl-(1»2)-O-5-deoxy-3-C-formyl-alpha-L-lyxofuranosyl-(1»4)-L-myo-inositol. Using quantum-chemical studies, the analysis of calculated enthalpies of formation of model molecules shows that the most thermodynamically stable are all model derivatives of streptomycin; the analysis of charge characteristics on atoms in model molecules shows that the reaction center for nucleophilic attack is oxygen with a single bond in the hydroxyl group of streptomycin derivatives and nitrogen with a double bond in the guanidine group; the analysis of values of electric dipole moments allowed us to determine that the model molecules are the most stable.

Next, the presence of pharmacological properties and toxicity in the 4 models was predicted using PASS Online 2.0. The analysis shows that the presence of H_3PO_4 residue in the structure of streptomycin #2 significantly increases the probability of having antifungal effect, and decreases the toxicity scores: Mutagenicity, reproductive dysfunction and carcinogenicity; the absence of guanidine group and the presence of H_3PO_4 residue in the structure of streptomycin #3 significantly increases the probability of having antifungal and antibacterial effects than in molecule #2 and decreases the toxicity indicators; the absence of guanidine group in the structure of streptomycin #4, significantly increases the probability of having antitubercular activity compared to other models and increases the toxicity indicators of the compound; absence of guanidine group in the structure of streptomycin and replacement of $-NH_2$ by -OH group in the structure of molecule #5, significantly increases the probability of antitubercular activity compared to other models of streptomycin and reduces toxicity indicators: mutagenicity, reproductive dysfunction, carcinogenicity, visual toxicity.

STRUCT-PLM: ENHANCING PROTEIN REPRESENTATIONS WITH STRUCTURAL INFORMATION

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Protein representations are widely used in various tasks in bioinformatics. The growth of the number of publicly available protein sequences made it possible to apply top-performing approaches from natural language processing to the field of bioinformatics. Recently, large language models made a breakthrough in the protein representation learning [1, 2]. At the same time, structural information about any protein has also become available with the revolutionary method AlphaFold2 [3]. Current state-of-the-art approaches in dealing with protein 3D structures rely on graph neural networks, which have a big problem in maintaining molecule or protein rotation and translation invariance, resulting in complicated pipelines with high computational cost. Contrariwise, there is a ProstT5 approach [4] that already uses the knowledge about the protein structure together with protein sequences inside a protein language model. ProstT5 encodes information about tertiary interactions between residues. However, this model's protein representations mostly perform worse than a sequence-only ProtT5 model [2].

Our work introduces StructPLM, Structural Protein Language Model, a novel protein language model which uses both structural and protein sequence information in a novel way. The spatial structure of a protein is uniquely defined by the torsion angles of the protein backbone along with the position of all amino acid side chains. Since for each amino acid there are only several possible side chain conformations (or rotamers), which depend on the backbone torsion angles, one can encode the 3D structure of the protein with the combination of the amino acid type, backbone torsion angles and corresponding side-chain rotamers. This representation is rotation and translation invariant by design. We trained a small 12-layer RoBERTa model with a masked language modeling objective on more than 500 k structures predicted with AlphaFold2. Further, we finetuned it on 41k experimentally obtained protein structures from Protein Data Bank. To evaluate the quality of learned protein representations, we used them in the task of prediction of protein stability change (ΔΔG) due to single mutations. We used the concatenation of StructPLM and ESM2 embeddings to train ABYSSAL [5], a recently developed top-performing neural network for ΔΔG prediction. This approach scored first among other ΔΔG predictors on S669 [6] dataset increasing the Pearson correlation coefficient from 0.50 to 0.55 compared to ABYSSAL trained on ESM2 embeddings. At the same time, StructPLM embeddings alone perform on par with embeddings from a 12-layer ESM2 model of the same size. Overall, StructPLM offers an opportunity to easily enhance protein representations of large language models. Furthermore, there is a potential for increasing the quality of protein representations with training larger models.

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INVESTIGATION OF *LEISHMANIA DONOVANI*'S KEY PATHWAYS BY COMPARATIVE NETWORK ANALYSIS TO UNCOVER NEW THERAPEUTIC TARGETS

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The emergence of many computational biology disciplines, including Bioinformatics, System Biology, has provided ample opportunity to research and identify effective therapeutic compounds for diseases by using *in silico* methodologies. Leishmaniasis, a serious health issue impacting 88 nations, is a vector-borne sickness spread by the bite of female sandflies (Phlebotomine). East Africa and the Indian subcontinent states like Bihar, West Bengal, and Uttar Pradesh are said to be most affected regions by the illness. There are other clinical forms, including diffuse cutaneous leishmaniasis, mucocutaneous leishmaniasis, and visceral leishmaniasis (VL). *Leishmania donovani* causing VL has been described as the most severe type, which can be deadly. Due to developing resistance against existing medications, increase in costs, toxicity and side effects of available treatments there is an urgent need for new efficient drugs.

Finding a common drug targets for multiple pathways could be an effective strategy to eliminate the pathogen and to treat VL. This study focuses to explore disease associated pathways followed by a comparison of the networks and identification of a common hub proteins by integrating the behaviour of proteins linked through a protein-protein interaction (PPI) network. There are three primary steps in the research technique. The first step involves retrieving data on pathways and enzymes specific to *L. donovani*. The second step involves building a network using information on protein-protein interactions that were obtained from web databases. Finally, in the third step, the networks are subjected to topological analysis and gene enrichment analysis. For this study we have selected five essential pathways. First, we compared two carbohydrates metabolic pathway - glycolytic pathway (GP) and pentose phosphate pathway (PPP) with glutathione metabolic pathway (GMP). Next, we have compared two nucleic acids metabolic pathway - purine metabolic pathway (PuMP) and pyrimidine metabolic pathway (PyMP) with GMP. These pathways are essential for parasitic survival as they perform significant functions such as ATP supply, defence against oxidative stress, maintenance of cellular redox potential, majority of the cellular essential processes, etc. From databases we have collected a total of 16, 15, 18, 24, and 18 enzymatic reactions for GP, PPP, GMP, PuMP, PyMP, respectively. PPI with associated enzymes were then constructed and the topological analysis were done using Cytohubba plug-in of Cytoscape. The high betweenness centrality (BC), bottleneck, closeness centrality (CC), degree (k), along with other centrality measures analysis assisted us in identifying a total of four proteins, which were top ranked. Gene ontology (GO) analysis reveals number of genes associated with GO terms corresponding to molecular functions, cellular components and biological processes. According to the MCODE analysis, proteins from top modules contains those four proteins with the highest degree, closeness, and BC values.

In conclusion, we are proposing two common targets from three different pathways and another two common targets from two discrete pathways. Previous reported studies have also supported our proposed tentative targets as potentials drug targets. For further analysis, small molecule-based anti-leishmania inhibitors would be screened from various databases that will help us to gain insights towards drug development taking them as therapeutic targets.

IN SILICO SCREENING OF COMMERCIAL DRUG-LIKE COMPOUNDS FOR COVALENT INHIBITION OF TC80: INSIGHTS INTO MECHANISM AND PROMISING CANDIDATES FOR THE TREATMENT AGAINST CHAGAS DISEASE

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Chagas disease (CD), an endemic tropical illness prevalent in Latin America caused by the protozoan parasite Trypanosoma cruzi (T. cruzi), is accountable for approximately 12,000 fatalities annually, exhibiting a mortality rate ranging from 1.5% to 51%. Currently, there are only two therapeutic agents for the management of CD, nifurtimox (Lampit) and benznidazole (Rochagan). These medications exhibit efficacy exclusively during the acute or early phases of infection; however, their long administration can result in unfavorable effects. Tc80, a serine protease enzyme in T. cruzi, is involved in parasite maturation and invasion. Studies have tested many inhibitors targeting Tc80, highlighting a selective irreversible inhibitor Chloromethyl ketone TIC derivative (1A) [1]. Covalent drugs offer a viable alternative featuring higher target affinity and longer shelf life. This study aims to identify drug-like compounds with chloromethyl ketone warheads from covalent commercial databases as potential candidates for Tc80 inhibition, through virtual screening based on similarity with 1A, activity probability, ADME properties, as well as Molecular Docking based on the study of inhibition mechanism by DFT. The selection of templates for the construction of the 3D secondary structure model of Tc80 was executed through the Swiss-Model web server. Then, the best model was refined using the GalaxyWeb server and validated using the SAVESv6.0 structure validation web server. On the other hand, the compounds were extracted from Life Chemicals, ChemDiv, Enamine, ChemSpace, and CovalentInDB building a library of 2842 unique molecules from which 1542 resulted in a similarity score above 0.7 using Ftrees software. The probability of the Serine protease unspecified inhibitor activity of these compounds was calculated with the PASSONLINE web server using 1A probability activity value as a threshold. Toxicity filtering was applied using the ProTox web server to avoid potential hepatotoxicity, immunotoxicity, mutagenicity, and cytotoxicity. Pharmacokinetic filtering was applied using the SwissADME web server searching for compounds with high gastrointestinal absorption, avoiding PAINS alerts and activity with cytochrome P450 family resulting in 122 compounds. The 122 compounds were covalently docked against HIS667 residue of Tc80 by SeeSAR 13.0.1 software and estimated affinity were determined. We obtained promising compounds with better-estimated affinity than 1A, highlighting compound C1794 that presented multiple interactions with residues of the active site, including a hydrogen bond with the residue SER548 of the catalytic triad of Tc80. The reaction mechanism proposal employed the Density Functional Theory (DFT) methodology, the level of theory that was used for the optimizations were B3LYP/6-311G (d, p) and B3PW916-311G (d, p). The mechanism began with the ligand binds to the enzyme by two covalent bonds, the first from the carbonyl carbon of the ketone of the ligand with the deprotonated serine, which produced the tetrahedral adduct. The next step was followed by the formation of an epoxy ring releasing the chlorine atom, then the binding of histidine with the ligand led to the inactivation of the Tc80 protein. Population analysis revealed that the mechanism predominantly exhibited synchronicity, substantiated by the notable magnitudes of the Wiberg synchronicity index. Additionally, a comprehensive investigation of non-covalent interactions was conducted at every phase of the reaction. In summary, through the amalgamation of virtual screening, computational protein modeling, and structural insights, this exploratory research offers a valuable step toward advancing Chagas disease treatment strategies.

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GENERATIVE HETERO-ENCODER MODEL FOR DE NOVO DESIGN OF SMALL-MOLECULE COMPOUNDS AS POTENTIAL INHIBITORS OF BCR-ABL TYROSINE KINASE

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Currently, machine learning methods have been significantly developed and are used to solve many problems related to various fields of science and technology. Application of these methods in bioinformatics, cheminformatics, and medicinal chemistry has accelerated the development of new drugs and increased the effectiveness of pharmaceutical research programs. Development of efficient deep learning algorithms has given impetus to the formation of a new line of research focused on de novo design of molecules with preset pharmacological properties and synthetic availability. To date, a large number of generative deep learning models which have demonstrated the promise of their use for generating new drug candidates have been proposed [1]. However, despite these models are becoming more common in bio- and cheminformatics, their potential in this area has not yet been fully exploited. In this regard, the development and application of deep generative methods for computer-aided drug design are of great scientific and practical importance.

In this study, a deep generative neural network based on the hetero-encoder model was developed and used in combination with molecular modeling tools for de novo design of small- molecule compounds that can inhibit the ATP-binding site of the native and mutant ($T^{315}I$) Bcr-Abl tyrosine kinase, the enzyme playing a key role in the pathogenesis of chronic myeloid leukemia (CML) [2]. To reach the object of view, the following studies were carried out: (i) development and implementation of the hetero-encoder architecture, an improved version of the autoencoder capable of simultaneously processing input data on a molecule in several different formats, allowing one to get more stable and cost-effective generative models with improved results compared to autoencoders, (ii) assembly of a training library of small molecules potentially active towards the native and mutant Abl kinase which is resistant to a number of anticancer drugs used to treat patients with CML [2], (iii) training of the neural network on a set of drug-like compounds from the assembled molecular library followed by validation of the learning outcomes, (iv) generation of a wide range of potential Abl kinase ligands with the given threshold value of binding free energy using the developed neural network, (v) molecular docking of the generated compounds with the ATP-binding site of the enzyme, (vi) analysis of the data from molecular docking and selection of lead compounds promising for the development of novel inhibitors that can block both the native and mutant Abl kinase.

As a result, four top-ranking compounds that exhibited the low values of binding free energy comparable with those calculated by the same computational protocol for the FDA-approved anticancer drug Ponatinib were selected as the most probable dual-targeted inhibitors of the ATP-binding site of the enzyme. These findings testify to that the developed neural network is a promising computational model for de novo design of small molecules potentially active against the native and mutant Abl kinase, as well as can be used to develop novel, potent and broad-spectrum anticancer agents.

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A COMPREHENSIVE DATABASE FOR PREDICTING METABOLISM OF XENOBIOTICS BY HUMAN MICROBIOME

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The human intestine is inhabited by an estimated 10^{13} microorganisms collectively known as the gut microbiota [1]. Among these inhabitants, bacterial species play an important role in metabolizing xenobiotics, including pharmaceuticals, environmental contaminants and drugs. The latter have a crucial impact on the efficacy and safety of pharmaceutical treatment. Drug metabolites produced by the human gut microbiota can differ drastically in their basic properties, including lifetimes, bioavailabilities, and biological effects. Understanding these complex interactions is important for drug development.

In vitro studies of microbiome metabolism are challenging due to the complexity and variability of the gut microbiota, resulting in a large investment of time and resources. The *in silico* method allows microbiome researchers to reduce a number of candidates for *in vitro* testing by generating valid hypotheses prior to labor-intensive studies. However, the computational approach also has a number of limitations. One of the biggest challenges in creating an *in silico* tool to facilitate the work of microbiome research is the lack of compliance data that may use as training set. Incorporating such data into *in silico* drug development approaches provides a good basis for the creation of predictive models to evaluate xenobiotic biotransformation pathways in the human gut, taking into account the influence of the gut microbiota.

To address this challenge, our work has resulted in a new database containing a wide range of data on 368 structures metabolized and 310 structures not metabolized by the human gut microbiota. Information about metabolizable compounds includes their metabolites and specific genera and species of gut microbiota responsible for their metabolism, as well as information about the consequences that biotransformation leads to. All data presented in the database were extracted from scientific publications.

The usability of the database is validated by building a working model of MDM-pred. This is a web service that uses our database as a training set to predict incoming structure metabolites and the bacterial genera that may be driving this metabolism [2].

The created database is freely available on the Internet (http://www.way2drug.com/hgmmx). For informational needs it allows user to perform a search query on the names of parent compounds, metabolites, reactions, genera and species of bacteria. To build computational models, our database allows downloading the structures of chemical compounds as SDF or CSV files.

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FIRST QSTR REPORT ON RAT'S CHRONIC AND SUB-CHRONIC TOXICITY OF DIVERSE CLASS OF CHEMICALS

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Humans and other living species of the ecosystem are constantly being exposed to a wide range of chemicals of natural as well as synthetic origin. A wide multitude of compounds exerts profound long-term detrimental health effects. The chronic toxicity profile of chemicals is of utmost importance for long-term risk assessment. Experimental testing of chronic toxicity of compounds, apart from being resource intensive in terms of time, limited availability of experimental data, and associated cost, is not always a feasible option considering the magnitude of the number of chemicals, which necessitates utilizing in-silico approaches to overcome the associated limitations. Herein, QSAR (Quantitative Structure-Activity Relationship) models were developed employing the regression-based PLS method with strict adherence to the OECD guidelines. For this study, the chronic and sub-chronic toxicity datasets with LOEL and NOEL as the endpoints were used for model development. The validated models are robust, reliable, and predictable. The statistical results of the models are as follows: :-0.6-0.96,:-0.51-0.96, and :-0.52-0.96. From the validated models, it was concluded that lipophilicity, electronegativity, presence of aromatic ethers or aliphatic oxime group, presence of complexity in the structures, state of unsaturation in molecules, and presence of halogen and heavy atoms (phosphate, sulphur, etc.) are responsible for chronic/sub-chronic toxicity. The QSAR models developed in our study can be utilized for effective gap-filling of toxicity data sets, categorization, and prioritization of chemicals along with chronic toxicity prediction of new synthetic compounds.

Edgar – A DEEP LEARNING-BASED PROGRAM FOR PREDICTION OF FOLDING ENERGY OF NUCLEIC ACIDS

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Nowadays there are a number of discovered noncoding RNA variations participating in different cell processes. The spatial structure is important for functioning of ribosomal RNA, transport RNA, small nuclear RNA, small nucleolar RNA, microRNA and matrix RNA. It also provides the possibility of ribosome interaction or RNA interference, etc. Alteration of RNA spatial structure is important for riboswitches action. Knowledge about the secondary structure makes it possible to predict RNA functions and properties. Experimentally, secondary structure of a single chain RNA is obtained with physical (X-Ray crystallography, NMR, CryoEM) or modern sequencing methods (NGS) with chemical modifiers (DMS-seq, Structural-Seq, icSHAPE and others). Despite the diversity of the experimental methods, the data on secondary structures is still limited. To overcome this problem different prediction methods are used. RNA secondary structure prediction methods based on homology modeling, dynamic programming and deep learning. Homology-based prediction requires a large number of different RNA structures. The dynamic programming methods are based on finding minimum energy using scoring functions and require a set of thermodynamic or statistical parameters. Deep learning based methods show a high potential in prediction tasks, but require experimental data to be trained on. Most of the secondary structures known for today are obtained by NGS methods, however their quality is questionable. We present Edgar – a deep learning based program for assessing the nucleic acids folding energy. Edgar predicts the folding energy, which characterizes stability of a certain nucleic acid conformation, using only its secondary structure without spatial information. It can be used in modeling for a nucleic acid stability evaluation. It works for both RNA and DNA with high quality *R2* – 0.958, *RMSD* – 36.478 kkal/mol. Edgar has a fast inference time within 100 ms and also evaluates an uncertainty of its own prediction. With Edgar it was shown that modern RNA datasets and benchmarks used in model training contain mostly low quality secondary structures compared to physical methods datasets.

ARTEMIS: STUDYING THE COMMUNICATION OF BIOMOLECULES USING INFORMATION THEORY

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Allosteric communication is an important internal mechanism of functioning of biomolecular systems that regulates the interaction of proteins in the cellular environment. The binding of the effector in the allosteric site leads to conformational changes in the protein, due to which its functional activity changes. The study of allostery is of fundamental importance and helps in the understanding of diseases, the development of drugs, and the description of physiological cell signaling [1]. Currently, there are many experimental and computational methods for studying allostery. Among the former, NMR should be noted as a powerful tool to assess the conformational dynamics of biomolecules and associated allosteric effects. Theoretical models of allosteric communication based on the analysis of the spatial structure of proteins and/or molecular dynamics (MD) data are also being developed [2].

We propose a universal information-theoretical approach to treat allostery, implemented in the form of the ARTEMIS software package written in Python/C++ (https://github.com/nalsur-veallam/ARTEMIS). The method is based on the analysis of mutual information (MI) matrix for all pairs of residues in the protein, obtained from MD data using the PARENT software package [3].

First, conformational assemblies are obtained via MD simulation carried out in internal molecular coordinates (bonds, angles, dihedral angles). Based on the MD data, distributions are calculated for each internal degree of freedom, as well as for each pair of degrees of freedom, which makes it possible to obtain entropy and mutual information values [4]. A distinctive feature of this algorithm is that a priori no assumptions are made about the specific structure of the molecule and the nature of communication itself. This, allows the method to be used to study disordered and unstructured systems. By examining the MI 2D matrix, one can determine strongly coupled positions (residues) in a biomolecule (e.g., in a protein), reconstruct communication network, characterize a perturbation induced by an interacting partner, and assess specific contribution of different molecular regions to communication.

We illustrate the potential of the framework by analyzing of the SARS-CoV-2 spike receptor-binding domain (RBD) and its complex with Angiotensin-converting enzyme 2 (ACE2) using data from microsecond MD simulations.

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EXPANDING THE EPIGENETIC RELEVANT CHEMICAL SPACE: IDENTIFICATION OF DNA METHYLTRANSFERASE I ACTIVATORS

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The DNA methyltransferase family regulates the DNA methylation process. There are two types of methylation processes: *de novo* and maintenance methylation. *De novo* methylation is carried out by the enzymes DNMT3A and DNMT3B during early gametogenesis and embryogenesis. On the other hand, DNMT1 of maintenance methylation, in cooperation with the enzymes DNMT3A and DNMT3B [1, 2].This project is focused on DNMT1 due to its importance in maintenance methylation. This protein contains a C-terminal catalytic domain and a N-terminal regulatory region [3].Today there are no approved drugs that activate the catalytic activity of DNMT1 enzyme, only inhibitors, however, for several research groups it has been considered that it is an area that should not be left aside, since it could be another way to treat some types of cancer. The goal of this project is to identify activating molecules for DNMT1 enzyme capable of being investigated as a possible drug against diseases that are faced due to DNA hypomethylation. For that objective, a research was made for compounds that have been reported as activators of the catalytic activity of the enzyme DNA methyltransferase 1 to have them as a reference. Subsequently similarity searching was carried out to find new molecules with activating properties of the catalytic activity of DNMT1 enzyme to finally carry out the biochemical assays of enzymatic activity. Enzymatic activity assays were conducted on ten small molecules commercially available. Six were found to activate DNMT1 with an enzymatic activity greater than 150%.

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DEVELOPMENT OF A STANDARDIZED APPROACH FOR TRANSFER LEARNING WITH QSAR MODELS

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Transfer learning, is a machine learning technique that can use different datasets/models to improve the performance of a target task. Although widely used in the broader data science community, were transfer learning and fine tuning of extremely large pre-trained models on more specific tasks is common, this technique still lacks the same degree of applicability and usability on chemical problems. The few published instances of the usage of this technique in the cheminformatics community are more focused on improving the task at hand rather than discuss the transfer learning process itself. Notably, the current literature lacks articles discussing how transfer learning improves performance on chemical datasets, when transfer learning should be used and, most importantly, which datasets/models should be used as source domains for the task of interest [1]. Therefore, unless expert knowledge of the techniques and underlying datasets is available, transfer learning cannot be properly applied.

First, we aim to understand when transfer learning should be used, which datasets should be used as sources for a specific transfer and how to avoid spurious transfers. Secondly, we developed several transferability metrics to quantify how likely a transfer with a given source dataset will produce positive results. Based on these metrics, we create a transferability prediction algorithm that is capable of selecting promising source datasets for individual QSAR transfer learning tasks.

In order to simulate potential transfers, we used the datasets present in the ChEMBL database. After cleaning and pre-processing steps, we trained Random Forest classifiers for all available datasets in order to establish a baseline performance for each dataset. Then, we split the datasets into training and validation subsets and generated 50,000 random transfers between the datasets present in their respective subset using the Feature Augmentation domain adaptation algorithm. We compared these transfers with their equivalent baselines in order to establish their outcome (positive/negative) and developed transferability metrics based on the chemical space and endpoint information of the successful training set transfers. Afterwards, a Balanced Random Forest classifier was applied to the training subset, with the transfer outcomes as response variables and its related transferability metrics as features, this model was then evaluated on the validation subset for its capability to predict successful transfers. Lastly, we randomly selected 25 endpoints from the validation subset and applied the created algorithm in order to predict which datasets present in ChEMBL could be used as viable sources for each dataset selected. The potential source datasets predicted positive by the model were used for single-source and multi-source transfer learning.

The results demonstrate that although a significant transfer is very rare in the sample space, the transferability between datasets can be predicted in a reliable manner with appropriate metrics, with a massive increase in precision compared to random chance (140x increase). Furthermore, the transferability metrics patterns observed on the positive transfers match very well with their intuitive meanings and are clearly capable of separating to a considerable degree positive transfers from negative ones. The increase in performance when transfer learning was applied varied significantly across tasks, we observed an average MCC increase of 0.17 with single source transfer and average MCC increase of 0.42 with multi source transfer. Remarkably, we observed that human cell-lines are highly transferable amongst each other with cases of improper baseline models with negative MCC achieving upwards of 0.8 in some cases. The created algorithmic approach abstracts way the intrinsicalities of transfer learning and endpoint expertise, making it possible for anyone with basic machine learning knowledge to leverage the potential model performance increase of transfer learning.

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SEARCH FOR NEW ANXIOLYTIC SUBSTANCES BY NEURAL NETWORK MODELING USING MULTIPLE DOCKING

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According to the developed methodology of multiple docking [1] we have built an artificial neural network model that predicts the level of gamma aminobutyric acid type A ($GABA_A$)-agonistic activity depending on the docking energies spectrum of chemical compounds in 27 spaces of the target protein. Molecular mechanics (MarvinSketch 17.1.23 [2]) and quantum chemistry (MOPAC2012 [3]) approaches were used to optimize 3D models of ligand structures. We constructed 27 spaces for multiple docking in the 6D6T [4] 3D model of the $GABA_A$ receptor using the MSite v21.04.22 program [1]. With the AutoDock Vina 1.1.1 program [5] we performed ensemble docking. Neural networks were trained using the Statistica program [6]. The resulting model shows high prediction accuracy: total F_0=94.8%, highly active compounds (sensitivity) F_a=83.3% and not highly active compounds (specificity) F_n=96.4%.

We made a forecast of the level of anxiolytic activity of new derivatives of quinazoline-2,4(1*H*,3*H*)-dione. From the data obtained, it follows that one compound out of five should exhibit a high level of $GABA_A$-agonistic activity, comparable to the reference drug diazepam. The substance was synthesized and experimentally tested. It was shown that the compound, predicted as highly active, is comparable in terms of activity with the comparator drug diazepam, although somewhat inferior to it.

In the present study, new tricyclic benzimidazole derivatives were selected to predict the level of anxiolytic activity. According to the *in silico* prediction, nine compounds out of ten should have pronounced activity.

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CHEMOINFORMATIC ANALYSIS OF NATURAL PRODUCTS FROM MEXICO

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Natural products databases have great importance in drug discovery projects. Since 1981 to 2019 a total of 1881 molecules have been approved for clinical use, of which around 3.8% are unaltered natural products while around 18.9% are natural products derivatives [1]. Furthermore, chemical databases are part of the major cheminformatics tools. Chemical databases main objective is to store, organize, manage and to recover small molecules and their properties [2]. In natural products research there has been developed a variety of natural products databases which contain compounds from a specific geographic region. BIOFACQUIM [3] is one of the first natural products databases developed in Mexico, it includes around 500 compounds that have been isolated and characterized in the School of Chemistry at the National Autonomous University of Mexico. As new natural products are isolated each year in our country, the update of BIOFACQUIM is needed.

Our work aims to update and characterize the Mexican natural products database BIOFACQUIM using cheminformatics tools. In order to do this, bibliographic research has been done to explore projects in which new molecules were isolated and characterized from natural sources. Also, each article was read to extract the following information: Structure, SMILES, bibliographic source , information about the natural source (kingdom, genus and species), and location from where the natural source was collected. The data was curated using Molecular Operating Environment Software (MOE), version 2022.02. To characterize the new BIOFACQUIM´s version, six physico-chemical properties of pharmaceutical interest were calculated with Knime. The six properties were partition coefficient , topological polar surface area, molecular weight, number of rotatable bonds, number of hydrogen bond acceptors and donors. In the same way, a statistical analysis was done, which allows us to compare this dataset with eight reference compound databases (seven natural products databases and approved drugs).

A scaffolds analysis content of BIOFACQUIM was made to identify the most frequent scaffolds included in the data set. In order to generate a visual representation of the chemical space of BIOFACQUIM, two visualization methods were used: principal component analysis and t-distributed stochastic neighbor embedding.

BIOFACQUIM is an initiative to represent the diversity in natural products from Mexico. Its update and chemoinformatic characterization will allow the use of this dataset in future drugs discovery projects. The BIOFACQUIM update contains 605 natural products isolated in México and will be of free access.

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A NEW TARGET TO OVERCOME ABC TRANSPORTER ACCOSITED CHEMORESISTANCE OF TUMOR CELLS

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P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), transmembrane transport proteins of the ABC family, are ones of the integral elements of the cell. Their function consists in efflux of various undesirable compounds from the cell, including small molecule xenobiotics, and anticancer drugs are also considered by the cell to fall into this category. Thus, inhibition of ABC transporter activity is considered as a way to overcome drug resistance of tumor cells.

All proposed inhibitors of ABC transporters failed to show significant clinical efficacy, which indicates the need to find a new approach to inhibit these transport proteins. These compounds are united by a common mechanism of action: such substances bind to the protein cavity located inside the cell membrane, competing with the molecules transported by the protein.

The key point of the activation of ABC proteins is ATP binding to the nucleotide-binding domain (NBD), a conserved structural element of these transporters. The NBD blocking can lead to dysfunction of the transporters and a decrease in drug efflux. At the same time, it is advisable to consider compounds that are structurally similar to ATP, but functionally unable to provide the activation of transporters.

The aim of this work is to validate NBD as a new target for the transporter inhibition by studying the interaction of ATP mimetics (AMP, AICAR, ribavirin, own developments of the laboratory) with the ABC transporters and evaluating the biological activity of the compounds.

The affinity of the ATP mimetics to the ABC proteins was determined by semi-rigid docking within NBD and a protein cavity located inside the cell membrane. It was revealed that ATP and its analogues show low scores during the interaction with the substrate-oriented cavity of the proteins and high scores during the interaction with the nucleotide-binding domain. At the same time, the best simulation results were obtained when considering the closest ATP analogs, whose structure includes purine base, ribose, and phosphate group. The structural similarity of the compounds with ATP allow them to reproduce the nucleoside posing in NBD, which leads to a strong interaction of ATP mimetics with ABC proteins.

The biological activity evaluation of the ATP mimetics confirmed the results of computer modeling. The binding of the ATP mimetics to P-gp NBD that leads to a decrease in its ATPase activity was confirmed by luminescent analysis using the recombinant protein. The treatment with the ATP mimetics allowed us to increase the accumulation of the Hoechst 33342 dye, a substrate of the transporters, in human colon adenocarcinoma cells with ABC transporter-mediated chemoresistance, as well as to restore the sensitivity of chemoresistant cells to the cytostatic taxol.

Thus, the validity of the concept of creating NBD targeted efflux inhibitors proposed in the work was confirmed both *in silico* and *in vitro*. Based on these findings, NBD can be considered as a new target for the design of ABC transporter inhibitors that increase the effectiveness of antitumor therapy.

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PREDICTION OF TOXICITY ENDPOINTS AS A PATHWAY TOWARDS MINIMISING RISKS IN DRUG DEVELOPMENT

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Medicinal chemistry filters are guidelines or rules used in drug design&development to help identify molecules with desired properties and increase their chances of success in drug development. These filters such as PAINS [1], Ro5 [2], Veber rules [3], etc. are typically derived from the knowledge of previous successes and failures in drug discovery and help medicinal chemists prioritize and select potential hit compounds or drug candidates for further H2L or L2D programs. It's worth mentioning that satisfying these filters do not always guarantee success; however, they provide useful guidance to medicinal chemists and drug discovery scientists. They help prioritize compounds for further testing and optimization, increasing the likelihood of finding successful drug candidates.

Our work aims to construct toxicity models via machine learning techniques which can be used as medicinal chemistry filters. It is important to note that such filters can minimize risks of bringing drugs with severe side effects to clinical trials or (even) to the market. We performed analysis of state-of-the art methods of toxicity prediction. We decided to compare complexity of the methods (including the complexity of their implementation in typical industrial environments) with their efficiency of toxicity prediction.

In our report we will present results of this study and some general remarks about current trends in this field. We will also discuss potential problems as well as some ideas how to overcome them.

In short - we discovered that most useful algorithms for this task are CatBoost and GCN. Our study revealed that at their current stage of development FCNN, AutoML, other gradient boosting methods (XGBoost or LightGBM) or simpler approaches such as Linear Regression are not so effective for this task. We will present models with an improvement on classification and regression problems for some endpoints from TOXRIC, Tox21 and previous publications [4-6].

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ABSTRACTS

SYNTHESIS AND MOLECULAR DOCKING STUDIES OF SOME PYRANO[2,3-C] PYRAZOLE DERIVATIVES AS AN INHIBITOR OF SARS-CORONAVIRUS 3CL PROTEASE

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The coronavirus (SARS-COV-2) causing COVID-19 diseases was detected for the first time in the Hubei province of china then spreading to several countries, which have created a real threat to the human population worldwide. In humans, coronaviruses infect the lower respiratory tract and induce the common cold. This alarming situation worldwide needed the researchers' intervention to discover an effective drug therapy able to block the viral replication of this virus. Therefore, finding an inhibitor for COVID-19's protease may be the first step to beating this contagious respiratory illness.

In order to achieve this goal, some heterocyclic compounds, namely Pyrano [two, 3-c] pyrazole have been identified in the current study as inhibitors due to their wide biological deeds, including antiviral proprieties. Five pyrano [2,3-c] pyrazole compounds 5(a-e) was targeted against the Main protease (Mpro), which plays a vital role in the replication and transcription of the Corona viral genome. The 3CL Protease (PDB ID 6LU7) was modeled, and the compounds were docked using Autodock Vina software and ADMET data have been studied via siwss ADMET tools [1].

All synthesized compounds were well engaged into the active site of the main protease with strong hydrogen bond interaction and a good score of energy. The 5b have been classed as the best inhibitor with an energy score of -6.2 kcal/mol, similar to the one given by Favipiravir. Moreover, the molecular interaction studies showed that protease structure had multiple active site residues for all studied compounds. Our finding confirms the potential of these derivatives as lead compounds against the selected target protein of coronavirus, which needs further analysis and dynamic simulation studies to propose then develop a new antiviral treatment that can be added to the literature surveys on the existing antiviral drugs.

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PHENOLIC WONDER MOLECULES: A NETWORK PHARMACOLOGY APPROACH FOR THERAPEUTIC EXPLORATION

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Antimicrobial resistance (AMR) presents a pressing global concern in today's healthcare landscape. The ongoing development of resistance has led to an alarming increase in infections that are challenging to treat effectively. Phenols are organic compounds with a hydroxyl (-OH) group directly attached to an aromatic ring. They display diverse chemical and biological traits, piquing interest across research areas. Phenolic compounds are notable for their various biological effects. Several act as antioxidants, countering detrimental free radicals in the body for potential health gains. Furthermore, phenols showcase antimicrobial, anti-inflammatory, & anticancer properties. With distinct molecular structures & broad therapeutic impacts, phenols hold promise for novel drug development. Therefore, this work aims to apply network pharmacology approach to some synthesized phenol molecules whose antimicrobial potential and toxicity profiles have been studied. Computational models were employed to investigate the absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of the compounds. The protein targets linked to the growth & virulence of microorganisms were identified using the PharmMapper server. A network based on string interactions was established & assessed using Cytoscape. Through a topological evaluation of the network, targets were screened based on their degree values. The analysis identified & filtered 22 targets in *Klebsiella pneumoniae* & 13 targets in *Staphylococcus aureus*. These identified targets were collected & integrated into a pathway enrichment analysis, utilizing PANTHER database & KOBAS 3.0. The predominant hub genes in *K. pneumoniae* were linked to secondary metabolism biosynthesis, while in *S. aureus*, they were connected to glycolysis, followed by carbon metabolism. To further investigate, molecular docking was employed to uncover the most potent target & explore the interactions between phenolic compounds and the chosen potent targets. This analysis was subsequently confirmed through molecular dynamic simulations.

The results demonstrated varying degrees of antimicrobial activity among the tested phenolic compounds, with some compounds exhibiting potent inhibitory effects against both *K. pneumoniae* & *S.aureus.* The *in silico* analyses provided insights into the binding modes of the phenolic compounds with microbial target proteins & potential mechanisms of action. This comprehensive study contributes to the understanding of the antimicrobial potential & toxicity considerations of selected phenolic compounds. The computational approach offers a holistic perspective on the compounds' biological activities, aiding in the identification of promising candidates for further development as antimicrobial agents. Further investigations can build upon these findings to explore the compounds' efficacy in more intricate biological contexts, potentially leading to practical applications in the domain of infectious disease management.

DESIGN, SYNTHESIS AND EVALUATION OF TRIAZOLOPYRIMIDINES AS POSSIBLE GSK-3 INHIBITORS AND/OR ANTIGLYCATING AGENTS

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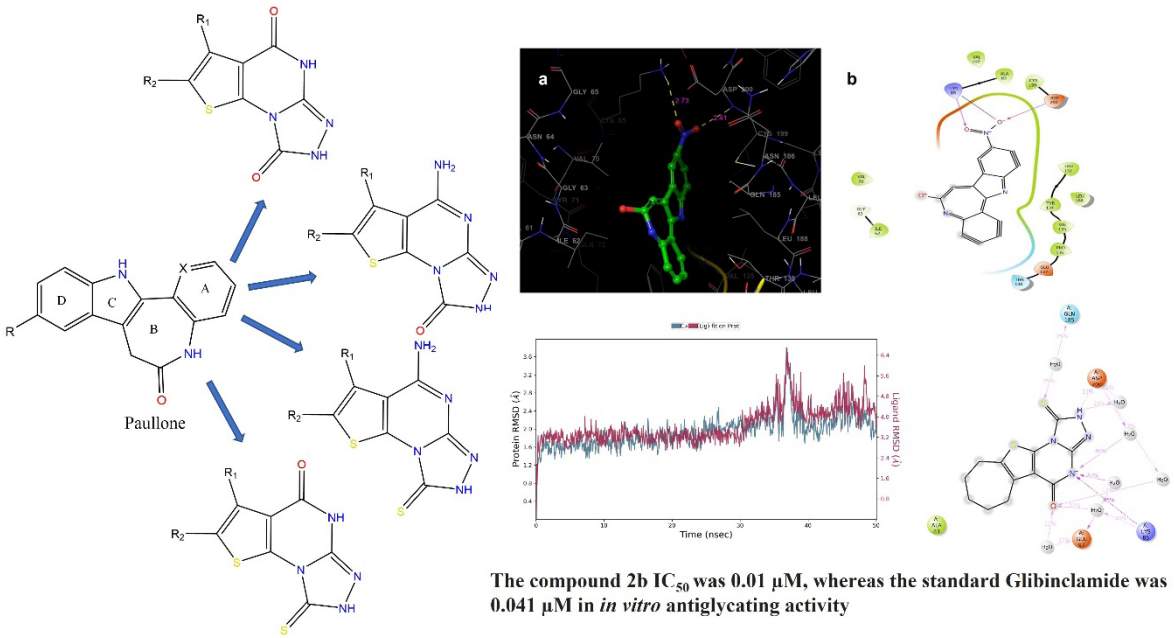
Paullones are a class of chemical structures from 7, 12-dihydro-indolo [3,2-*d*] benzazepin-6-(5*H*)-ones and were found to be having applications in the treatment of neurodegenerative and cancer disorders. Thiophenes and quinazolines possess an extensive spectrum of pharmacological activities. In the present investigation novel triazoloquinazolines **1a-b, 2a-b** and triazolothieno [2,3-*d*] pyrimidine derivatives **3a-h, 4a-h** were synthesized that are structurally related to paullones. The synthesis of novel triazoloquinazolines is achieved through Niementoski reaction, which involves the condensation of anthranilic acid with urea. The synthesis of triazolo thienopyrimidines was performed through the Gewald reaction, which was typically base catalyzed condensation of a ketone or aldehyde with α-cyanoester and elemental sulphur. They were subjected for evaluation of *in vitro* antiglycating activity and GSK-3β Protein binding activity were studied by docking method.

All the synthesized molecules were characterized by spectral analysis along with physical data. All the tested compounds were actively inhibiting the glycation in micro molar range. Specifically, the compounds containing substitution of ketone on pyrimidine ring (2b, 2c, 2d, 3b and 3c) were found to be more potent among the others along with standard Glibinclamide. The compound 2b was found to be the potent molecule (IC_{50}=0.01 µM) compared with the standard (IC_{50}=0.041 µM). The hydrogen bond forming capability of the molecules was found to be the key for their activity. The series of novel triazoloquinazolines and triazolo thienopyrimidines were synthesized and tested for the *in vitro* antiglycating potential. Some of the compounds have shown better activity than the standard compound. However, further investigations are to be performed to identify the ideal triazolo pyrimidine derivatives for clinical applications in the diabetes and Alzheimer's Disease.



The compound 2b IC_{50} was 0.01 µM, whereas the standard Glibinclamide was 0.041 µM in *in vitro* antiglycating activity

MOLECULAR DOCKING ON 5-LIPOXYGENASE, LIPOPHILICITY AND IONIZATION CONSTANTS IN THE STUDY OF THE "STRUCTURE-ANTI-INFLAMMATORY ACTIVITY" RELATIONSHIP IN A SERIES OF AMIDES AND HYDRAZIDES OF N–AROYL SUBSTITUTED HALOGEN(H)ANTHRANILIC ACIDS

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Inflammation is one of the body's defense mechanisms, it helps protect the body from foreign bodies, injury, and microbial infection. It can be acute or chronic if local acute inflammation remains uncontrolled, this can lead to chronic or systemic serious inflammatory disorders. Arachidonic acid is one of the main components of phospholipids of cell membranes and acts as a normal substrate for various enzymes, such as: 5-lipoxygenase (5-LOX) and cyclooxygenase (COX).

The aim of the work is to study the dependence "structure-anti-inflammatory activity (AIA)" based on molecular docking by the enzyme 5–LOX program AutoDock 4 using scoring functions and lipophilicity and ionization constants in a series of amides and hydrazides of N-aroyl substituted halogen(H)anthranilic acids.

Progress, in comparison with previous studies, consists in expanding the number of targets in the study of the structure-activity relationship, as a result, the number of application points of models for the search for new drugs with the selected biological activity increases. Earlier studies of the dependence of anti-inflammatory and analgesic activity on the scoring functions of COX 1 and 2 in a number of anthranilic acid derivatives have shown good results [1, 2]. The study of the relationship "structure-anti-inflammatory activity" using 5-LOX will allow, separately and in combination with COX 1 and 2, to assess the prospects for the use of poly-enzyme models in predicting AIA.

Modeling of ligand–receptor interactions was carried out by the AutoDock 4.0 program as part of the MGL Tools 1.5.6 software package, using a three-dimensional model of the 5-LOX molecule, information about which was obtained from the RCSB Protein Data Bank database: PDB ID code: 3V99 [3].

Multiple linear regression analysis was performed using the Statistica 6 program by step-by-step inclusion of parameters, the dependence of the AIAexp. from scoring functions ($Be_{5\text{-}LOX}$, $Ime_{5\text{-}LOX}$, $Ki_{5\text{-}LOX}$) and calculated values of physico-chemical descriptors ($logP_{calc.}$, $pKa_{calc.}$, $pKb_{calc.}$). As a result, three equations were chosen with the highest values of the multiple regression coefficient (R), the Fisher criterion (F) and the minimum value of the mean quadratic error (S) of the AIAexp. dependence from the descriptors $logP_{calc.}$, $Be_{5\text{-}LOX}$, $Ime_{5\text{-}LOX}$, $Ki_{5\text{-}LOX}$. The coefficient of determination of predictions Q^2_{LOO} is determined, showing the significance of the compiled equations. The highest value of Q^2_{LOO} is obtained for equation No. 1 ($Q^2_{LOO} = 0.60$). The analysis of the prediction of AIA on an external sample of 6 compounds of anthranilic acid derivatives using regression equation 1 (AIAcalc.1) was performed. A high value of the correlation coefficient (Rpred.) of the predicted values of AIA (AIAcalc.1) with experimental values equal to 0.776 and the minimum value of the standard deviation of the forecast (Spred. = 9.61).

The obtained results of the "structure-anti-inflammatory activity" studies in the form of an equation will be used to search for new biologically active compounds with AIA in a number of anthranilic acid derivatives that are planned to be synthesized.

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IDENTIFICATION OF M6A MODIFICATIONS IN THE HEPG2 CELL LINE USING DIRECT RNA-SEQ OXFORD NANOPORE TECHNOLOGIES

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The alphabet of the building blocks of RNA molecules greatly exceeds the standard four nucleotides due to post-transcriptional biochemical modifications of these nucleotides. Some of these modifications play an important role in the functionality of the entire RNA, while others serve as dynamic markers that regulate the fate of specific RNA molecules. Together, these modifications form the epitranscriptome, a significant biochemical layer within the cell.

One of the most common post-transcriptional modifications is N6-methylacinosine (m6A), which has been associated with various diseases, including liver cancer. The aim of our study was to detect m6A modifications in the HepG2 cell line, which is a widely used model of the liver in various studies ranging from oncogenesis to the study of cytotoxicity of substances on the liver.

To detect m6A modifications, we used triplicate direct RNAseq (Oxford Nanopore) data for the HepG2 cell line. Data analysis was performed using Guppy software (version 6.2.1) and Minimap2 (version 2.24-r1122). The search for m6A modifications was carried out using the nanopolish (version 0.14.0) and m6anet (version 2.0.2) algorithms.

As a result of the analysis, we found 2227 modification sites in 1044 genes that are involved in the histone ubiquitination, regulation of transcriptions and signaling processes. Interestingly, the histone ubiquitination process is important for the development of oncogenesis. The maximum number of modification sites for one gene was 15, and the minimum was one. We found 171 genes with the modification sites were repeated between three repetitions. These genes are involved in pathways important for the development of oncogenesis and apoptosis, such as ubiquitination, insulin-like growth factor receptor binding, death domain binding and misfolded protein binding.

The results obtained may be of significance for further research and the search for new approaches to the diagnosis, drug development and treatment of liver cancer.

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DESIGN AND EVALUATION OF NOVEL SMALL MOLECULE ACTIVATORS FOR *AMPK*: AN *IN SILICO* APPROACH

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AMP-activated protein kinase (AMPK) plays an important role in regulating energy homeostasis in eukaryotic cells. AMPK is an attractive therapeutic target for managing metabolic diseases such as type 2 diabetes and cancers[1-3]. Nowadays, In Silico study and evaluations are applied through virtual screening tools, such as molecular docking simulations and predictions of ADMET-related properties to investigate new potent activators for target proteins. The molecular docking simulation is performed to achieve the best binding affinity and docking scores. This is done by comparison between the standard recently reported activator and high-scoring selected ligands. Using data servers' libraries as PubChem, some similar compounds selected and simulation molecular docking has occurred. Active site was studied and newly selected ligands were applied to molecular docking simulation in active site and other active cavities in target protein. The results were evaluated and high quantities in binding affinities were selected as candidate ligands. Then prediction of ADMET related properties occurred using *ADMETLab 2.0* and prediction results were compared with molecular docking results. Finally, 5-[[6-chloro-5-(3-methyl-1*H*-indol-5-*yl*)-1*H*-benzimidazol-2-*yl*]oxy]-2-methylbenzoic acid and 6-[2-(3-carboxy-4-methylphenoxy)-6-chloro-1*H*-benzimidazol-5-*yl*]-3-methylindole-1-carboxylic acid have best results and must be considerate as potent activator for AMP-activated protein kinase.

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PHARMACOPHORE-GUIDED VIRTUAL SCREENING FOR RAF-1 KINASE INHIBITORS: IDENTIFYING POTENTIAL THERAPEUTIC COMPOUNDS

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The Raf-1 proto-oncogene, also known as Raf1, is a key component of the RAS/RAF/MEK/ERK signaling pathway, which plays a crucial role in transmitting signals from the cell surface to the nucleus in response to various extracellular stimuli. This pathway is involved in regulating several cellular processes, including cell growth, proliferation, differentiation, survival, migration and apoptosis. The Raf-1 kinase has been a validated target for cancer treatment and has attracted significant research interest in the field of oncology. The downregulation of Raf-1 protein holds significance in context of highly aggressive and drug-resistant tumors, such as triple-negative breast cancers (TNBCs). In case of TNBCs, the therapeutic interventions are limited, only chemotherapy, radiotherapy and surgery are available options. Therefore, the need of investigations for the drug targets are in demand for the better treatment of TNBCs. Over the years, several compounds have been reported, such as Raf-1 kinase inhibitors but the development of more inhibitors is essential for overcoming challenges associated with cancer treatment, such as multi-drug resistance, side effects and limited efficacy. By expanding the range of available inhibitors, researchers and clinicians can offer more targeted and effective treatment options to patients, ultimately improving their outcomes and quality of life.

In order to identify potent and selective inhibitors of Raf1 kinase, we developed a hierarchical ligand-based virtual screening methodology. 72 Raf1 kinase inhibitors with known experimental activity were used to build ligand-based pharmacophore models using Schrodinger suite 2023-1. The molecules were first docked in the crystal structure of B-Raf and then the best poses were selected and clustered on the basis of Tanimoto similarity. The developed pharmacophore model underwent validation and was employed to screen the phytochemicals from Zinc15 database. The compounds that matched the criteria of pharmacophore were subjected to molecular docking to identify potential hits with novel scaffolds. Compounds exhibiting low binding energies and best interaction pose were selected as the final hits. Molecular Dynamics simulations were carried out for the top 10 best hits followed by MM-GBSA analysis to validate the potential of the screened compounds.

The present study will potentially simplify the identification and strategic development of new compounds that possess strong inhibitory properties. The approach employed in this study holds substantial significance in designing drugs targeting Raf-1 kinase due to its pivotal role in cellular signaling pathways and its implications in various cancers including breast cancer, particularly TNBCs.

LIGAND-BASED PHARMOCOPHORE MODELING AND VIRTUAL SCREENING STUDY TO IDENTIFY NOVEL CANNABINOID RECEPTOR TYPE 2 INHIBITORS

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Cannabinoid receptor type 2 (CB2) is a crucial component of the endocannabinoid system which is primarily found on immune cells, peripheral tissues and cells involved in immune response modulation. It plays a significant role in regulating immune functions and inflammation. CB2 antagonists could be used to modulate the immune response and inflammation in conditions like inflammatory bowel disease, rheumatoid arthritis and other autoimmune disorders. By blocking CB2 receptor these antagonists may help reduce excessive immune responses. The therapeutic potential of CB2 receptors is hindered by their propensity to cause adverse effects, rapid tolerance development and potential for abuse due to their involvement in the central nervous system. Developing drugs that selectively target CB2 receptors to minimize these issues remain a challenging goal for utilizing their medical benefits effectively. It is essential to address the challenges related to adverse effects and abuse potential while further investigating the therapeutic applications of CB2 molecules in clinical trials. In this study ligand-based method was used along with virtual screening of database compounds to obtain potent and selective CB2 inhibitors. 1856 CB2 inhibitors with experimentally known IC_{50} values were collected from Binding DB and were used to build ligand-based pharmacophore models utilizing Schrodinger suite 2023-1. The molecules were first docked in the inactive CB2 receptor structure and then the best poses were selected and clustered on the basis of Tanimoto similarity. The developed pharmacophore was validated and used to screen phytochemical compounds from the Zinc database. The compounds that matched the pharmacophore were further analyzed through molecular docking to identify potential hits with novel scaffolds. Specifically, compounds having low binding energies and best interaction pose were selected as best hits. The first 10 best hits were subjected to the MD simulation and MM-GBSA calculations were done to validate the screened compounds. This research demonstrates that employing a ligand-based pharmacophore approach offers advantages in identifying a range of promising hits with enhanced binding affinity to the protein's active site. The methodology used in this study holds significant potential for designing drugs that bind to different molecular targets.

CLASSIFICATION ANALYSIS OF BITTER AND SWEET COMPOUNDS WITH NOVEL C-RASAR AND MACHINE LEARNING (ML) STRATEGIES

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Nowadays, *in silico* approaches have drawn more attention to exploring the dichotomy of sweet and bitter taste relationships with their chemical structures instead of traditional experimental tests. Classification read-across structure–activity relationship (c-RASAR), is an emerging cheminformatic approach that combines the usefulness of a QSAR model and similarity-based Read-Across predictions. The current study describes the development of the classification LDA (Linear Discriminate Analysis) approach using structural and physicochemical descriptors followed by the development of c-RASAR models of sweet and bitter compounds based on the most exhaustive database [1].The RASAR models involved read-across-derived similarity descriptors along with 2D structural descriptors. The developed models for sweet and bitter datasets were validated by various internal and external validation metrics like G-means, F-measure, MCC, sensitivity, specificity, accuracy, and precision for both the training and test sets. Various Machine Learning (ML) algorithms such as RF (random forest), SVM (Support Vector Machine), LR (linear regression) were also tried using the selected descriptors from the LDA c-RASAR model. The SVM algorithm systematically improved the predictions (for the test sets), through the best learning algorithm for both the datasets. Thus, c-RASAR along with ML performs significantly well in terms of statistical and validation, thus showing the merits of c-RASAR approach. Thus, this work provides a simple and efficient novel strategy to classify with good prediction accuracy the sweet and bitter compounds that hold a key value toward the taste sensation.

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COMPUTER-AIDED ANALYSIS FOR IDENTIFICATION OF NOVEL ANALOGUES OF KETOPROFEN BASED ON MOLECULAR DOCKING FOR THE TREATMENT OF INFLAMMATION

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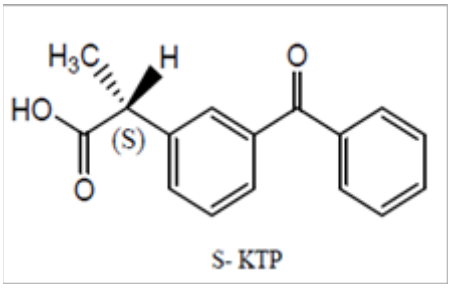
Computer-based drug design is increasingly used in strategies for discovering new molecules for therapeutic purposes. In silico drug design methods facilitate the search for bioactive molecules, make it possible to reduce costs, identify potentially therapeutic molecules more quickly and reduce in vivo / in vitro tests. The targeted drug is ketoprofen (KTP), which belongs to the family of non-steroidal anti-inflammatory drugs, which are widely used for the treatment of pain, fever, inflammation and certain types of cancers. To carry out this work we have rationalize 72 new potential anti-inflammatory compounds on the COX-2 enzyme, we carried out a theoretical study mainly based on molecular docking. It's an important tool in computational drug design by which one can predict the pharmacological activity and predominant binding mode(s) of a ligand with a target protein. For that, a molecular docking analysis was performed by using AutoDock Vina 1.1.2 program implemented in UCSF Chimera 1.15 software. The optimized analogues were subjected to a molecular docking study against human prostaglandin synthase protein 5F1A (chain A). We consider the protein as a macromolecule and the candidates as ligand where the KTP drug was considered as control and derivatives binding affinity was compared with the parent drug, which is a known COX-2 inhibitor. The 3D visualizations and 2D non-bond interactions of the complex receptor-ligand structure were performed using Discovery Studio 2020 software to analyze the docking result. Therefore, at the end of this study only 20 compounds were selected and predicted to be the most active systems since they are characterized by a lower binding energy compared to the starting compound S-KTP towards the COX-2 target.

This work was supported by the Ministry of Higher Education and Scientific Research under the PRFU project (approval no. B00L01UN130120220006).



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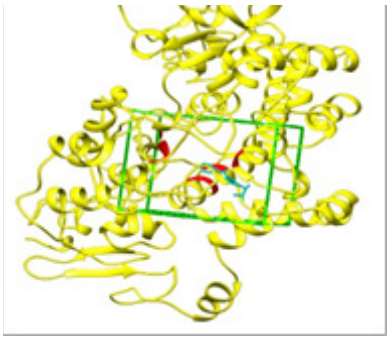

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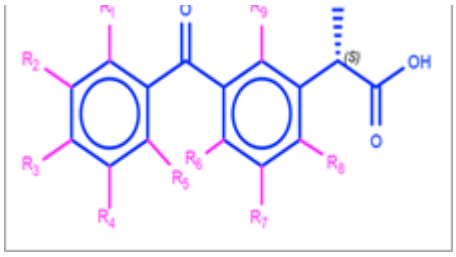

(c)

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ATOM BASED 3D-QSAR AND MOLECULAR MODELLING STUDIES OF G- PROTEIN COUPLED ESTROGEN RECEPTOR 1 (GPER 1) INHIBITORS FOR NOVEL THERAPEUTIC INTERVENTION OF TRIPLE-NEGATIVE BREAST CANCER (TNBC)

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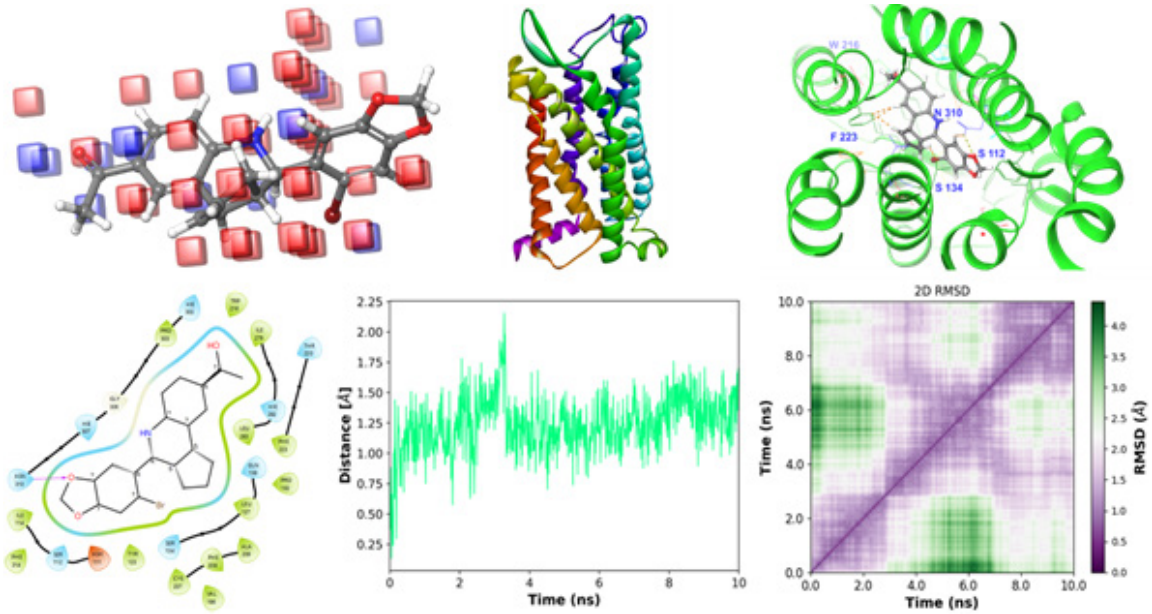
Contemporary research works have strongly evidenced the pivotal role of G-protein coupled estrogen receptor 1 (GPER 1) in driving tumor progression in triple-negative breast cancer (TNBC), a disease previously deemed to be estrogen-independent. Activation of GPER 1 leads to a reduced level of miR-148a which in turn increases the expression of human leukocyte antigen-G (HLA-G) known to be implicated in the tumor-driven immune escape in malignancies [1]. With no available FDA approved therapeutics, the present situation underscores the need to develop potential compounds with targeted GPER 1 inhibitory activity to take advantage of this recently unveiled novel therapeutic intervention for TNBC. Herein, the present work aims to study the quantitative structure-activity relationship (QSAR), molecular interactions and protein-ligand complex stability of the GPER1 inhibitors. A predictive atom-based 3D-QSAR model was developed using a set of curated 83 compounds with defined GPER 1 inhibitory activity (IC_{50}) with acceptable validation metrics (R^2=0.65, Q^2=0.63, Pearson correlation coefficient =0.80). It was found that hydrophobic groups and acceptor (electron-withdrawing) groups are necessary for GPER 1 inhibitory activity. Due to the non-availability of representative X-Ray/cryo-EM structures, a knowledge-based homology model of GPER 1 employing five similar protein sequences was built in Schrodinger. The SiteMap module of Schrodinger was used to predict the ligand binding site with the highest fitness score. Glide SP docking revealed compound 62 (IC_{50} = 9.7 nM) with the highest dock score (-8.9 kcal/mol) and a strong hydrogen bond with allosteric site residue ASN 310 of GPER 1 was traced. Molecular dynamics simulation (MDS) of the docked complex demonstrated a very low (1.24 Å) positional change of the catalytic site residues throughout the simulation. Molecular mechanics with generalised born and surface area solvation (MM/GBSA) estimated a high binding free energy (-40.31 kcal/mol) to the complex obtained after MDS. The current findings offer key structural features which can modulate GPER 1 inhibitory activity, and highlights compound 62 as a prospective lead template to design targeted therapeutics for TNBC treatment.



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EXPLORING THE PROSPECTIVE APPLICATION OF 2-AMINOBENZIMIDAZOLE SCAFFOLD AGAINST LEISHMANIASIS USING QSAR AND READ-ACROSS ALGORITHM

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Neglected Tropical Diseases **(**NTDs**)**, the word signifies that these diseases generally affect people belonging to underserved, impoverished, and marginalized communities, lacking access to basic services. These diseases don't get the required attention, but they are all seriously unpleasant and pose real threats to health and quality of life. NTDs are a set of 20 diseases that include parasites, protozoa, bacterial, and viral diseases primarily seen in tropical regions. Among them, leishmaniasis is one of the neglected tropical diseases affecting millions of people worldwide. Protozoan parasites of the genus Leishmania spp. are the causative agents of leishmaniasis and get transmitted through the bites of infected female sandflies, with different clinical manifestations, including the visceral form which is fatal known as kala-azar and a cutaneous form that causes disfiguring skin lesions. Very few QSAR studies are available on compounds showing activity against NTDs. This study aims to develop a regression-based-QSAR model using 47 complex compounds with the scaffold of 2-aminobenzimidazole against Leishmania infantum with a defined endpoint (IC_{50}). Feature selection was done using genetic algorithm followed by model development using the best subset selection method. The final model was developed by partial least squares (PLS) method. The final (PLS) model was validated using different globally accepted internal and external validation parameters and their statistical results (= 0.688, = 0.612, = 0.735, and = 0.698) demonstrate that the developed model was reliable, robust, accurate, and predictive. Read-across algorithm was employed to improve the predictivity (=0.744,=0.707) of models. It was found that predictivity of read-across model was better than the PLS model. The present work highlights that electronegativity is an essential parameter for activity whereas polarity decreases the activity. Thus, these structural insights can be used to design and development of novel chemical entities with prospective applications for the treatment of Leishmaniasis.

RATIONAL DESIGN OF 5α-REDUCTASE 1 ENZYME INHIBITORS

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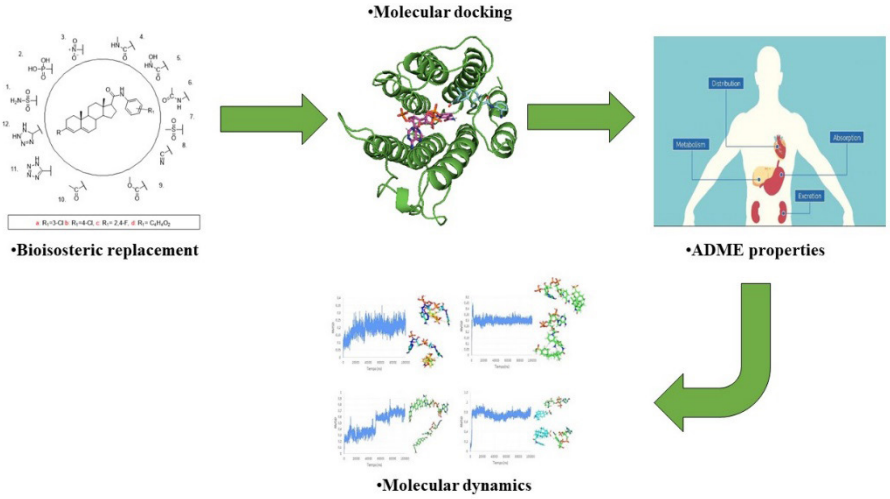
The search for new inhibitors of the enzyme 5α-Reductase 1 is crucial to address common and serious medical conditions, such as benign prostate hyperplasia (BPH) and prostate cancer (CaP), in addition to having the potential to contribute to the development of more selective and effective hormonal therapies. This study proposes a set of 48 compounds inspired by the substituted 17-arylcarbamoyl androst-3,5-dieno-3 carboxylic acid, from which 4 ligands exhibiting promising profiles as inhibitors of the 5α-Reductase enzyme 1 were identified. To achieve this, the 3D structure of isoform 1 was modeled using the protein homology method. Additionally, the 3D structure of the 5-alpha reductase enzyme type 1 was optimized and validated using ligands with reported inhibitory activity. Once the enzyme was optimized and validated, the set of ligands was designed using the bio isosteric replacement method, targeting the A ring and aromatic ring of the base structure. Once constructed, the ligands underwent a three-step filtering process: ADME-T property analysis, docking, and molecular dynamics. The information obtained in this research could serve as a foundation for the development of bioactive compounds against the 5αR1 enzyme, as well as benign prostatic hyperplasia and prostate cancer.



VIRTUAL ANALYSIS OF IMMUNOGENIC EPITOPES OF NONSTRUCTURAL PROTEIN, NUCLEOCAPSID PROTEIN, GLYCOPROTEIN, AND RNA-DEPENDENT RNA POLYMERASE OF SEVERE FEVER WITH THROMBOCYTOPENIA SYNDROME VIRUS (SFTSV)

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With innumerable pathogens hiding in the shadows, infectious diseases pose a threat in this interconnected world, while research and development resources remain constrained. The emergence of the COVID-19 pandemic further highlighted this concern and underscored the urgent need of being prepared for a potential pandemic outbreak in the future. At this crucial point, building up defenses against new health hazards becomes of utmost importance. In 2009, an emerging tick-borne bunyavirus was detected in China and was later identified as the severe fever with thrombocytopenia syndrome virus (SFTSV), with a fatality rate of up to 30%. Despite the recognition of the World Health Organization (WHO) of this virus as a pathogen with pandemic potential, effective treatments, and vaccines against SFTSV are still lacking. With the recent interest in recombinant subunit vaccines, attempts have been made in utilizing this type of vaccine against SFTSV. However, contrasting results were reported which necessitates the pursuit for good protein candidates for an effective vaccine against the virus. Thus, utilizing *in silico* approach, this study aimed to identify and analyze the immunogenic epitopes of the structural and nonstructural proteins of SFTSV. The methods applied in this study were divided into three main steps: target protein analysis, immunogenic epitope analysis, and the construction of transfer vectors. In target protein analysis, highly conserved sequences were identified using Clustal Omega and the Protein Variability Server. The 3D models and secondary structures of the target proteins, signal peptides, and cleavage sites, as well as the presence of transmembrane helices in the sequences of the target proteins, were also analyzed. Additionally, linear B lymphocyte (BL), cytotoxic T lymphocyte (CTL), and helper T lymphocyte (HTL) epitopes were predicted and underwent further assessment for antigenicity, allergenicity, cross-reactivity to humans, epitope conservancy, and toxicity. Lastly, the construction of pFastBac-1 transfer vectors for insect cell expression systems was conducted using Snapgene. The results provided in this study can serve as preliminary data and contribute to the pursuit of good protein candidates for the development of an effective vaccine against SFTSV.

A total of 98 highly conserved fragments were identified from the SFTSV target proteins. However, only glycoprotein contains a signal peptide and transmembrane helices, increasing its likelihood to be recognized by the immune system. Nonetheless, all target proteins generated an array of immunogenic epitopes. Moreover, construction of pFastBac-1 transfer vectors for each SFTSV target protein was successfully designed using Snapgene. Overall, the results of this study suggest the potential use of SFTSV nonstructural proteins, nucleocapsid protein, glycoprotein, and RNA-dependent RNA polymerase as an attempt to develop a recombinant protein subunit vaccine. This may be further analyzed through molecular dynamics simulation and *in vitro* and *in vivo* investigations.

NEW OPPORTUNITIES IN THE SYNTHESIS OF MONASTROL

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Antibacterial drug discovery peaked shortly after the middle of the twentieth century with the discovery of most compound classes that are still in clinical use. After the introduction of streptogramins and quinolones in 1962, no novel class of antibiotics was identified and approved for clinical use until linezolid was launched in 2000. This fact is rather surprising because not only was research heavily supported during this time but also novel technologies such as genomics and high-throughput screening were introduced and applied to improve productivity. The results of the present study will improve efficiency and reduce costs for anti-tuberculosis and anti-staphylococcal activity prediction for known substance Monastrol. Random, high throughput screening will be changed to a rational, computationally-based and scientifically intelligent approach. Drug designers will be in a position to obtain and use a modern system of effective design of anti-bacterial preparations, as one of the main results of the basis for development of new drugs. The computer-aided prediction of new biological activity spectra of known Monastrol which show to inhibit kinesin Eg5 has been used. This approach was included prediction of spectra of biological activity (PASS software) as well as the toxicity by DEREK. Docking studies demonstrated that DNA GyrB inhibition, probably, may explain the anti-bacterial action of Monastrol, while inhibition of lanosterol 14-alpha-demethylase (a cytochrome P-450 enzyme), as was expected, probably, is involved in the mechanism of antifungal activity. Thus, Monastrol could serve the role of lead compound in search for new potent antimicrobial agents. One-pot synthesis conditions makes it possible to obtain target compound Monastrol via interaction of acetoacetic ester, thiourea, and 3-hydroxybenzaldehyde in the presence a eutectic mixtures (synthesized based on 3-(carboxymethyl)-1-vinyl-1*H*-imidazole-3-ium chloride, bromide, hexofluorophosphate and thiourea.

This research has been performed within the State Program of the Republic of Moldova (2020-2023) Project no. 20.80009.5007.17 “Hybrid materials functionalized with carboxyl groups based on plant metabolites with activity against human and agricultural pathogens”.

pyGROMODS: A PYTHON PACKAGE FOR INPUT FILES GENERATION AND RUNNING MOLECULAR DYNAMIC SIMULATION WITH GROMACS

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The application of computer-aided drug discovery (CAAD) is gaining improved acceptance in the field of drug development. With advances in technology and availability of improved hardware resources for computational studies, CAAD is not just a powerful alternative in rational drug development, but it's also faster, cheaper, effective and more robust. An important application of CAAD is molecular dynamics (MD) which has revolutionize our understanding of biomolecular structures and functional activities. It is now possible to integrate molecular docking and MD with Network Pharmacology, coupled with multi-omics integration, with a view to gaining better understanding of the biomolecular mechanisms of action of multi-component products. Also, such integration is leading the way for Network Pharmacology-driven drug repurposing and multi-target drug discovery. However, successful application of CAAD, not only depends on the availability of the required computational resources, which must be able to combine speed with efficiency, but also should be affordable and user friendly. Today, many of the available resources require the knowledge of command-line argument to use, limiting their potential adoption by many biological scientists. While attempts have been made to ease the process of using them using third-party user-friendly codes, none of the available codes is able to combine generation of input files with running MD simulation.

Here is presented pyGROMODS, an easy-to-use cross-platform python-based package, with graphical user interface, having the capacity to aid in the generation of molecular dynamic (MD) input files and subsequent running MD simulation (MDS) of proteins, peptides and protein - ligand complex using GROMACS. Four routes, with underlining python scripts, are implemented in pyGROMODS for the generation of MD input files. They are "RLmulti" for processing multi-ligands protein complex, "RLmany" for processing multiple ligands against single protein target, "RLsingle" for processing multiple pairs of protein and ligand, and "PPmore" for processing peptides or proteins without ligands or non-standard residues. In addition, package provides opportunity to run MD simulation with GROMACS using the generated input files or other appropriate input files generated from other sources The pyGROMODS is implemented with unique ability to search the host machine systems for the installation of the required software, update and/or install required python packages, allow the user to pre-define working directory, and generating unique workflow organization with well-defined folders and files in a well-organized manner. The pyGROMODS, which is released under the MIT License, is freely available for download via Github repository (https://github.com/Dankem/pyGROMODS) and Zenodo repository (https://doi.org/10.5281/zenodo.7912747), and a video tutorial can be downloaded from https://youtu.be/I4OKc6uVx1M.

This study is currently under review for publication by *Journal of Biomolecular Structure and Dynamics.*

DETERMINATION OF PHARMACOLOGICAL PROPERTIES AND TOXICITY OF NEW PIPERIDINE DERIVATIVES USING PASS REFINED 2014 PROGRAM

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The objective of the study. Determination of the likelihood of desired pharmacological properties as well as evaluation of possible toxicity risks of novel piperidine derivatives.

The advancement over previous studies. The use of the PASS Refined 2014 program is relevant because it provides tools for more efficient and faster selection of promising drug candidates, reducing risks and increasing the probability of successful development of new drugs. The results obtained by the program help to evaluate and compare the pharmacological action and toxicity of different chemical compounds of piperidine derivatives in various aspects.

The results and accomplishments and their significance. Seven piperidine derivative models were analyzed using the PASS program: 4-hydroxy-1- (2-hydroxyethyl) piperidine-4-carboxylic acid (№2); 1-(2-hydroxyethyl)-4- (propanoyloxy) piperidine-4-carboxylic acid (№3); 4-(benzoyloxy)-1- (2-hydroxyethyl) piperidine-4- carboxylic acid (№4); 1-(2-hydroxyethyl) piperidin-4-ylbenzoate (№6); 2-[4-(benzoyloxy) piperidin-1-yl] ethylbenzoate (№7); {1-[2-(propanoyloxy) ethyl] piperidin-4-ylidene} aminopropanoate (№10); {1-[3-(propanoyloxy) propyl] piperidin-4-ylidene} aminopropanoate (№15). It is these piperidine derivatives that are the most stable according to quantum-chemical studies (arranged by increasing enthalpy value): (№6) - contains 1 benzoyloxide radical; (№7) - contains 2 benzoyloxide radicals; (№10) - contains 1 carboxyl group and 1 aminopropanoyl radical; (№15) - contains 1 propanoyl radical and 1 aminopropanoyl radical; (№4) - contains 1 carboxyl group and 1 benzoyloxide radical; (№2) - contains 1 carboxyl group; (№3) - contains 1 carboxyl group and 1 propanoyl radical. The 7 models were searched based on the required pharmacological effects: anesthetic, antineurotoxic, antispasmodic, antitussive. The following toxicity parameters were taken for toxicity analysis: teratogenicity, mutagenicity, carcinogenicity, embryotoxicity, toxicity to the respiratory center, anaphylactic shock, neurotoxicity, hematoxicity, visual toxicity.

The following conclusions were made during the study using the PASS program: the higher the calculated value of pharmacological activity of a compound, the higher the calculated value of its toxicity; the presence of benzoyloxide radical in the structure of a piperidine derivative significantly increases the probability of the presence of an anesthetic effect, and reduces the toxicity indexes of the compound in direct dependence on the number of them - the higher their number, the better the prognosis; the absence of benzoyloxide radicals and the presence of propionate radicals significantly reduces the prognosis indexes.

By comparing the data of the obtained predictions for each compound, of the 7 selected compounds, compound №7 is the most interesting for synthesis and subsequent preparation of a dosage form from it. Compounds №4 and №6 can also be recommended for synthesis because of its relatively low toxicity and high predicted values of the required pharmacological effects (antispasmodic and anesthetic) in comparison with all studied models.

COMPARISON OF TWO SARS-COV-2 VIRUS GENOME SEQUENCES WITH DIFFERENT PLAQUE PHENOTYPES IN VERO CELL CULTURE

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At the end of 2019, a highly contagious and pathogenic coronavirus (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strain) appeared and caused a pandemic COVID-19. Despite the end of the pandemic, people around the world continue to get sick, and therefore obtaining universal neutralizing antibodies for different strains is relevant. Due to variability, the strains currently circulating are very different from the original Wuhan strain. Recent studies have shown that some therapeutic antibodies no longer bind to mutant Spike proteins and therefore no longer neutralize. In this regard, mutations in the receptor-binding and N-terminal domains of the Spike protein are currently being widely studied [1]. Mutations and deletions in the N-terminal domain have been shown to have a strong effect on immunogenicity but are less studied than mutations in the receptor-binding domain.

In our work, we performed sequencing of two variants of Delta SARS-CoV-2 that differed phenotypically (in terms of plaque size, when Vero cell culture was infected). We have found two nonsynonymous substitutions in the open reading frame 1ab (ORF1ab) and a previously undescribed insertion of 12 nucleotides, leading to a frameshift and the appearance of new 5 amino acids in the sequence in the N-terminal domain of the Spike protein. We assume that the insert we found probably affects the phenotype and, therefore, may affect the interaction of the protein with the receptor.

The SARS-CoV-2 virus variant Delta was cultivated in Vero cells. Viral RNA was isolated from the infected cell culture and whole genome sequencing was performed using Illumina technology. Bioinformatics processing of the obtained sequencing data was carried out.

The quality of sequencing was checked using the FastQC tools. After analyzing the results of the program output, adapter sequences (TrueSeq), the first 15 nucleotides (parameter - HEADCROP:15), as well as reads with a quality less than 30 (parameter – TRAILING:30) were deleted in reads ~~(reads)~~ using the Trimmomatic program. Then, reads were mapped with BWA program to the SARS-CoV-2 reference genome (NC_045512.2 Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1) with default parameters. The search for mutations was performed using the set of utilities BCFtools with a coverage parameter of 1000 (--max-depth 1000) in comparison with the reference genome. The identified mutations were checked manually in the IGV program.

The aim of our future work is the investigation of these substitutions on receptor binding and pathogenesis in an animal model.

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DOCKING-REVEALED POSSIBLE MOLECULAR TARGETS FOR 4-METHYLUMBELLIFERONE AMONG *PSEUDOMONAS AERUGINOSA* PROTEINS INCLUDING INVOLVED IN PIGMENT BIOSYNTHESIS

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Pseudomonas is a diverse genus of bacteria that includes strains pathogenic to humans, cattle, insects and plants [1]. Due to the risk of resistance developed to currently used drugs and crops-protecting agents, the research of novel interactions of bacterial biotargets with various chemical substances is appears to be important. Computer-aided calculations are helpful with respect to roadmaping of experimental research. One of the methods in demand is protein-ligand docking allowing *in silico* evaluation of the interactions in terms of geometric details (poses) and binding energies (E_{bind}). 4-methylumbelliferone (4MU) is a naturally occurring coumarin which serves as a plant regulator causing plant-symbiotic pseudomonads accumulation in rhizomes [2] as well as an inhibitor of hyaluronan biosynthesis [3] and anti-cancer compound [4]. Recently, we have synthesized 4MU and O-methyl-4MU and docked the structure against vast majority of 3D structures of cytochromes P450 using Autodock Vina engine and FYTdock helper programs [5-7]. To the best of our knowledge, there is a lack of information about possible 4MU interactions with proteins of *P. aeruginosa* at *in silico* level. We have found that among 2100 PDB structures 4MU can realize the most affine interactions with PHZD (pdb 1NF8, 1NF9), quorum sensing regulator LASR (6D6M, 6D6P, 4NG2, 6D6N, 6D6O) showing E_{bind} values from −9.4 to −8.5 kcal/mol. Interestingly, both PhzD [8] and LASR [9] control pyocyanin production. *In vitro* 4MU was found to reduce real pyocyanin production by 25±5 %.

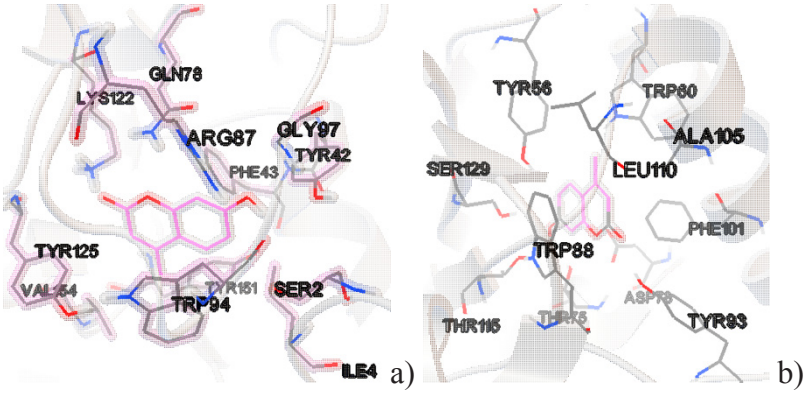

Figure. Docking poses of 4MU with PHZD (pbd 1NF8, a) and LASR (pdb 6D6M, b) structures

The obtained results may open prospects for the design of new bioregulators.

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APPLICATION OF BIOISOSTERISM AND PREDICTION OF ACTIVITY AND TOXICITY IN THE SEARCH FOR GSK3 ENZYME INHIBITOR COMPOUNDS

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The enzyme glycogen synthase kinase 3-beta (GSK3β) plays a critical role in various metabolic and cellular signaling pathways. This protein, in addition to being associated with the regulation of glucose metabolism and cellular signaling pathways, also influences apoptotic processes. Recent researches establish an association between GSK3β and tumor proliferation and metastasis formation. Based on this connection, the study of potential GSK3β inhibitors presents itself as an appropriate strategy for developing new agents for use in tumors associated with this enzyme. In the field of drug discovery, in silico tools such as the application of bioisosterism to previously identified compounds, virtual screening of molecular databases, and the prediction of their biological activity and toxicity are widely used. The purpose of this study is to search for potential inhibitors of the GSK3β enzyme that can act as antitumor agents and exhibit reduced toxicity. In the search for candidate inhibitor molecules, the MolOpt software, available online at (https://xundrug.cn/molopt), was used for bioisosteric research. The rules for data mining method was used in this study to suggest the molecular regions or groups to be used in bioisosteric substitution. The prediction of interaction targets/biological activity of the generated bioisosteres was carried out using the Similarity Ensemble Approach (SEA) software, available at https://sea.bkslab.org/. The prediction of toxicity effects including hepatotoxicity, carcinogenicity, mutagenicity, cytotoxicity, immunotoxicity, and interactions with androgen and estrogen receptors, as well as PPAR-gamma, for the bioisosteres was performed using the Protox II – Prediction of Toxicity of Chemicals website (https://tox-new.charite.de/protox_II/). For this specific study, a molecule with recognized activity against GSK3β, identified by the SMILES code FC(F)(F)C4(=C(C1(=NC(=C(N)N=C1)C(=O)NC3(=C(N2(CC(N)CCC2))C=CN=C3)))C=CC=C4), was chosen as the starting point. This compound is also recognized for its activity as an inhibitor of the protein kinase C. In the bioisosterism study, the software suggested 18 molecular positions for alteration in the GSK3β inhibitor's structure. Initially, the alteration of the substituted aromatic functional group connected to trifluoromethyl, which is at the end of the side chain and connected to the pyrimidine ring, was suggested. The results allowed the identification of 200 molecules as isosteres to the starting compound, with various classic and non-classic substitutions. These molecules were subjected to the prediction of interaction targets/biological activity against GSK3β using SEA, and only 5 compounds showed interaction with the enzyme. The most promising was number 17, which showed an interaction probability of 2.737E-26. These molecules were subjected to toxicity prediction with Protox II, and 2 of them, numbers 30 and 135, showed a low probability of inducing toxicity. Among the molecules, 2 emerge as promising candidates for subsequent studies involving chemical synthesis and in vitro and in vivo biological activity evaluation. These molecules present proposals for the potential development of new antitumor agents targeted at GSK3β inhibition.

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IDENTIFICATION OF NOVEL CURCUMIN ANALOGUES TO INHIBIT MITOGEN-ACTIVATED PROTEIN KINASE 1 USING *IN SILICO* COMBINATORIAL LIBRARY DESIGN AND MOLECULAR DOCKING APPROACH

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Due to emerging and ongoing pathogen outbreaks, pandemic situations have always been destructive to living organisms, especially the human host. MAP kinases, also known as extracellular signal-regulated kinases (ERKs), cascades are key signalling pathways that regulate a wide variety of biological functions such as cellular processes, including proliferation, differentiation, and apoptosis through the regulation of transcription, translation, cytoskeletal rearrangements. The MAPK3/ERK1 and MAPK1/ERK2 are cascaded that activate the MAP kinases signalling pathways which play a major role in the regulation of cell signalling in normal and pathological tissues, and also the activation of these ERKs is fundamental for the development and progression of cancer. Among the ERKs, Erk2 is thought to have its specific function, such as demyelinating inflammation by inducing inflammatory mediators and gliosis, making it an ideal target for therapeutic development. Based on the role of MAPK1/ERK2 in inflammation and other signalling pathways, we shed light on curcumin for its potential role against the disease. Curcumin (diferuloylmethane), an orange-yellow component of turmeric or curry powder, is a natural polyphenol that has drawn much attention in the current situation in the field of natural drug discovery due to its excellent therapeutic effects, such as its antioxidant, anti-inflammation, anti-microbial, anti-arthritic, and anti-cancer as well. Curcumin has a long history as a medicinal plant used in Ayurveda, Unani, and Siddha medicine as home remedies for various diseases. However, no data is available on the analogues and derivatives of curcumin that can inhibit MAPK1/ERK2. Based on that, this study aims to find a novel analogue of curcumin that can inhibit the mitogen-activated protein kinase 1. With the help of advanced computational rigorous steps, the analogue molecules are constructed with database search and the SmiLib combinatorial library approach. The in silico molecular docking analysis of analogues referenced to curcumin and its derivatives revealed some analogues that could be gained as drugs to inhibit mitogen-activated protein kinase 1 based on the multiple interactions. The current study found that analogues referenced to curcumin and its derivatives inhibit mitogen-activated protein kinase 1 and can lead the therapeutics development; however, a wet lab experiment is required to validate the results.

QUANTITATIVE READ-ACROSS STRUCTURE-ACTIVITY RELATIONSHIP (q-RASAR): A NEW APPROACH METHODOLOGY TO MODEL AQUATIC TOXICITY OF PESTICIDES CONSIDERING THREE DIFFERENT FISH SPECIES

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Pesticides can poison many non-target environmental species, the most prominent of which are various aquatic species, especially fishes. In addition, several other non-target creatures, such as aquatic and soil organisms and humans, are harmed by the non-specificity as well as improper usage and unspecified doses of these pesticides. To assess the unwanted toxicity of pesticides and other chemicals towards non-target organisms and to reduce unwanted animal experimentations associated, the regulatory agencies have adopted the 3Rs strategy (reduction, replacement, and refinement of animal testing), and thus they are promoting alternative in silico predictive approaches for quite some time. There are various studies in the literature that are concerned with the aquatic toxicity of multiple pesticides and their risk assessment. However, most of these studies focus only on toxic class prediction and global toxicity modeling [1]. Thus, it is very difficult to obtain quantitative predictions of aquatic toxicity for a proper risk assessment. On the way forward for a proper risk assessment of organic pesticides, we have developed quantitative toxicity models considering different fish species using a novel quantitative Read-across structure-activity relationship (q-RASAR) approach. The current study describes the development of q-RASAR models using experimental (Log 1/LC50) data of organic pesticides to various fish species, including Rainbow trout (RT – *Oncorhynchus mykiss*: 715 data points), Lepomis (LP – *Lepomis macrochirus*: 136 data points), and (Others – *Pimephales promelas*, *Brachydanio rerio*: 226 data points). The validation of the developed models and the analysis of structural features that are important for aquatic toxicity towards fishes have also been discussed in this study. The read-across-derived similarity, error, and concordance measures (RASAR descriptors) have been extracted from the preliminary 0D-2D descriptors; the combined pool of RASAR and selected 0D-2D descriptors have been used to develop the final models by employing partial least squares algorithm. All the q-RASAR models are acceptable in terms of goodness of fit, robustness, and external predictivity superseding in quality the respective QSAR models, as seen from the computed validation metrics (RT: n_{train}=537, R^2=0.52, Q^2_{Loo}=0.50, n_{test}=178, Q^2_{F1}=0.58; LP: n_{train}=102, R^2=0.67, Q^2_{Loo}=0.59, n_{test}=34, Q^2_{F1}=0.74; and other species: n_{train}=113, R^2=0.54, Q^2_{Loo}=0.52, n_{test}=113, Q^2_{F1}=0.59).The software tools used in this study are user-friendly, and most of them are free, making our methodology quite cost-effective when compared to experimentation.The q-RASAR is an effective approach that has the potential to be used as a good alternative way to enhance external predictivity, interpretability, and transferability for aquatic toxicity prediction as well as ecotoxicity potential identification.

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STRUCTURE-BASED VIRTUAL SCREENING AND IDENTIFICATION OF NOVEL POTENTIAL INHIBITORS OF β-KETOACYL-ACYL CARRIER PROTEIN SYNTHASE I FROM MYCOBACTERIUM TUBERCULOSIS

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In 2020, about 10.1 million people fell ill with tuberculosis (TB) and over 1.5 million patients died, including 214,000 patients with HIV. Unfortunately, this alarming trend continues presently, as evidenced by the fact that over 10.6 million people were infected with TB in 2021, an increase of 4.5% from 2020 [1]. These data indicate that TB continues to be one of the top ten causes of death worldwide and is the leading reason of death in patients with HIV and diabetes mellitus, primarily due to resistance to antimicrobials used in clinical practice. The increasing prevalence of drug resistance poses a major challenge to effective TB control [1]. In this regard, one of the key problems facing the scientific community is the treatment of drug-resistant TB, which necessitates the development of new potent and broad-spectrum antibacterial agents that can inhibit different vulnerable spots of Mycobacterium tuberculosis (Mtb).

In the present study, 28,860 bioactive compounds assembled into a virtual molecular library from the open access chemical databases DrugBank, ZINC15, and Selleck Chemicals were screened using molecular modeling tools to identify novel potential inhibitors of β-ketoacyl-acyl carrier protein synthase I (KasA), one of the key enzymes involved in the biosynthesis of mycolic acids of the Mtb cell wall [2]. To do this, semi-flexible molecular docking of these compounds with the malonyl binding site of the C171Q KasA enzyme was carried out by the AutoDock Vina program and the values of binding free energy for the docked ligand/protein complexes were predicted using the scoring functions AutoDock Vina, RF-Score-4, and NNScore 2.0. The exponential consensus rank (ECR) [3] was then calculated for each compound from the values of these scoring functions, resulting in the 30 top-ranked molecules which were selected for analysis of their complexes with C171Q KasA by molecular dynamics (MD) simulations.

As a result, analysis of the data from the MD simulations revealed 6 top-ranking compounds exhibiting a strong attachment to the malonyl binding site of the enzyme, as evidenced by the values of binding free energy (ΔG) which are significantly lower than those predicted for the KasA inhibitor TLM5 used in the calculations as a positive control. So the averages of ΔG calculated for the dynamic models of these compounds bound to C171Q KasA varied in the range from -28.91±7.28 kcal/mol to -22.08±4.73 kcal/mol, while the corresponding value for TLM5 was -14.94±4.93 kcal/mol. Importantly, the data on the ligand–C171Q KasA binding affinities obtained using molecular docking and MD simulations are consistent with each other, allowing one to suppose that the integrated computer-aided approach used in this study enabled one to evade false-positive results and properly estimate the power of the ligand–C171Q KasA interaction. In light of the data obtained, the identified compounds are suggested to form a good basis for the development of new antitubercular molecules of clinical significance with activity against the KasA enzyme of Mtb.

This study was financed by the Consortium and the Drug Resistant Tuberculosis Portal Program (https://tbportals.niaid.nih.gov).

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UNDERSTANDING THE BINDING INTERACTION MECHANISM OF NAVOXIMOD (GDC- 0919) WITH INDOLEAMINE 2,3-DIOXYGENASE 1 INHIBITORS (IDO1) AND HUMAN SERUM ALBUMIN (HSA): A BIOPHYSICAL APPROACH

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Navoximod is a compound under investigation that belongs to the class of IDO1 (Indoleamine 2,3-dioxygenase 1) inhibitors. ID01is an enzyme that plays a crucial role in the metabolism of the amino acid tryptophan. In certain types of cancer and immune-related diseases, IDO1 is overexpressed, resulting in increased tryptophan metabolism and the production of immune-suppressing metabolites. By inhibiting IDO1, navoximod aims to modulate the tumour microenvironment and enhance the immune system's capacity to combat cancer cells. Mainly, the role of IDO1 in cancer varies with tumour type and microenvironment. Targeting IDO1 in certain malignancies is promising, but there are some obstacles in achieving durable responses and overcoming resistant mechanisms. This study focused to investigates the fundamentals of navoxemod and its interactions with IDO1 and HSA complex system. In order to understand the binding interaction mechanism, molecular docking and molecular simulation are performed. In addition to that, density functional theory (DFT) calculation was performed to explore intermolecular for navoximod drug.

1,2,4,5-TETRASUBSTITUTED IMIDAZOLES BEARING PHENOLIC MOIETY AS A POTENTIAL UREASE INHIBITORS

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Urease is considered to be an important virulence factor for different bacterial species (*Helicobacter*, *Proteus*, *Klebsiella*, *Pseudomonas*, and *Staphylococcus*) and plays a crucial role in pathogenesis of several diseases [1]. It was found that several *Proteus* species may cause urinary tract infections that are typically complicated by the formation of bladder and kidney stones (urolithiasis), permanent renal damage and may progress to bacteremia and sepsis [2]. Imidazole and benzimidazole derivatives (omeprazole, lansoprazole) were found to inhibit urease through chelate interaction by binding to the urease active site in a normal substrate-like mode. Phenolic compounds are efficient chelators for many metals and antibacterial agents [3]. In this interconnection the design and synthesis of hybrid molecules bearing phenolic and imidazole moieties may be of interest in the field of development of novel urease inhibitors with antimicrobial activity. Tetrasubstituted imidazole derivatives were synthesized via four-component condensation of 4,6-di-*tert*-butyl-2,3-dihydroxybenzaldehyde, amine, benzil and ammonium acetate in the presence of glacial acetic acid. According to the results of pharmacological screening, the compounds obtained show moderate antibacterial activity against Gram-positive (*B. subtilis*, *S. saprophyticus*) and Gram-negative (*P. putida*, *P. vulgaris*) bacteria. The compounds tested completely inhibit the process of urea hydrolysis *in vitro* in whole cells of *Proteus vulgaris* at the concentrations of 0.168–0.083 μmol/mL. *In silico* results demonstrate that the synthesized imidazole derivatives possess moderate to high affinity towards *Helicobacter pylori* urease (pdb 1e9y) and *Klebsiella aerogenes* urease (pdb 1fwj) with E_b ranging from −6.93 to −8.13 kcal/mol.

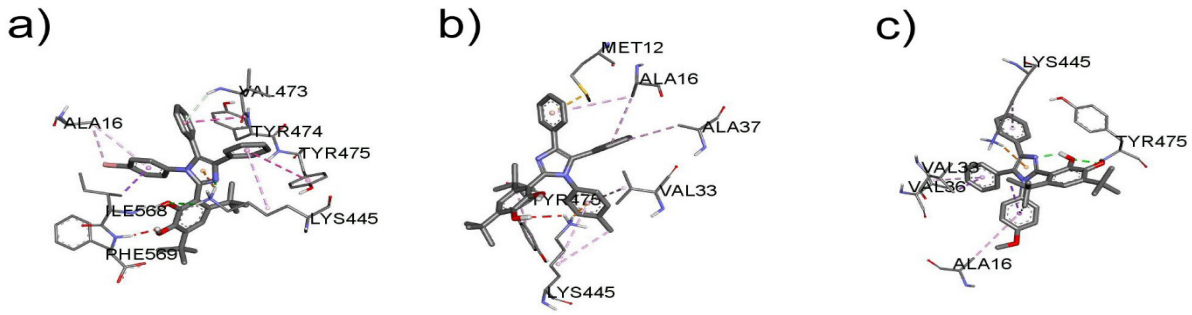

Figure. A theoretically computed binding site of ligands on *Helicobacter pylori* (pdb 1e9y) surface highlighting the compound position with respect to the certain amino acid residues

The compounds obtained may pave the way for future advances in the design of novel antibacterial agents with urease inhibition activity.

The work was carried out within the framework of the task 2.2.01.05 SRP "Chemical processes, reagents and technologies, bioregulators and bioorgchemistry".

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CHALLENGES IN THE DEVELOPMENT OF HUMAN TISSUE TRANSGLUTAMINASE INHIBITORS

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Celiac disease is a chronic genetic autoimmune disorder, which can cause serious multi-organ complications such as malnutrition, osteoporosis, infertility, and certain types of cancer. However, despite the prevalence of the disease (up to 1% of the population worldwide), there are currently no registered drugs specific110ally for the celiac disease, and the only treatment for it is a strict gluten-free diet, which in turn imposes restrictions on the patient's life. The importance of drug development for celiac disease is due to the improvement of the life quality for such people, and the most promising drug target for computer-aided drug discovery in the field is human tissue transglutaminase (tTG).

The protein is actively involved in the processing (deamidation, transamidation) of gluten polypeptides entering the body with food. Computer-aided tTG inhibitor design involves both target-based and ligand-based drug discovery. Our work aims to find the most effective and precise approaches to the design of compounds used to bind tissue transglutaminase. The target protein switches between two different conformations (open state of tTG and closed state of tTG) depending on the external conditions, and both conformations may form dimers. While the closed form of tTG acts as a GTPase, the open form is involved in the modification of gluten polypeptides, triggering an immune response behind celiac disease, and therefore ligands are designed to bind to the active site of open form tTG specifically [1].

We found 4 resolved structures for the open human tissue transglutaminase conformation in the ProteinDataBank (2Q3Z, 3S3J, 3S3S, 3S3P), each in complex with a different ligand. To define the most suitable structure for the design of tTG inhibitors we conducted molecular docking of ligands and receptors from the four found structures using AutoDock Vina program. The calculated binding energy was significantly different between the receptors using same compounds as ligands (although all the receptors were open form tTG variants), and the detailed analysis of the four protein structures showed a substantial subunit mobility in the protein conformation, resulting in the shown variability within the binding site. To predict the possible variations in the open tTG structure, we tried to use AlphaFold, however, the program always predicted the closed state of the target protein. The introduction of mutations associated with the open state of the transglutaminase in amino acid sequence of the protein did not change the outcome of the calculations, as well as the change in initial parameters of AlphaFold.

An alternative approach to the development of the target-oriented inhibitors is the analysis of the existing ones. For human tissue transglutaminase we found a list of 149 compounds with known binding energy and other parameters in ChEMBL database, which were then clustered by molecular fingerprint similarity.

According to the performed research, the open conformation of human tissue transglutaminase has the active site with several flexible amino acids and, therefore, flexible docking is required. AlphaFold is unable to find different conformations of the protein, predicting the closed state of tTG independently of the input data. The clustering of known tTG inhibitors demonstrated the best efficiency and precision at this stage of the study.

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HYDROPYRIMIDO[1,2-a]BENZIMIDASOLS AS POTENTIAL AGONISTS OF CRHR1 RECEPTORS

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Corticotropin-releasing hormone (CRF) is known to play a key role in integrating various neuroendocrine, autonomic and behavioural responses to stress [1]. Disorders of the CRF system are associated with the following disorders: psychiatric pathologies such as depression, anxiety, addictions, abnormal neuroendocrine function, and the emergence and development of neurodegenerative diseases such as Alzheimer's disease [2]. CRF performs its physiological functions through three receptor subtypes (CRF_1, $CRF_{2\alpha}$, $CRF_{2\beta}$) belonging to the subfamily of G_S-related class B G-protein-coupled receptors [3]. CRF_1 receptor antagonists are promising targets for the treatment of stress-related disorders and of particular interest. To date, several low-molecular-weight CRF_1 receptor antagonists have been proposed and clinically tested in patients with various types of psychiatric disorders. However, these substances have never been able to prove their usefulness as CRF_1 receptor antagonists. It is assumed that the key reason for this is not the mechanism of action but rather parameters such as logP and logD, which are key parameters determining not only the lipophilicity of the molecule but also the ADME profiles [4]. Derivatives of 3,4-dihydropyrimido[1,2-a]benzimidazole and their analogues were found to be optimal, i.e. having potent binding activity and desirable properties in this respect [5].

Preliminary computer screening of the functionalized derivatives of hydropyrimido[1,2-a]benzimidazoles obtained by us in the software package PASS [6] allowed us to select two compounds with maximum activity against the CRF1 receptor: 10-amino-2-oxo-2,3,4,10-tetrahydro-N-(5-chloro-2-methylphenyl)-pyrimido[1,2-a] benzimidazole-4-carboxamide (I) and 2-oxo-N-(5-chloro-2-methylphenyl)-1,2,3,4-tetrahydropyrimido[1,2-a] benzimidazole-4-carboxamide (II). For a more accurate assessment of the activity of these derivatives, taking into account the stereoisomers formed with respect to the indicated receptor, we performed molecular docking (in Vina Autodock [7] using a fully flexible docking method).

According to the data obtained, compounds I-R, I-S, II-R and II-S were able to form one to two H-bonds with residue N283. Since this hydrogen bond is observed in compound CP-376395 from the crystal structure, it can be assumed that the pyrimido[1,2-a]benzimidazoles studied would bind to the CRF_1 receptor. According to the values of the estimated function, I-S will have the highest affinity to the receptor. The configuration of the chiral carbon atom will largely influence the way the ligands bind.

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DESIGN AND IN SILICO SCREENING OF NOVEL 2-ARYLAMINOPYRIMIDINE-BASED COMPOUNDS AS EFFECTIVE INHIBITORS OF BCR-ABL TYROSINE KINASE

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Over the past 2 decades since the discovery of imatinib, the second- and third-generation drugs that inhibit the catalytic activity of Bcr-Abl tyrosine kinase by targeting the ATP-binding site of the enzyme have been developed to treat patients with chronic myeloid leukemia (CML) [1]. However, despite significant progress in the CML therapy, this problem has not been completely resolved [2]. Unfortunately, all current therapeutic agents for CML exhibit high toxicity causing a number of side effects. Furthermore, mutations can occur in the ATP binding site of Abl kinase, causing resistance by preventing the binding of many of these drugs and leaving patients with limited treatment options [2]. In this connection, development of novel potent Abl tyrosine kinase inhibitors with acceptable toxicological properties is of great importance.

In this work, 126 chimeric structures of the derivatives of 2-arylaminopyrimidine, a key structural motif of imatinib and nilotinib, were designed and screened using molecular modeling tools to identify novel potential inhibitors of the native and mutant ($T^{315}I$) Bcr-Abl tyrosine kinase. The calculations included (i) molecular docking of the designed compounds with the ATP-binding site of Abl kinase, (ii) molecular dynamics simulations of the ligand/Abl complexes, (iii) prediction of the binding affinity in terms of classical and machine-learning scoring functions followed by selection of the most probable drug candidates.

Based on the calculation data, 4 top-ranking compounds that potentially could effectively block the ATP-binding site both of the native and mutant ($T^{315}I$) enzyme, which is resistant to a number of anticancer agents used for the CML therapy, were identified. According to the post-modeling analysis, these compounds exhibit close modes of binding to the Abl kinase active site that are mainly provided by hydrogen bonds and multiple van der Waals contacts and show high binding affinity to the native and mutant enzyme. At the same time, the values of binding free energy predicted for the analyzed molecules are comparable with those calculated for the FDA-approved kinase-targeted inhibitors imatinib and ponatinib. These molecules were therefore synthesized and subject to in vitro assays, allowing one to identify lead compound which showed antiproliferative activity on the K562, HL-60, and RPMI1788 target cells with the half-maximal inhibitory concentration (IC_{50}) values of 2.80±0.76 μM, 3.51±0.23 μM, and 3.08±0.19 μM, respectively.

The data obtained suggest that the identified hit compound may serve as good scaffold for the design of novel potent anticancer agents able to target the ATP-binding pocket of the native and mutant Abl kinase. For this purpose, the current QSAR strategies widely used for a lead optimization approach in drug discovery may be applied [3].

This study was supported by the State Program of Scientific Research “Convergence 2025” (subprogram “Interdisciplinary research and emerging technologies”, project 3.4.1).

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AN ANALYSIS OF THE NOVEL METAL-ORGANIC COMPOUNDS AS POTENTIAL ANTITUMOR DRUGS

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More than 19 million new cases of cancer are revealed annually over the world. An increase of the frequency of oncological diseases, the acquisition of tumor resistance to standard therapy and their subsequent progression are the key problems of modern oncology. Therefore, the development of new anticancer drugs with high cytotoxicity for malignant tumors seems to be relevant and promising problem. This study proposes an original approach to study the antitumor activity for agents of a new type - heterometallic coordination compounds (HCCs), type [M(phen)3][Y(NO3)5] and [M(bpy)3][Y(NO3)5] (M= Co^{2+}, Ni^{2+}, Zn^{2+}; phen = 1,10-phenanthroline; bpy = 2,2′-bipyridine).

As follows from the publications, tumor cells are characterized by high levels of expression of aquaporin family proteins (AQPs) - hydrophobic transmembrane protein homotetramers. The development of AQPs inhibitors with the prospect of their use as antitumor agents is an urgent task. Our work objective is to confirm the assumption that HCC inhibit the AQPs, disrupting the permeability of cell membranes, signaling and vital activity of tumor cells, inducing their death [1].

The purpose of this study is to develop an algorithm for the bioinformatic analysis of HCC interactions with the AQPs family of integral proteins. The HCCs, which were studied here, for the first time were synthesized at N.S. Kurnakov Institute of General Chemistry of the Russian Academy of Sciences, within the framework of this project. The developed algorithm includes: 1) 3D-graphical representation and visualization of ligands using web application the Molview; 2) analysis of published results and The Human Protein Atlas (HPA) database to identify subtypes of AQPs specific for different cancer subtypes; 3) the search for different AQPs in the PDB database; 4) modeling using the Rosetta online server, using the Rosetta Symmetric Docking protocol in presence of a homomer molecule; 5) search for a certain type of homomers in the AlphaFoldDB database if they absent in the PDB database; 6) modeling of molecular interactions using the Rosetta online server according to the Rosetta Ligand Docking protocol, both with the investigated HCC and with reference compounds, as a proven significant control. Additional screening of HCC *in vitro* on model human tumor cell lines.

Table. Simulation results obtained by Rosetta Ligand Docking, the scores are indicated as Interface Scores.

Symbol		$[M(phen)3]^{2+}$			$[M(bpy)3]^{2+}$			Reference	
Zn		Co	Ni	Zn	Co	Ni			
AQP 5	3D9S	-14,9	-28,6	-28,4	-22,5	-22,5	-21,8	Acetazolamide	-8,5
AQP 4*	3GD8	-20,4	-28,7	-26,8	-18,8	-18,3	-19	TGN-020	-7,72
AQP 3**	AF	-13,3	-20,9	-21,8	-13,5	-15,8	-13,3	Phloretin	-7,04

Notes: - in the database there is a single monomer from which the tetramer was synthesized, ** - in the database there is not even a monomer, the AlphaFold monomer model and symmetrical docking has been used.*

Thus, we have developed an approach for the bioinformatic analysis of HCC interactions with the AQPs family of aquaporins, which made it possible to analyze the intermolecular interactions of the compounds under study. A high evaluation functions (scores) during HCCs interaction with AQP3, AQP 4 and AQP 5 target proteins has been shown. The cytotoxicity analysis of these HCCs *in vitro* confirmed the high activity of these HCC against a number of different human tumor cell lines and less - for normal cells. The results indicate that these compounds are potential antitumor agents. The mechanisms of their cytotoxicity for tumor cells require a comprehensive study.

This study is supported by the Russian Science Foundation Gant No. 23-23-00601.

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ACCELERATION OF VIRTUAL SCREENING OF ULTRA-LARGE LIBRARIES BY REGRESSION-BASED ACTIVE LEARNING

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Virtual screening is a method by which potential ligands are extracted from a library of compounds. The approach is based on molecular docking, a computationally difficult algorithm, and uses libraries of a constantly growing size. This leads to significant time cost of the virtual screening stage. Machine learning methods can speed it up: for example, some model can predict molecules with the best molecular docking score, and only this subset will be sent for screening.

In this work, an active learning approach based on linear regression was applied. The iterative algorithm which extracts the most promising compounds was constructed. At each step, the model was trained at docking scores as targets, using binarized Morgan fingerprints as features; then, based on model predictions, the best 1% of compounds were used for molecular docking, and the training set was augmented. The effectiveness of the algorithm was tested on the structures of adenosine A_{2A} (A_{2A}AR) and cannabinoid type 2 (CB_2) receptors, docking of which was performed by the ICM-Pro software (Molsoft), as well as on the results of screening of AmpC beta-lactamase and D_4 dopamine receptor in the Dock software, published earlier [1]. It was measured how many compounds from the top-1% of the screening library ("hits") were retrieved by the algorithm, depending on how many times the screening library was reduced (Table):

Table. Percentage of hits found depending on the desired acceleration of virtual screening

Dataset	10x reduction	3x reduction
A_{2A}AR, ICM-Pro	51 ± 3 %	85 ± 1 %
CB_2, ICM-Pro	48 ± 3 %	80.3 ± 0.4 %
AmpC, Dock	91.3 ± 0.4 %	97.5 ± 0.1%
D_4, Dock	60 ± 1 %	87.6 ± 0.3 %

The results of the iterative algorithm highly depended on the target of virtual screening. At the same time, regardless of the specific case, it was possible to achieve a multiple acceleration of virtual screening when extracting a significant percentage of hits. The constructed algorithm can accelerate molecular docking by 10 times, while preserving 60% of the molecules with the best result, or by 3 times, preserving about 80%. This approach allows for large-scale virtual screening with available computing resources in an adequate time.

This work was supported by the Russian Science Foundation (project no. 22-24-00454, https://rscf.ru/project/22-24-00454).

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STRUCTURE-CHROMATOGRAPHIC RETENTION CORRELATIONS FOR BIOLOGICALLY ACTIVE QUINOLINE DERIVATIVES

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The study of the sorption characteristics dependence on various physicochemical parameters is of particular importance in the study of biologically active substances, since the establishment of patterns and mechanisms of their sorption in many cases makes it possible to predict the physiological effect of potential drugs. One of the most suitable methods for these purposes is high-performance liquid chromatography (HPLC), which makes it possible, by varying the conditions of the chromatographic process, to reveal the types of intermolecular interactions in the system, determined by differences in the structure of compounds, to establish the relationship between the structure of substances and their sorption characteristics, and even to simulate biochromatographic processes observed during the introduction of physiologically active substances in a living organism. Moreover, the study of the regularities of the chromatographic behavior of substances under HPLC conditions can provide answers to many questions of pharmacokinetics and pharmacodynamics. A significant proportion of substances with pharmacological activity falls on nitrogen-containing heterocyclic compounds, and, in particular, quinoline derivatives.

The aim of our work was to simulate the retention of quinoline derivatives under conditions of reverse phase high performance liquid chromatography (RP HPLC). To establish the influence of structural features that determine the nature of intermolecular interactions in a chromatographic system, and, thus, the sorption characteristics of the studied compounds, the values of polarizability, lipophilicity, dipole moment, volume and surface area of molecules, solvation energy in a water-acetonitrile mixture, and other descriptors were calculated. using the programs Gaussian 09 (using the DFT/B3LYP/6-31G(d) method), Marvin, CrystalExplorer. The retention characteristics of quinoline derivatives were determined under RP HPLC conditions, hypercrosslinked polystyrene and octadecyl silica gel were used as sorbents, and an acetonitrile-water mixture in various ratios was used as an eluent. It has been established that the sorption characteristics correlate best with the polarizability, lipophilicity, and surface area of molecules of quinoline derivatives. An increase in these parameters leads to an almost linear increase in the retention factor on hypercrosslinked polystyrene due to an increase in the dispersion interactions of sorbates with the sorbent surface. However, for retention on octadecyl silica gel, significant deviations from a linear dependence are observed, probably due to the possibility of the formation of hydrogen bonds between sorbate molecules and residual unmodified hydroxyl groups on the surface of the sorbent. The influence of the solvation energy of quinoline derivatives in the eluent solution turns out to be different depending on the structure of the sorbate molecules and the nature of the sorbent. In addition, calculations have shown the possibility of different orientations of molecules of quinoline derivatives relative to the surface of sorbents, depending on the nature of the substituent [1]. In the presence of polar substituents or atoms with unshared electron pairs in the structure of the molecule, the orientation of the molecules by the functional group towards the bulk solution of the eluent turns out to be preferable, which reduces the area of contact with the sorbent and, thus, reduces the values of sorption characteristics.

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PROTON-PUMP INHIBITORS: A COMPARISON OF THE SAFETY AND PHARMACOKINETIC PARAMETERS AS TREATMENT FOR HYPERACIDITY *IN SILICO*

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Gastrointestinal hyperacidity is mainly caused by acid hypersecretion and one of the most common treatments for hyperacidity are proton-pump inhibitors (PPIs). Proton pump inhibitors are drugs that inhibit an enzyme in the parietal cells of the stomach which suppresses the secretion of gastric acid. The significance of the research lies in studying the differences of these PPI and comparing their efficacy as treatments to certain acid-related diseases, considering several factors such as chemical structure, dosage, solubility, physicochemical properties, and pharmacokinetics parameters. Online databases such as ADMETLab, SwissADME, and Way2drug were used as in silico tools to generate information and predict datasets that estimate the bioavailability and pharmacokinetics of each PPI. In general, PPIs are potent, safe, and are considerably good acid suppressors. All compounds possess excellent oral bioavailability. PPIs were identified to have high intestinal permeability but poor CYP450 inhibition. All PPI are inhibitors of CYP1A2 and CYP3A4 suggesting that these medications are poorly metabolized leading to potential accumulation in the plasma affecting other metabolism of other drugs, thus, increasing enzymatic activities of other CYP450 enzymes. Rabeprazole was the fastest compound to be half-activated due to its pKa value and has the most optimal acid stability; it is also a non-substrate of CYP2C19 and CYP2D6, indicating higher concentrations present after activation. Omeprazole, pantoprazole, and lansoprazole reduce the absorption of other drugs due to drug-drug interactions that induce absorption inhibition and potentially interactions with the cytochrome P450 pathway. Notably, all PPI were assessed to possibly induce hepatotoxicity, drug-induced liver toxicity, carcinogenicity, and respiratory toxicity based on the eight toxicophores predicted in silico. Among the PPI, dexlansoprazole, and lansoprazole were predicted to possibly induce cardiac failure when PPI were used for long-term medication of hyperacidity.

Overall, PPIs showed promising results in absorption which made them effective in reducing the production of acids. However poor distribution, metabolism, and excretion parameters indicate that these PPI can be metabolized longer leading to drug accumulation induced toxic effects such as liver damage, cardiotoxicity, particularly, in long term use. The result of this study requires further study on the pharmacokinetics and pharmacodynamics of PPI using *in vitro* and *in vivo* approaches to validate the predictions made *in silico*.

PREPARATION OF COMBINATORIAL LIBRARIES BY USING SCAFFOLD'S PROTEIN LIGAND INTERACTION FINGERPRINTS (PLIF)

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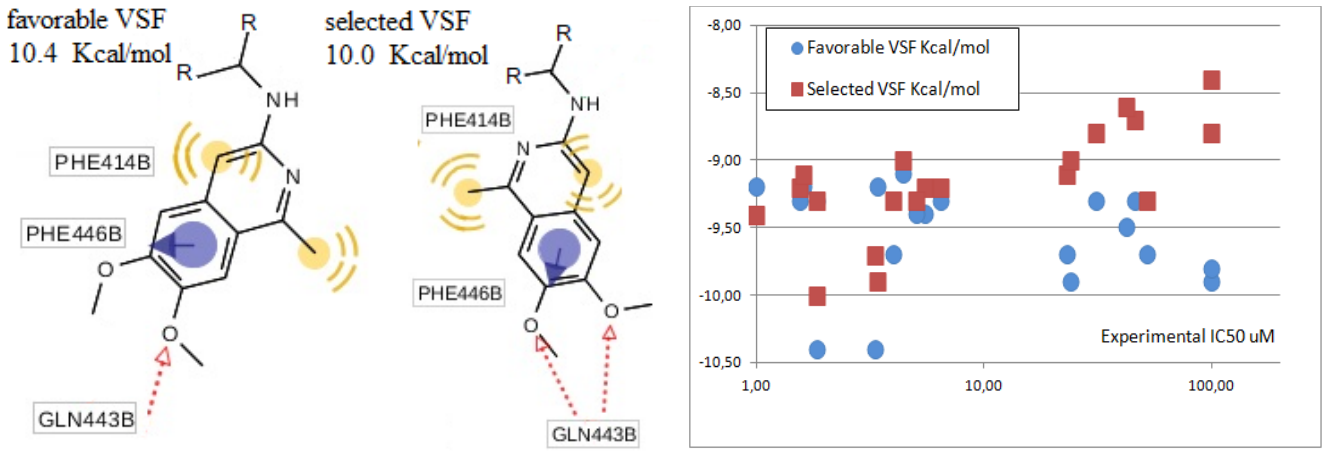
Protein-ligand interactions fingerprints (PLIF) allow to constraint docking scoring functions for more rational evaluation and cross validation of docking results, etc [1]. Compounds of combinatorial library (CL) contain some "main scaffold" and "decorative elements" like side radicals, additional cycles, pseudo-cycle, etc. Obviously both parts are critically important to provide sufficient input in protein-ligand interactions. We believe that the PLIF approach has a limitation in some situations since operate with information about whole molecule. Comparison of complete PLIF and separation similar or dissimilar compounds could reduce chemical diversity of CL. We were trying to avoid this limitation when used only "partial PLIF" for scaffold only. We were trying to answer to c117ouple of questions. How to separate constant part of scaffold's PLIF from variable part? Would be beneficial to use only scaffold's PLIF to design of combinatorial libraries?

We used simplest rules to determine PLIF of ligands and phosphodiesterase of cyclic nucleotide PDE4B [2]. Scaffold's PLIF were determined from several files: piclamilast-1xm4.pdb ciclomilast-1xlx.pdf and papaverine-3iak.pdb as a combination of F414-HP (hydrophobic bond), Q443-HB (two hydrogen bonds) and F446-PP (pi-pi-interactions). Compounds of CL were docked into PDB4B 1xm4.pdb by the Vina-protocol. It was selected set of compounds with appropriate scaffold's PLIF only. Figure shows that selected way of proposed ligand and the most favorable pose by the Vina-protocol were different. The diagram shows that Vina scoring function (VSF-binding energy Kcal/mol) of selected compounds were less than most favorable VSF of those compounds. Nevertheless the correlation between VSF of selected compounds and experimental IC_{50} [3] was much better than between favorable VSF and experimental IC_{50}: R2=0.51 vs R2=0.07.

This approach based on scaffold's PLIF could be used as a general way to select, range and score new virtual compounds for new CL. Chemical diversity of CL made by this approach would be compared with traditional approaches of CL planning.



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DEVELOPMENT OF LIGANDS TO NON-CANONICAL CHLORAMPHENICOL BINDING SITE USING VIRTUAL EVOLUTION OF LOW-MOLECULAR COMPOUNDS AND MD SIMULATIONS

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The ribosome is an antibiotic target of paramount importance because of the conservatism of its structure in different pathogens: about 60% of antibiotics target the ribosome, and about half of them bind in the nascent peptide exit tunnel (NPET) and the peptidyl transferase center (PTC). Resistance to these antibiotics is rapidly spreading, thence the search for fundamentally new antibiotics is an important, but unloved by drug manufacturers, task.

The ribosome undergoes many conformational transitions during its action. Binding sites of antibiotics can dynamically arise due to these transitions. For example, a non-canonical binding site of chloramphenicol and linezolid, dynamically arisen in the A/A, P/P-state of the *E. coli* ribosome, was previously identified. We attempted to create a ligand structure for this binding site using the method of low-molecular compounds virtual evolution. To do this, we chose 4 conformations of the non-canonical chloramphenicol binding site, that were most frequently encountered in the previous molecular dynamics simulations of the ribosome. With each conformation we ran a genetic algorithm, in which the initial population of 50 low-molecular weight drug-like fragments evolved. At each step of the genetic algorithm structures with the highest affinity for the binding site were selected by rDock program. Further their structural fragments were recombined, generating the next population, into which mutations were introduced: removal, insertion and replacement of atoms, as well as cycle closure. Every 10 generations the populations were exchanged between site conformations in order to take into account the conformational movability of the ribosome.

Such cross-conformation virtual evolution was carried out until complete degeneration in each of the populations. It was achieved in 50-70 generations depending on a conformation. The identified 4 evolutionary leaders were rationally refined and introduced into molecular dynamics simulation with 100 ns duration in the GROMACS package using the amber14sb force field. Analysis of the molecular dynamics results showed that one of the obtained structures (Figure 1) forms a stable complex, in which the ligand is held in the non-canonical chloramphenicol binding site by stacking interactions and multiple hydrogen bonds. This structure is the most promising for further study and synthesis.

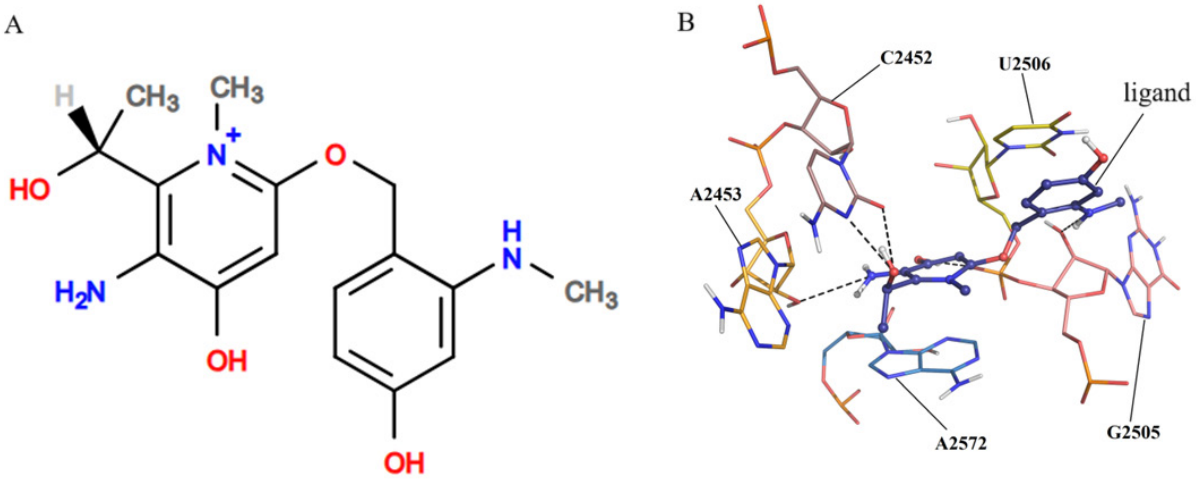

Figure 1. Ligand leader: **A** – structural formula; B – stable complex formed by non-canonical chloramphenicol binding site in A/A, P/P-ribosome and ligand

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VIRTUAL SCREENING AND MOLECULAR DOCKING OF COMPOUNDS PRESENT IN MEXICAN MEDICINAL PLANTS AS POSSIBLE INHIBITORS OF DPP-4

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Diabetes Mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia [1]. The disease has diverse etiologies, including autoimmune destruction of β cells in the pancreas, resulting in defects in insulin secretion, action, or both, as well as insulin resistance. Diabetes treatment typically involves insulin, particularly for patients with type 1 diabetes, and non-insulin hypoglycemic drugs [2]. A novel approach for type-2 diabetes treatment involves the inhibition of dipeptidyl peptidase 4 (DPP-4). This inhibition prevents the inactivation of glucagon-like peptide 1 (GLP-1), leading to increased active GLP-1 levels, which, in turn, enhance insulin secretion and reduce glucagon secretion, thereby lowering glucose levels [3].

In Mexico, as well as in some other countries worldwide, traditional medicinal plants are still used to alleviate symptoms of diabetes [4]. These plants may contain compounds that can potentially serve as drugs for diabetes control. Thus, the objective of this study was to identify plants used for diabetes management in Mexico and explore the reported compounds in each plant. Additionally, the study aimed to evaluate the behavior of these compounds in the body and their potential as DPP-4 inhibitors through Molecular Docking.

For this purpose, a search was conducted to identify plants traditionally used in Mexico for diabetes treatment. Thirty such plants were selected for this study. The compounds reported for these plants were obtained from databases, including KNApSAcK, CMAUP, and Phyto4Health, resulting in a total of 991 compounds with their corresponding SMILES codes. To ensure safety, a filtering process was applied to exclude compounds with a high probability of being carcinogenic, hERG blockers, genotoxic, having more than 1 PAIN, or not complying with the Lipinski rules. The ADMETlab 2.0 [5] platform was used for this filtering, resulting in 205 compounds suitable for further analysis.

The selected 205 compounds were subjected to molecular docking analysis with DPP-4 (4A5S) as the pharmacological target. Docking scores or binding free energies were predicted and calculated using AutoDock Vina [6]. Among the compounds tested, only 19 showed binding energies in the range of -7.0 to -9.9 kcal/mol. The three compounds with the highest binding energies were: (2α,3α,22R,23R,24S)-2,3,22,23-Tetrahydroxyyergostan-6-one (-9.9 kcal/mol), (4R,5R) -4,5-dihydroxy-2-isobutyryl-4-(3-methylbut-2-en-1-yl)-5-(4-methylpent-3-enoyl)cyclopentane-1,3-dione (-9.6 kcal/mol), and 6α-hydroxy-6-deoxocastasterone (-9.5 kcal/mol). Although the co-crystallized ligand showed a higher binding energy (-10.5 kcal/mol) during redocking, the present study suggests that it is possible to find potential DPP-4 inhibitor drugs from plants for diabetes treatment.

Our approach can serve as a means to suggest predicted targets for natural products, which could be validated experimentally, facilitating drug optimization through in silico steps.

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VIRTUAL SCREENING OF NATURAL COMPOUNDS AS POTENTIAL M^{PRO} INHIBITORS FOR SARS-COV-2 VIRUS: MOLECULAR DOCKING AND MOLECULAR DYNAMICS SIMULATION GUIDED APPROACH

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The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has significantly impacted human lives, overburdens the healthcare system and weakens global economies. The lack of specific drugs against SARS-CoV-2 is a significant hurdle towards the successful treatment of COVID-19. Plant-derived natural compounds are being largely tested for their efficacy against COVID-19 targets to combat SARS-CoV-2 infection. The SARS-CoV-2 Main protease (M^{pro}) is considered an appealing target because of its role in replication in host cells. To discover hit compounds that can be used alone or in combination with repositioned drugs, we curated a set of 2,24,205 natural product structures from the ZINC database and virtually screened against COVID-19 M^{pro}. The three sequential docking protocols (HTVS, SP, and XP) were performed to screen a library of natural compounds. Final 88 compounds were selected and post-processed using the MM-GBSA analysis for the generation of binding free energies. The top four compounds (ZINC000085626103, ZINC000085569275, ZINC000085625768 and ZINC000085488571) showing docking affinity against covid-19 M^{pro} enzyme in the range of -12.68 to -11.87, have been selected for MD simulation studies. The RMSD, RMSF and RoG analysis of the all four compound-protein complex indicated the absolute stability during 100ns MD run. Further the post MD simulation binding energies were calculated for all four compounds using gmx_MMPBSA and were found to be in range of -38.29 to -18.07 kcal/mol. Our *in silico* results suggests that all the above mention natural compounds have the potential to be developed as a COVID-19 M^{pro} inhibitor and can be explored further for advanced experimental research to evaluate the *in vitro* and *in vivo* efficacy of these compounds for the treatment of COVID-19.

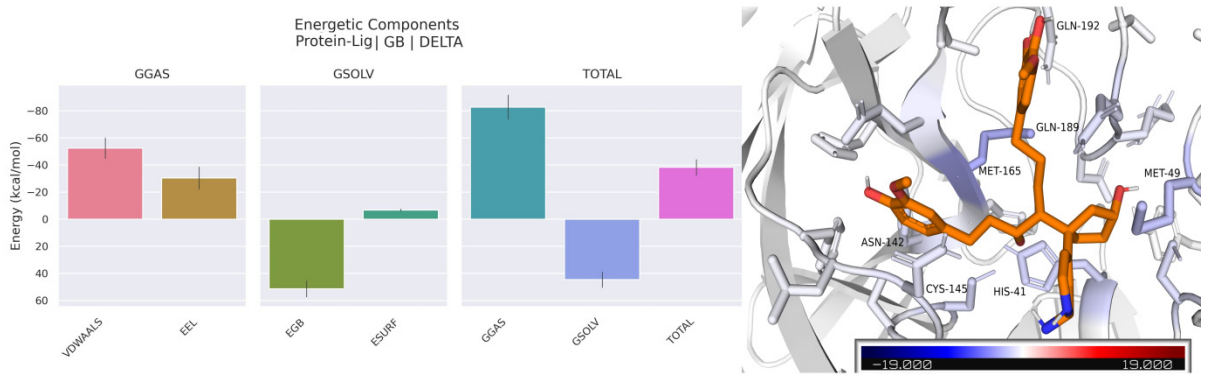

Figure. Diagrammatic representation of binding energy and binding pose obtained after MD simulation studies for ZINC000085626103-M^{pro} Complex

VIRTUAL SCREENING FOR DUAL-TARGETING LIGANDS AGAINST LASR AND PQSR RECEPTORS IN PSEUDOMONAS AERUGINOSA

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Pseudomonas aeruginosa is a Gram-negative, opportunistic, and pathogenic bacterium that is responsible for various nosocomial infections, classified as a critical priority by the WHO. It causes high morbidity and mortality rates due to acute and chronic infections. The bacterium exists both in planktonic form and as part of microbial associations, involving the extracellular production of polymeric substances that provide stability and protection against adverse conditions. Consequently, resistance to a wide array of conventional antibiotics is established, with one mechanism arising from intercellular communication mediated by signaling molecules within the quorum sensing (QS) system. This communication mechanism is responsible for the production of virulence factors and biofilm formation, regulated by the LasI/LasR, RhlI/RhlR, and PQS/PqsR systems. In this context, the research aimed to identify molecules with potential affinity against the transcriptional receptors LasR and/or PqsR (MvfR) of P. aeruginosa through drug repositioning using consensus virtual screening by molecular docking. The targeting of LasR and/or PqsR receptors (MvfR) is supported by the previous proposal of QS proteins as a strategy to overcome bacterial resistance. In addition, the PQS system has been reported to offer advantages in being specific to P. aeruginosa [1]. To achieve the stated objective, a consensus strategy was employed, utilizing two molecular docking programs and protein-ligand interaction fingerprints. According to the obtained results, drugs such as ketanserin, risperidone, and donepezil, among others, could potentially act as dual active molecules against LasR and/or PqsR receptors. Experimental assays would be necessary to confirm the activity of the selected candidate drugs with promising potential.

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EXPLORING THE THERAPEUTIC POTENTIAL OF *NIDUS VESPAE* IN NON-ALCOHOLIC STEATOHEPATITIS: NETWORK PHARMACOLOGY AND MOLECULAR DOCKING STUDY

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The emergence of non-alcoholic steatohepatitis as a growing health concern, contributing to severe conditions like liver cirrhosis and hepatocellular carcinoma, can be attributed to factors such as the Western diet, lifestyle changes, and underlying predisposing diseases. While existing medications offer treatment options, the quest for alternative therapies with fewer side effects necessitates extensive research. *Nidus vespae* (Honeycomb), a traditional medicinal remedy with history, has demonstrated lipid-lowering, antiinflammatory, and anticancer properties in HepG2 cell studies. In this research, the potential of *N. vespae* in addressing non-alcoholic steatohepatitis is explored through bioinformatics assessment. The study identifies chemical components from *N. vespae* via reputable journals, evaluating their drug-like characteristics and toxicity profiles. Databases are then employed to pinpoint targets relevant to non-alcoholic steatohepatitis. Gene enrichment analysis is applied to establish a network illustrating interactions between chemical constituents, proteins and pathways. KEGG pathways associated with the disease are predicted based on peer-reviewed literature. Prominent genes are selected from the network and assessed for disease progression involvement, along with the comparison of their protein sequences across organisms to support future *in vivo* studies.

These chosen targets are subsequently subjected to docking studies with corresponding compounds to predict binding interactions. Network pharmacology uncovers key protein targets including CYP1A2, PPARA, PPARG, PTPN1 and TNF with a focus on PPARG and PPARA validated through the therapeutic target database. These proteins influence molecular pathways such as metabolic pathways, AGE-RAGE signaling pathway in diabetic complications, NOD-like receptors, NF-kappa B and HIF-1 signaling patways. Comparative analysis shows protein sequence similarity between these targets in *Homo sapiens*, *Rattus norvegicus* and *Mus musculus*. Molecular docking of Isorhamnetin (B.E. -9.9 kcal/mol) and Chrysoeriol (B.E.-9.5 kcal/mol) with CYP1A2 exhibits promising results comparable to standard drugs. Overall, this study suggests that *N. vespae* potentially exerts its effects by influencing specific proteins and pathways associated with non-alcoholic steatohepatitis. Therefore, it is imperative to investigate the potential of *N. vespae* through both preclinical and clinical approaches.

GSK 137, WK 500B AS A POTENT SMALL MOLECULE BCL6 INHIBITOR: A COMPUTATIONAL SIMULATION APPROACH

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B-cell lymphoma 6, is a transcriptional repressor that plays a critical role in the development and function of B-cells, which are a type of white blood cell responsible for producing antibodies. However, BCL6 has also been implicated in the development of certain types of B-cell lymphomas, which are cancers that affect B-cells. In some cases, BCL6 may be inappropriately regulated or overexpressed, leading to uncontrolled cell growth and cancer development. Recently, researchers were trying to identify the small molecule which can inhibit BCL6. GSK137 and WK500B heterocycle compounds designed to specifically target and block the activity. By inhibiting BCL6, GSK137, WK500B compounds aim to disrupt the growth and survival of cancerous B-cells, making them potential candidates for targeted therapies in B-cell lymphomas and other BCL6-dependent malignancies. This work focused on understanding the binding interaction mechanism of the GSK137, WK500B in complex with BCL6 using various computational approach such as molecular docking, molecular dynamics, and DFT. Also, ADMET parameters were also analysed to know the compatibility of the drug within the human body.

IN SILICO EVALUATION OF BRACHYDINS COMPOUNDS WITH INHIBITION POTENTIAL AGAINST RESPIRATORY SYNCYTIAL VIRUS (RSV)

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Acute respiratory infections (ARI) are the main causes of morbidity and mortality among children under 5 years of age, accounting for 120 to 156 million cases annually. Respiratory infections occur when a virus infects the cells of the respiratory mucosa. Among viruses, respiratory syncytial virus (RSV) has multiple fusion glycoproteins (RSV-F), anchored through transmembrane domains, which may be determined in pre- and post-fusion stages, these proteins are key pieces for viral infection. Currently, about 35% of medicines originate directly or indirectly from natural products. Studies prove the antiviral activity of flavonoids, a class that has a variety of active and promising compounds, among these compounds, stands out the Brachydinas. Computational approaches represent valuable and essential tools for the discovery of new drugs, optimizing time and reducing costs. In this sense, the present work aims to evaluate the inhibition potential of Brachydinas, against an RSV-F in the post-fusion stage. For this, the smile codes and chemical structure of 3 types of Brachydinas (A, B and C) were obtained, later computational predictions of the ADMET properties were performed using the ADMETlab 2.0 program. Also, tests of molecular anchorage of Brachydinas against an RSV-F were carried out. Therefore, the RSV protein was obtained from the Protein Data Bank (PDB). The RSV-F (PDB code: 3rrr) protein and the ligands were optimized in the Avogrado and AutoDock Tools programs, for the visualization and minimization of the energy of the molecules. Subsequently, the Docking calculation parameters were determined, informing AutoDock Tools of the search algorithm and scoring function.

Prediction of pharmacokinetic characteristics demonstrated results within the parameters of Lipinski's Rule of Five, with good theoretical oral bioavailability, acceptable toxicity, and low penetration of the blood-brain barrier of Brachydinas (A, B and C). The molecules showed significant binding to plasma proteins, and volume of distribution within reference values. Furthermore, the molecular anchoring of Brachydina A resulted in hydrogen bonds, π–π interaction and Van der Waals forces (VDW). Brachydina B, on the other hand, did not obtain VDW interaction. Brachydina C stands out, which presented different interactions, such as: interactions of hydrogen bonds and polar bonds. The calculated energy of the receptor-ligand complex demonstrated high binding stability and significant interaction between ligands and target site, evidencing a possible antiviral activity.

This study was funded by the Research Support Foundation for Scientific and Technological Research and Development of Maranhão – FAPEMA. Validity year 2023-2024.

SYNTHESIS OF NEW HETEROCYCLIC COMPOUNDS CONTAINING CYCLOPROPANE FRAGMENTS AND *IN SILICO* ANALYSIS OF THEIR POTENTIAL BIOACTIVITY

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On the basis of chalcones **1a-f**, a series of new pyrazoles **2**a-**f** was obtained, and selective addition to a multiple bond with the formation of new indoles **3**a-**f** was also realized. A efficient one-pot synthesis of 2-pyrrolo-3'-yloxindoles **4a,b** and indoles **5a,b** were realized on the basis of unsaturated ketones **6a,b**.

A series of new compounds containing a unique combination of pharmacophore groups, including cyclopropane fragments, has been obtained.

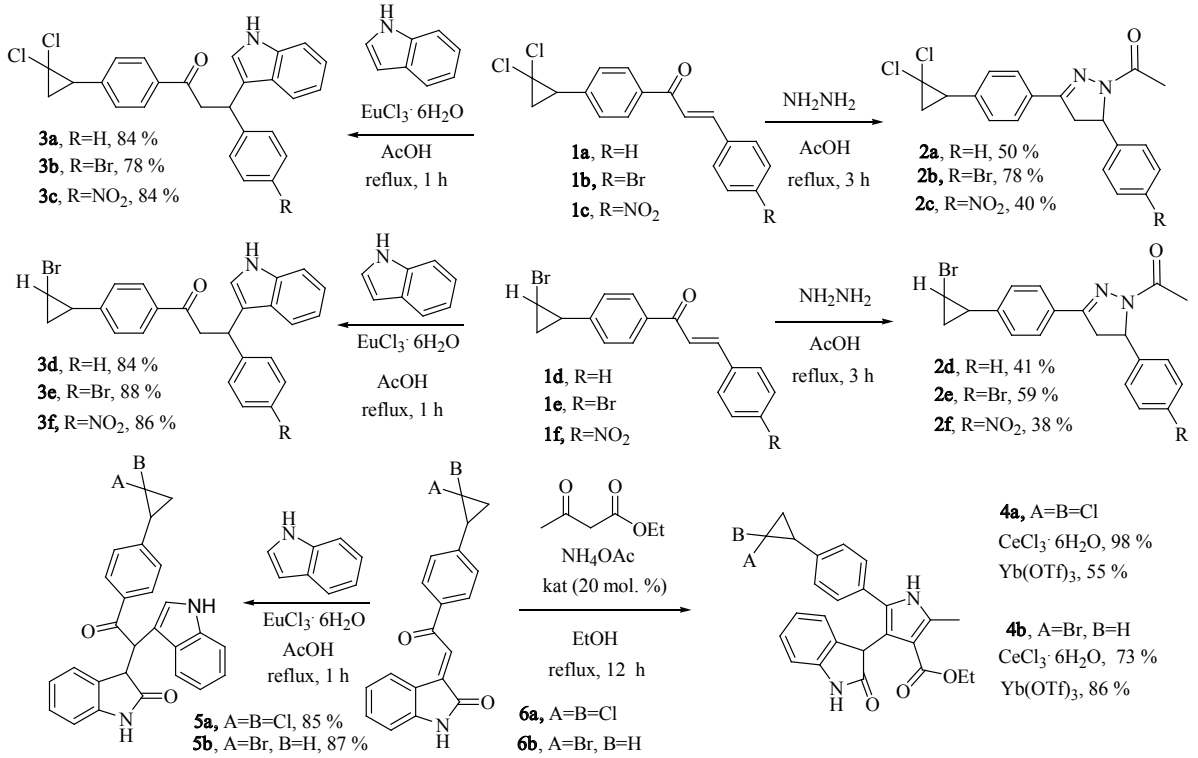

Figure. Structures and yield of all new compounds

The analysis of pharmacological activity 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, prediction of antibacterial, antifungal, antiviral activity, prediction of adverse drug effects using 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 with tumor and non-tumor cell lines, 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.

This work was supported by the SPSR (Belarus) no. 20211462.

SYNTHESIS OF 6-ARYL(ALKYL)-5-CYANO-2-THIOPYRIMIDINONE DERIVATIVES AND *IN SILICO* ANALYSIS OF THEIR POTENTIAL BIOACTIVITY

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A series of new compounds containing a unique combination of pharmacophore groups including thiopyrimidinone fragments with different functional moieties, has been obtained.

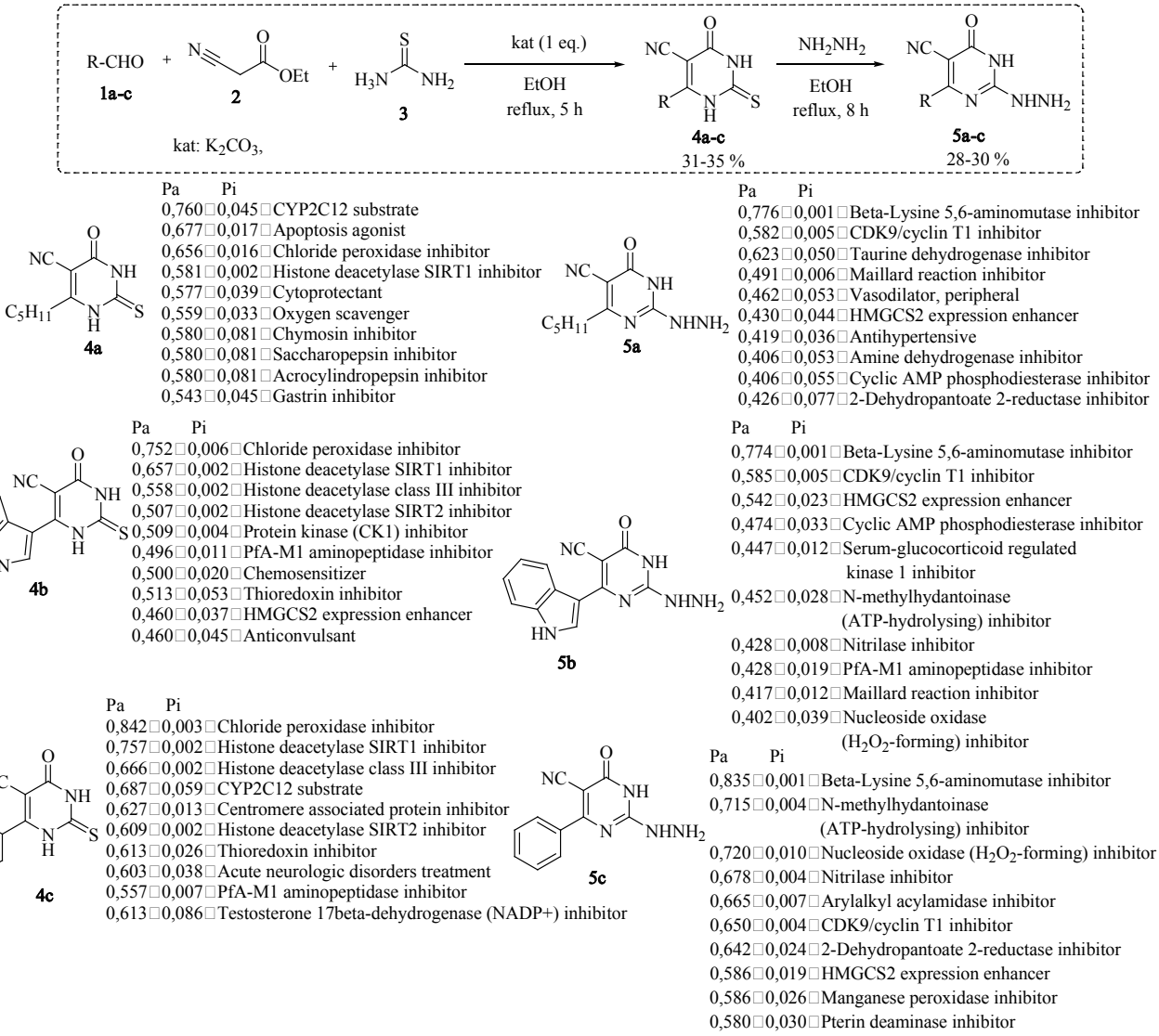

Figure. Structures, yield and predicted properties of compounds

The analysis of pharmacological activity 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, prediction of antibacterial, antifungal, antiviral activity, prediction of adverse drug effects using 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 with tumor cell lines, 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.

This work was supported by the SPSR (Belarus) no. 20211462.

TRENDS AND CHALLENGES IN CHEMOINFORMATICS RESEARCH IN LATIN AMERICA

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Chemoinformatics is an independent inter-discipline with a broad impact in drug design and discovery, medicinal chemistry, biochemistry, analytical and organic chemistry, natural products, and several other areas in chemistry. We have notice that several terms published in the literature refer to the same discipline and its use sometimes depends on the geographical region. It should be emphasized that the community has not yet agreed on a single title, unlike the closely related discipline "bioinformatics," whose term has mostly been approved. Regardless of the specific term, since the first applications of chemoinformatics in the '50s, the discipline has been evolving and expanding rapidly with the most recent and large advances in artificial intelligence (AI).

Through collaborations, scientific exchanges, and participation in international research networks, Latin American scientists have contributed to the development of this subject. Our work aims to discuss the current status and progress of the chemoinformatic discipline in Latin America. We team up to provide a perspective on the topics that have been investigated and published over the past twelve years, collaborations between Latin America researchers and others worldwide, contributions to open-access chemoinformatic tools such as web servers, and educational-related resources and events, such as scientific conferences. The principle of open science has been used to build many of the current chemoinformatics applications and developments, including teaching aids and research tools. Undoubtedly, the democratization of science would increase global connections between research teams and students of all academic levels. It would be easier to make connections between various geographical zones when we are aware of the study that has been done in various worldwide places.

The performed analysis revealed that linking and fostering collaboration within each nation as well as among other Latin American nations and globally is made possible by open science and the democratization of science. We also outline strategic actions that can boost the development and practice of chemoinformatic in the region and enhance the interaction between Latin American countries and the rest of the world. It is anticipated that the continued and sustained growth of research will attract funding and additional partnership between Latin American universities with industry and other public or private organizations. Overall, we anticipate that chemoinformatics will continue growing in Latin America.

MECHANISMS OF ENZYMATIC REACTIONS OF P-O BONDS CLEAVAGE IN NUCLEOSIDE PHOSPHATES

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For several decades, the problem of determining the type of mechanism for P-O bond cleavage of phosphoric acid esters both in a solvent and in a protein has been discussed. As a result of such processes, the leaving group (LG) is replaced by a nucleophilic agent (Nu). Substitution can occur either stepwise with the formation of a stable intermediate, or concerted through one transition state. In addition, a reaction may proceed through one of two pathway: a dissociative mechanism (Figure, violet) in which leaving group departure precedes nucleophilic attack or an associative mechanism (Figure, magenta) in which the nucleophile attacks prior to leaving group departure. In the case of a concerted mechanism, the degree of P-O_{Nu} bond formation and P-O_{LG} bond cleavage in the transition state determines whether the mechanism is dissociative and associative. Determining the type of mechanism experimentally or computationally is a time-consuming task. In this work, a method was proposed for determining the mechanism (associative or dissociative mechanism) of P-O bonds cleavage in various enzymatic reactions. This method is based only on the analysis of electron density in the structure of the enzyme-substrate complex.

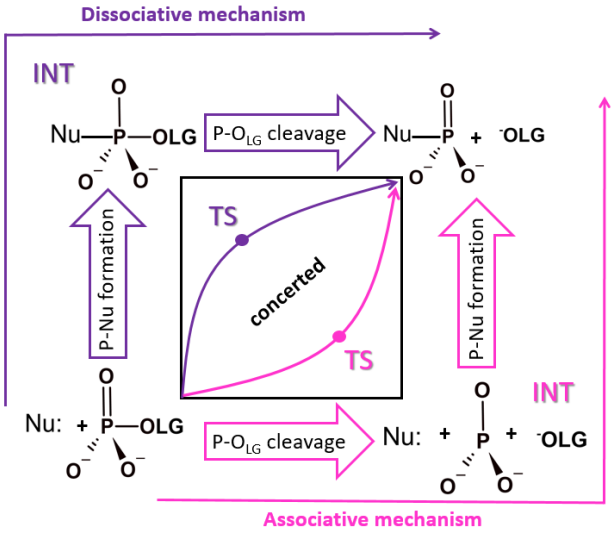

Figure 1. Mechanisms of the P–O bond cleavage.

Calculations of the electron density of enzyme-substrate complexes were carried out using a combined method of quantum and molecular mechanics. The calculations were carried out using the ChemShell Tcl software interface with the efficient DL-FIND optimizer and the TURBOMOLE quantum chemistry software package. The quantum subsystem was described by the electron density functional method with the PBE0 hybrid functional and D3 dispersion correction, as well as with a two-exponential basis with polarization functions on all 6-31G** atoms. Various electron density functions were calculated in the Multiwfn software package.

In this work, we proposed the Laplacian of the electron density $\nabla^2\rho(\mathbf{r})$ as a criterion for determining the type of mechanism. The sign of the electron density Laplacian indicates areas of electron density concentration ($\nabla^2\rho(\mathbf{r}) < 0$) or deconcentration ($\nabla^2\rho(\mathbf{r}) > 0$) around a given point $\mathbf{r}$. Thus, if a plateau with $\nabla^2\rho(\mathbf{r}) > 0$ is observed along the bond line, this indicates a tendency to break the bond between the phosphorus atom and the leaving group, which contributes to the nucleophilic substitution by the dissociative mechanism. In the case of the associative mechanism, a plateau with $\nabla^2\rho(\mathbf{r}) < 0$ is observed.

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IN SILICO PREDICTION OF CANCER-RELATED PROPERTIES OF *PASSIFLORA INCARNATA* ALKALOIDS

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Passiflora incarnata L. (wild passion flower, passion vine, or maypop) (*Passifloraceae*) is a climber herb with auxiliary tendrils with herbaceous or woody stems, brightly colored and conspicuous corona-shaped flowers, and yellow berrylike edible fruits. The expression "Passiflora" is derived from the Latin word "Passio" which was first found by Spanish explorers in 1529 and was characterized as a metaphor for "Christ's Passion". Its therapeutic use has been documented in conventional medical systems including Ayurveda, Siddha, and Unani. *P. incarnata* contains β-carboline alkaloids such as harmane, harmine, harmaline, harmol, and harmalol. In this research, interaction with tumor and non-tumor cell lines and organ-specific carcinogenicity of mentioned compounds were *in silico* studied by CLC-Pred and ROSC-Pred services, respectively, on the Way2Drug Platform.

Based on research consequences by CLC-Pred, the indicated highest anticancer effects of harmane, harmine, harmaline, harmol, and harmalol are on the Hs-683 Oligodendroglioma cell lines (primary glial brain tumor) with the 0.918 (0.002), 0.911 (0.002), 0.841 (0.003), 0.848 (0.003), 0.894 (0.002) P_a (P_i) values, respectively.

This ranking in the top three cell lines is followed for harmane and harmine by M19-MEL Melanoma (skin), NCI-H295R Adrenal cortex carcinoma (adrenal cortex); for harmaline by M19-MEL Melanoma (skin), PC-6 Small cell lung carcinoma (lung); for harmol by NCI-H295R Adrenal cortex carcinoma (adrenal cortex), PC-3 Prostate carcinoma (prostate); and for harmalol by HOP-18 Non-small cell lung carcinoma (lung), PC-6 Small cell lung carcinoma (lung).

At the same time, rodent organ-specific carcinogenicities were researched by ROSC-Pred, and some carcinogenic effects of known alkaloids were identified on the rats and mice organs. These effects were higher determined considering the male and female rats for harmane on the ear Zymbals gland; for harmine on the ear Zymbals gland, stomach; for harmaline and harmol on the all tumor-bearing animals, ear Zymbals gland; and for harmalol on the all tumor-bearing animals, respectively. Also, the results were observed considering the male and female mice for harmane, harmine and harmalol on the stomach, thyroid gland; for harmaline on the stomach, urinary bladder; and for harmol on the urinary bladder, thyroid gland, respectively. It should be noted that average P_a (P_i) values were 0.520 (0.0934); 0,4854 (0,1444); 0,701 (0,0968); and 0,664 (0,1232) for male and female rats, and male and female mice, respectively. When comparing the anticancer and carcinogenic P_a (P_i) values of these alkaloids, it can be concluded that the antitumor effects are higher with a significant difference.

In the end, being broad and profound anticancer properties of harmane, harmine, harmaline, harmol, and harmalol alkaloids contained in *P. incarnata* have been determined by Way2Drug Platform.

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A PROMISING MULTIDRUG ACTION OF PYRAZOLE DERIVATIVES AGAINST LUNG CANCER: A COMPUTATIONAL DYNAMICS APPROACH

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One of the serious health hazards undergoing in the world is cancer. Lung cancer is found to be one of the most frequently observed as malignancies in humans that causes serious illness and finally leads to death. According to medical history the lung cancer is divided into two sub types namely, small–cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The NSCLC develops very slower rate as tumour lumps than SCLC type. Furthermore, it has been discovered that almost 85% of patients who have lung cancer, were identified that they have NSCLC type infection than the SCLC. Moreover, NSCLC type can be detected only in the advanced stages of the disease [1]. But in the advanced stage of infection, the surgery is not an option, instead, cytotoxic drugs may be the best course of treatment. Patients with advanced NSCLC, however, may only have small survival gains with cisplatin-based treatment. Therefore, creating a novel and highly effective medicine to treat all generations of NSCLC forms of cancer is more difficult and continues to be a major problem for many researchers. Despite the great progress in drug development design, there are still two major drawbacks to the therapies that are now accessible. The first is the lack of selectivity for cancer tissues that results in undesirable side effects, and the second is the development of multidrug resistance in cancer cells. As EGFR undergoes generation-based mutations, it is interesting to note that tyrosine kinase inhibitors (TKIs) of EGFR provided a positive influence on the treatment of advanced NSCLC. Numerous studies have linked cancer to the increase of EGFR activity brought on either overexpression or mutation. As a result, EGFR has become a promising target for NSCLC anticancer drug research due to the EGFR's oncogenic mutations, which have resulted in the creation of three generations of very effective inhibitors. However, the majority of patients who take these medications for a long time acquire drug resistance. Three separate generations of EGFR mutations have so far been documented; each generation suffered mutations as a result of the medication therapy for NSCLC. However, the first generation of NSCLC cancer is treated with the medications Gefitinib and Erlotinib. Afatinib is also used to treat second-generation of NSCLC cancer. Osimertinib is now recognised as having remarkable efficacy against NSCLC cancer with the T790M mutation. A recent study found that even third-generation drugs have different sorts of mutations that encourage resistance to EGFR inhibitors [2]. Finding novel medications that might possibly treat all EGFR mutant malignancies is necessary to combat the treatment resistance that EGFR mutations produced in cancer. According to a recent analysis, one of the prospective medications that limit EGFR activity is pyrazole derivatives. In this regard, a number of pyrazole derivatives have been modelled, and the GROMACS programme has been used to determine the binding affinities of these compounds towards the EGFR and its mutants. Using the CHARMM force field, all EGFR-pyrazole binding affinities were calculated, including mutant EGFR structures that resulted pyrazoles showed better affinity than the control drugs which are available in the market as current drugs.

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STRUCTURAL-BASED INVESTIGATION OF NOVEL PYRAZOLE-THIAZOLE HYBRIDS AS DUAL CDK-1 AND CDK-2 INHIBITORS FOR CANCER CHEMOTHERAPY

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CDK-1 and CDK-2 are promising targets for cancer treatment as they are vital in tumor development, proliferation, and apoptosis during the cell cycle process. In treating cancers, CDK inhibitors (small molecules) are used to prevent the overproliferation and overexpression of cancer cells. Consequently, inhibiting CDKs is a promising treatment strategy in oncology. The limitations imposed by current CDK-1 and CDK-2 inhibitors, including neurotoxicity and the development of resistance, have prompted our group to use the novel synthesized pyrazole-thiazole hybrid analogues to investigate their possible potency against CDK-1 and CDK-2. The research study employed detailed computational approaches, including molecular docking, molecular dynamics (MD) simulations, post-MD analyses such as RMSD, RMSF, RoG, per-residue energy decomposition, hydrogen bond lifetime analysis, and drug-likeness studies like ADME properties prediction and cytotoxicity, to predict the properties and inhibitory potentials of synthesized pyrazole-thiazole hybrid analogues against CDK-1 and CDK-2. The in silico binding free energy and other analysis reported in the study revealed that four (7 g, 8a, 8b, and 8 h) of the tested molecules against CDK-1 demonstrated a higher binding affinity and structural influence on the target protein than the known inhibitor, Roscovitine (RVT). Similarly, in the case of CDK-2, four (7b, 8a, 8b, and 8f) of the tested compounds showed better results than (RVT). Furthermore, structural examination of the two proteins after binding to the inhibitors revealed that the compounds form stable complexes with the targets and significantly reduced the structural flexibility of the proteins. Therefore, this study suggests the novel pyrazole-thiazole hybrid analogues as potential CDK-1 and CDK-2 inhibitors and could be potential lead compounds for target-based anticancer drugs inhibiting the important proteins CDK-1 and CDK-2.

This study was supported by the Discipline of Pharmaceutical Sciences, College of Health Sciences, University of KwaZulu-Natal (UKZN) and Centre for High-Performance Computing (www.chpc.ac.za), both in South Africa. We also gratefully acknowledge National Research Foundation South Africa (NRF-SA) for funding this project (Grant No.112079 and 129247).

MOLECULAR TARGETS OF CAFFEINE IN BREAST CANCER TREATMENT: A NETWORK PHARMACOLOGY APPROACH

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Breast cancer presents an ongoing global health challenge, demanding innovative pharmacological interventions to improve patient outcomes. Concurrently, the surging consumption of caffeine-laden energy drinks raises concerns. However, the impact of caffeine on breast cancer risk remains a critical knowledge gap that needs exploration. Our study employs a robust network pharmacology and molecular docking approach to unravel the intricate molecular targets of caffeine in breast cancer. This investigation promises to deepen our understanding and unveil novel therapeutic opportunities, forging a path towards effective interventions against this pervasive disease. We identified breast cancer-related targets from GEO datasets (GSE20437) and TCGAdatabases, while caffeine targets were obtained from the SwissTarget Prediction database and literature. Common targets of both caffeine and breast cancer were considered for treatment using Venny software.PPI networks were generated using STRING and Cytoscape, identifying hub genes. Target proteins wereannotated using the GO database, and pathway enrichment analysis was performed using KEGG. To investigate the binding energies, target proteins were retrieved from the Protein DataBank and docking studies was conducted using AutoDock Vina to explore the binding interactions between caffeine and potential target proteins identified. We identified 108 targets, and 6 common targets, including CDK1, CCNB1, EGFR, and CCNB2, in the context of breast cancer. Gene Ontology (GO) and KEGG pathway enrichment analysis revealed their involvement in key pathways such as the P53 signaling pathway and Foxo signaling pathway, suggesting their critical roles in anti-breast cancer processes. Notably, caffeine exhibited the best overallbinding affinity when interacting with CDK1, CCNB1, EGFR, and CCNB2. These findings provide valuable insights into the potential molecular targets and pathways associated with caffeine's anti-breast cancer effects, offering new avenues for therapeutic strategies. Our study revealed CDK1, CCNB1, EGFR, and CCNB2 as potential targets of caffeine for breast cancer treatment. These findings provide valuable insights into the molecular mechanisms underlying caffeine's effects and offer new directions for therapeutic interventions, contributing to the advancement of breast cancer research and treatment strategies.

DEVELOPMENT OF A NOVELMACHINE LEARNING-DERIVED C-RASAR MODEL AND EXPLORING ITS SIGNIFICANCE OVER OTHER EXPERT SYSTEMS AND CONVENTIONAL CLASSIFICATION QSAR MODELS FOR MUTAGENICITY PREDICTIONS

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Mutagenic propensity is a significant insight for characterizing the comprehensive toxicological profile of chemicals and pharmaceuticals. The group of chemicals considered mutagenic is stressed in the REACH regulation for having their ability to influence human health. All types of chemical substances must have their mutagenicity evaluated as a part of their safety assessment.This requirement is outlined in the national legislations in the EU, Canada, the United States, and Japan.The ICH M7 guideline represented a milestone for the regulatory acceptance of computational methods for hazard assessment in pharmaceuticals. In accordance with the ICH M7 guideline (2017), pharmaceutical applicants may submit (Q)SAR data in place of traditional in vitro bacterial mutagenicity assay data for drug impurities.There are many commercial and non-commercial expert systems available for predicting the genotoxicity of chemicals. However, it is also important to develop freely available non-commercial models to complement the commercial models with models developed expanded chemical space and newer modelling algorithms.The majority of old-aged expert systems and QSAR models may show reduced performance over time for application on newer chemical candidates; thus, researchers constantly try to explore improving the modelling strategies or utilize previously unexplored chemical space. Lately a new methodology of Read-Across Structure-Activity Relationship (RASAR) has been introduced. This concept utilizes several Machine Learning (ML) based similarity functions in conventional QSAR modeling framework with the aim of increasing external predictivity of models from the available chemical information. This technique merges the advantages of statistics-based QSAR and grouping-based Read-Across method (two most widely used methods in toxicity assessment) to create interpretable models based on similarity and error based information [1]. We have developed here c-RASAR(classification-based RASAR) models using the benchmark Ames dataset (containing graded response values) of diverse organic chemicals (6512 compounds) for their potential mutagenic behavior[2]. The objective of the current study is to develop ML derived c-RASAR models and compare their quality to the corresponding conventional classification QSAR models in terms of various validation metrics.We have also checked the prediction quality of a true external set (216 compounds) containing a list of REACH-registered substances, biocides, endocrine disruptors, substances of very high concern, drugs, and drug impurities.In addition, we have also compared the performance of a free expert system OECD toolbox for the true external set chemicals and tried to understand the limitations of these model performances to explore the significance of new in-house model development and their application to the up-to-date current experimental data.

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IN SILICO PROTOCOL OF SIRNA DESIGN: APPLICATION IN CANCER AND COVID-19 TRANSCRIPTOME

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The current proteomics paradigm in biomedical research dictates that protein should be the focal point of drug and vaccine targets. Although this approach has provided progress and breakthroughs, especially in cancer and COVID-19 therapies, more work should be done for comprehending the exact molecular mechanism of these diseases. As current findings have pointed out that the flow of genetic information devises a transcriptomics paradigm with cascades of non-coding (nc)RNA, they become an alternative in devising future therapeutic agent design. One of the ncRNAs that are widely in use is the silencing (si)RNA. It has been widely applied in wet laboratory settings, with the help of in-silico methods. Thus, In silico transcriptomics refers to the use of computational methods to analyze and understand transcriptomes, which are the complete set of RNA molecules produced by an organism or cell type. One of the transcriptomics computational methods is the prediction of RNA structure. RNA structure prediction is a computational approach used to predict the secondary and tertiary structure of an RNA molecule based on its primary sequence. Several different algorithms and software tools can be used to predict RNA structure, and these can be organized into a pipeline that includes the following steps: The first step in an RNA structure prediction pipeline is to input the primary sequence of the RNA molecule that you want to predict the structure for. This can be done using a variety of formats, such as FASTA or GenBank. The next step is to predict the secondary structure of the RNA molecule, which refers to the base pairing patterns between the nucleotides in the molecule. After the secondary structure has been predicted, the tertiary structure of the RNA molecule can be predicted. This refers to the overall three-dimensional structure of the molecule, including any loops, bulges, or other structural features. After the structure has been predicted, it is important to validate the prediction to ensure that it is accurate. Herewith, the application of RNA structure prediction in cancer and COVID-19 transcriptome will be presented and discussed. The developed pipelines have successfully provided sufficient information on how to devise fine-grained siRNA design.

QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP ANALYSIS FOR ACYL GUANIDINE BACE-1 INHIBITORS

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Alzheimer's disease (AD) is clinically characterized with gradual loss of memory and cognition along with altered behavior and it accounts for 60-70% of all dementias. During AD, essential areas of the brain related to cognition get damaged and leads to loss of synapse, neuronal dysfunction, and brain atrophy. One of the attractive targets towards development of anti-AD therapeutics is (BACE1) and it is associated with major challenges like reduced brain permeability, short half-life and reduced oral availability. BACE1 inhibitors need to cross blood-brain barrier and neuronal membranes to access the target located in the brain and in the lumen of endosomes. In addition to the pharmacokinetic properties, understanding the essential structural features of the enzyme such as catalytic aspartic dyad, structural flexibility, and large binding pocket. Thus it is required to focus on development of small molecules with drug-like properties which can interact selectively with the large catalytic pocket (active site of BACE1). Based on the OECD guidelines, Quantitative Structure-Activity Relationship (QSAR) models have been developed for BACE-1 inhibitors comprising of forty nine acyl guanidine analogs. The QSAR models have been developed keeping in view the quantitative and qualitative applications. The model having good external predictive ability, which is reflected from high value of Q^2-F^n, R^2_{ex}, CCC_{ex}, etc. and robustness with respect to internal validation ($R^2_{cv} > 0.80$, $CCC_{cv} > 0.87$) was selected. Therefore, the models could be useful for prediction of BACE 1 inhibitory activity for yet-to-be synthesized derivatives. The close value of $R^2_{adj.}$ with R^2_{tr}, for all the models, indicates that the models have been built using appropriate number of molecular descriptors. Derived models are interpreted and identified the molecular descriptors which can be further used to implement the derived models.

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INTERACTION OF CURCUMIN WITH THE MAIN SARS-COV-2 PROTEASE: AN ANALYSIS BY MOLECULAR DOCKING

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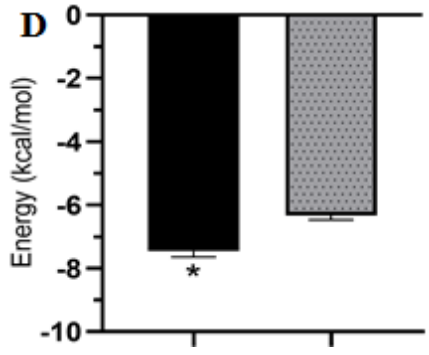
Over the past years, humanity has been engulfed in the pandemic caused by the SARS-CoV-2 virus. In light of this, antiviral therapies targeting the viral replication mechanism could prove immensely valuable in case management. Curcumin is a polyphenol derived from the rhizome of C. longa, exhibiting a diverse array of biological and pharmacological activities, including anti-inflammatory, antioxidant, and primarily antiviral properties.

Objective: The aim of this study was to assess, through molecular docking, the interaction between curcumin and the main protease (Mpro, 3CLpro) of the SARS-CoV-2 virus.

Methods: The main protease (Mpro, 3CLpro) was obtained from the Protein Data Bank (PDB ID: 7TLL), with a resolution below 2 Å and crystallized in complex with Nirmatrelvir (orally active type 3C protease inhibitor). Discovery Studio Visualizer (DS) 21.1.0 software was employed for ligand removal, and AutoDockTools 1.5.7 (ADT) software was utilized to add polar hydrogen atoms and Gasteiger charges to the target. Curcumin and Nirmatrelvir structures were retrieved from PubChem, and energy minimization was conducted using Avogadro 1.2.0 software, with the addition of polar hydrogen atoms and Gasteiger charges in ADT 1.5.7. Grid dimensions and anchoring coordinates were calculated using the AutoGrid module of AutoDock 4.2.6 software. The grid volume was set at 60x60x60 points (X, Y, Z dimensions) with a spacing of 0.375 Å for both tested targets. AutoDock Vina 1.2.0 was employed to perform molecular docking, using scripts for flexible and hydrated docking provided by the Center of Computational Structural Biology (CCSB) with 100 exhaustive runs. Ligand-target interaction images were generated using DS 21.1.0 and Pymol 2.5.4. The energy values underwent normality analysis using the D'Agostino & Pearson test, and data comparison was carried out through unpaired Student's t-test using GraphPad Prism 8.

Results and Discussion: The interaction affinity of Curcumin with the main protease (Mpro, 3CLpro) was significantly higher than that of Nirmatrelvir (Fig. D). This difference can be attributed to the larger number of conventional hydrogen bonds formed, which, when coupled with a greater number of Van der Waals interactions, contributes to complex stability. Furthermore, Nirmatrelvir formed an unfavorable bond with A:GLU:116, resulting in destabilization of the interaction. Both molecules formed hydrogen bonds with water. Interestingly, the most promising insight in our docking study was that curcumin exhibited a superior interaction affinity for (Mpro, CLpro) compared to Nirmatrelvir. Consequently, curcumin seems to have potential response in early stages of COVID-19 due to its possible effects against the inflammatory process, even though it might also be promising in the severe stages of the disease by virtue of its interaction with the main protease of the SARS-CoV-2. This outcome certainly does not confirm its anti-COVID-19 activity, but it can serve as a basis for further preclinical and clinical trials.



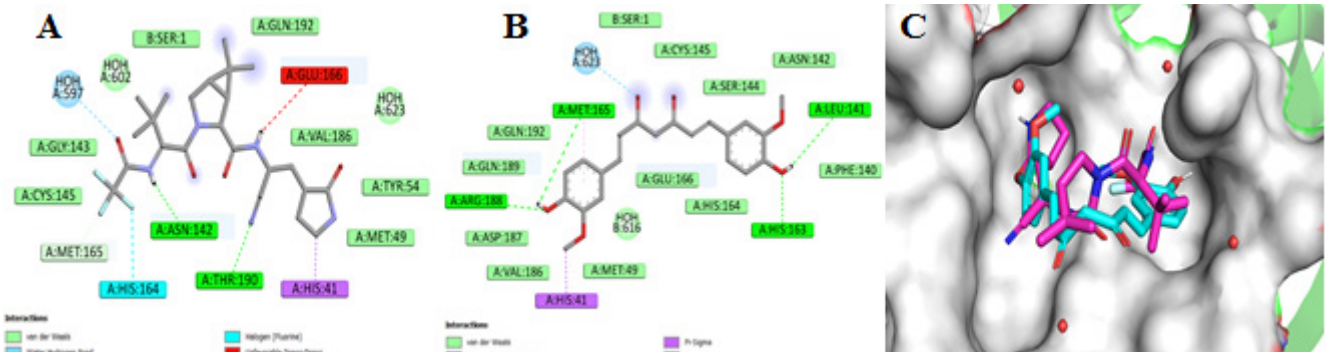


Figure. Ligand-target interactions.

VIRTUAL SCREENING AND DEVELOPMENT OF NOVEL SUBSTITUTED QUINAZOLINE DERIVATIVES AGAINST TARGETED ENZYMES FOR ITS ANTIPROLIFERATIVE ACTIVITY

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In 2020 WHO stated that, there was 2.3 million new cases and 685,000 deaths worldwide. According to the National Breast Cancer report, in 2023 an estimated 297,790 women and 2,800 men will be diagnosed with invasive breast cancer. Breast Cancer has become the number one gynaecological malignant tumor in the world and major health threats to women with a high mortality rate. Development of Multidrug resistance and cardio-toxicities of many existence drugs is the major problem in management of breast cancer.

To overcome the Multidrug resistance and lessen the cardio-toxic effects, it is an urgent need to develop novel drug candidates for improving chemotherapeutic efficacies with lower the toxicity against the molecular targeted enzymes such as HER2 (ERBB2), BRD4, PARP & EGFR. Most of the drugs for cancer treatment featuring quinazoline pharmacophore have shown promising therapeutic activity. In view of this biological significance, the present study involved Virtual screening and development of Novel substituted Quinazoline derivatives against targeted enzymes, to identify the Potential Hit Candidates specifically targeting against human breast cancer cell lines MCF-7 and MDAMB231.

A series of novel substituted quinazoline derivatives were designed and developed. Among the designed compounds, fifteen compounds were selected for further study based on its docking score using AUTODOCK, ADME property (SWISS ADME), Lipinski rule of five study (MOLINSPIRATION) and toxicity profile (OSIRIS & pRED hERG). All these studied compounds produced good binding interactions, ADME properties with no cardio-toxic effect against the targeted enzymes compared to standards (Tamoxifen, Imatinib).

The docking study results showed that compound RABP21 produced good binding score -9.20, -10.9, -10.2, -9.4 (kcal /mol) and RSUG38 showed good binding affinity -9.6, -10.1, -9.5, -8.8 (kcal /mol) compared to standards (Imatinib -8.7, -10.0, -9.0, -8.2 and Tamoxifen -6.4, -7.1, -8.8, -6.8) (kcal /mol) respectively against the targeted enzymes HER2 (ERBB2), EGFR, BRD4, PARP-I respectively.

The results showed compound RABP21 and RSUG38 with potential binding score and no cardio-toxic effect compared to standards (Imatinib and Tamoxifen). This strong observation, found to be that quinazoline derivatives as one of the biologically active scaffolds for the development of new potential clinical candidates with no toxic effects for the treatment of breast cancer.

APPLICATION OF THE MOLECULAR MODELING METHOD FOR THE DEVELOPMENT OF IMMUNOCHROMATOGRAPHIC TEST SYSTEMS ON THE EXAMPLE OF SARS-COV-2

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Rapid and effective diagnosis is an integral part of the infectious disease control system. One of the promising directions for achieving this goal is the creation of a biosensor device consisting of a biologically active component (antibody) and a fluorescent label that produces an analytical signal. One of the most actively developing types of immunoassay is immunochromatographic analysis (IHA). The widespread use of IHA is due to the fact that this analysis is rapid (test systems with an analysis time of 10-15 minutes), reproducible, requires the use of a minimum number of devices and devices, and is suitable for operational testing directly at the sampling site. A necessary condition for the reliability of the analysis result is the conjugation of proteins with a label with the preservation of their specific activity. Violation of the ability of antibodies to form a complex with the antigen directly affects the result of the analysis. A fundamental property of antibodies and other proteins is the isoelectric point, which is defined as the pH at which the macromolecule carries no net electrical charge. Knowing the surface charge distribution and the total pI, it is possible to predict the behavior of the antibody-substrate complex. Currently, there is no physicochemical method for determining the local charge on the AT surface; the influence of various factors on the surface charge can be calculated using molecular modeling [3]. Information about the surface charge of Abs is necessary for the conjugation of antibodies with QDs and obtaining a complex with high analytical characteristics (Fig.).

In this work, the isoelectric antibodies to Sars-Cov-2 CA521 FALA (PDB code 7e23) equal to 7.4 were calculated using the molecular modeling method using the Amber complex. Based on the results obtained, the covalent conjugation of this antibody with multilayer chalcogenide quantum dots was carried out by carbodiimide binding in combination with sulfo-N-Hydroxysuccinimide. The quantum dot-antibody complex was tested in an immunochromatographic assay and showed a 200% increase in fluorescence in the test and control zones, indicating successful conjugation under pH conditions below the isoelectric point.

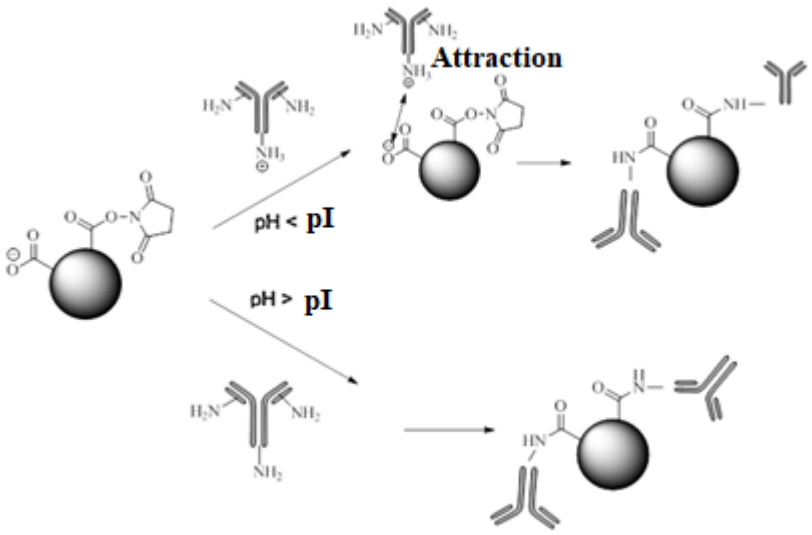

Figure. Carbodiimide binding activating reagents that provide the carboxyl-functionalized QD matrix with a distinct surface charge that can attract AT

IN SILICO AND MOLECULAR DYNAMICS STUDIES OF CORDYCEPIN FROM *CORDYCEPS MILITIARIS* AS POTENTIAL INHIBITORS FOR BIOMARKERS RELEVANT TO COLORECTAL CANCER

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Colorectal cancer (CRC) is notoriously known as the third most common cancer worldwide, and the fourth common cause of death caused by cancer, with 700,000 deaths per year. CRC incidence rates were observed to be rising in developing countries, including Malaysia, as was reflected by the increased prevalence of risk factors for CRC that are associated with westernization such as unhealthy diet, obesity, and smoking prevalence. The fungus family Cordyceps spp. has long been explored in Traditional Chinese Medicine (TCM) as food, tonic and folk medicine to treat diseases ranging from malaria to cancer. Cordycepin, an active component in *Cordyceps militaris* was shown to have anticancer and antimetastatic effects related to its adenosine and its derivatives. In the current study, cordycepin inhibitory property against several CRC biomarkers was explored in-silico [1]. Molecular docking and dynamics studies of cordycepin against 6 important CRC biomarkers, namely ca134spase-3, caspase-8, COX-2, IL-2 and IL-6 were performed and its affinity was compared with obatoclax, a Phase II clinical trial antitumor drug which induces apoptosis in cancer cells by functioning as an inhibitor for Bcl-2 family proteins. The findings show that cordycepin can inhibit the selected CRC biomarkers with comparable or higher affinity than obatoclax. The in-silico prediction study provides a screening platform for the development of anti-CRC drugs based on the Cordyceps spp., and in addition, provides a protocol to minimize the laboratory toxicological hazard and promotes the application of green chemistry computing in drug discovery research.

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OVULATION INDUCTION USING PHYTOESTROGENS IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME

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PCOS (Polycystic ovarian syndrome) is the common endocrinopathy in reproductive age women with a 6.5% prevalence rate. Polycystic ovaries and hyperandrogenism are the cardinal symptoms of PCOS. Due to their potential to act as modulators for estrogen receptor they interfere with the aromatase enzyme as shown in animal studies. So, phytoestrogens (PE) may be useful as a part for ovulation induction in polycystic ovary syndrome (PCOS). The following methods are employed for the work.

1. Generating designer ligands from information stored in crystallized receptor structure
2. Phytoestrogen-ER network construction for PCOS signaling pathway proteins in search of putative targets
3. Rescoring of docking score through the use of Machine Learning Methods
4. QSAR study for activity prediction of phytoestrogens and designer molecules

Based on the binding site conformation and residues involved structure-based drug designing methods were employed for designing molecules or to analyze the affinity of certain class of compounds *viz.* phytoestrogens to fit the ER receptor site crucial for binding. Construction of PE-ER network will highlight the synergy aspect of phytoestrogen if any such of them is found to be acting simultaneously on more than two proteins due to presence of genomic heterogenicity for PCOS and which are kept for further validation. Ligands that exhibit higher docking score accompanied by low nM activity value were considered for pharmacophore analysis that will help for the common molecular scaffold that can be used further to screen chemical libraries.

Finally, the chemical diversity of the phytoestrogens and ligands will be found through scaffold representations using molecular graphs so as to analyze the distribution of compounds. Regression analysis from the generated equation will give the predicted activity value of each such compound in nM concentration and the significance aspect of the equation and the co-relation will be further validated through the use of *F*-statistics.

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MOLECULAR DOCKING ANALYSIS OF DIETARY BIOACTIVE COMPOUNDS AGAINST APOPTOTIC INHIBITORS IN BREAST CANCER

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Breast cancer (BC) is currently the leading cause of death among women across the globe. Cancer cells possess distinct hallmarks that help them convert into malignant forms. Apoptosis resistance is one of the hallmarks of several cancers, including breast cancer. Bcl-2 proteins are essential regulators of apoptosis. Interaction of anti-apoptotic proteins (Bcl-2, Bcl2-A1, Bcl-xL, Mcl-1, Bcl-w) with pro-apoptotic proteins (Bax, Bak, Bad, Bim, Bik, Bid, Noxa, Puma, Hrk) leads to the induction of apoptosis. When the anti-apoptotic proteins are overexpressed, they help the cancer cells to evade apoptosis, induce breast tumorigenesis and develop therapeutic resistance. Therefore, anti-apoptotic proteins can be appropriate targets for developing therapeutic compounds against breast cancer. Tumor relapse, associated side effects, and drug resistance from chemotherapeutic drugs have increased the screening of natural compounds to prevent and treat breast cancer. Several dietary bioactive compounds have been shown to inhibit the proliferation, promote growth suppression and apoptosis of breast cancer cells. Therefore, we investigated the potential of dietary bioactive compounds available in the FooDB and PubChem database against Bcl-2 proteins of breast cancer using molecular docking analysis. Molecular docking was performed using AutoDock Vina for the study of binding efficiency. One hundred and sixty dietary bioactives were docked against the Bcl-2 protein target along with obatoclax [1] as the standard drug and three dietary bioactives mentioned in the literature – cucurbitacin, kaempferol, and mangiferin, inducing apoptosis in breast cancer cells.

Out of one hundred and sixty screened dietary compounds, nineteen bioactives exerted binding energies better than obatoclax and the standard bioactives. Bioactives with better binding energies were analyzed for their molecular interactions with the amino acid residues of the target. The top three scoring bioactives, currayanine, mahanimbine, and murrayazolinine, were studied to be present in different parts of *Murraya koenigii* (curry leaf plant), including root, stem, bark, fruit, seed, and leaves. Mahanimbine is also present in other medicinal plants like *Clausena anisata* (Horsewood) and *Murraya paniculata* (Kaamini). Therefore, dietary bioactive compounds can interact with anti-apoptotic targets of breast cancer and can be screened further for their potential in preventing and treating breast cancer.

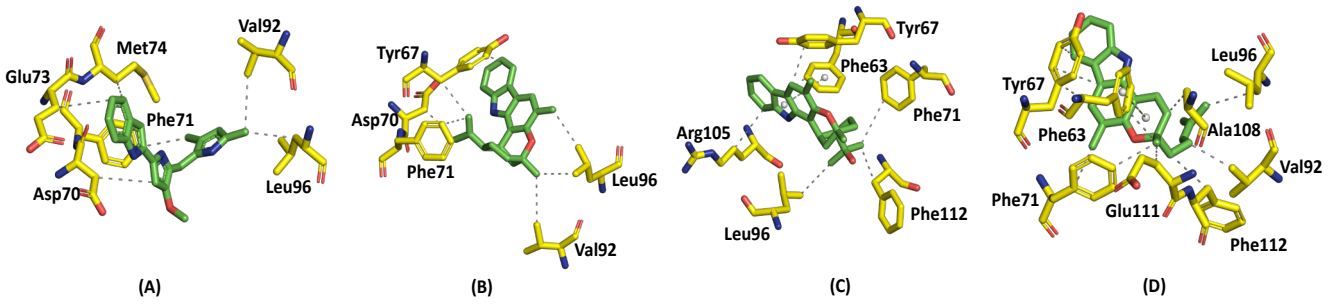

Figure. Molecular interactions of anti-apoptotic Bcl-2 protein (PDB ID: 2W3L) with (A) Obatoclax and bioactives exhibiting top binding affinities (B) Curryanine, (C) Murrayazolinine, and (D) Mahanimbine.

1. Sathishkumar, N., et al. (2012) *J. Enzyme Inhib. Med. Chem.,* **27**, 685–692.

INTEGRATION OF LBDD AND SBDD STUDIES ON DRUG DESIGN: A FATTY ACID AMIDE HYDROLASE (FAAH) CASE STUDY

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The inhibition of the fatty acid amide hydrolase (FAAH), an endocannabinoid system component, emerged as a potentially new therapeutic target for a range of clinical disorders such as acute and chronic pain and inflammation. Some α-ketoheterocycle derivatives demonstrated interesting analgesic and antiinflammatory activity in an extensive trial study. Some Ligand Based Drug Design techniques (such as HQSAR and kGCN models) using α-ketoheterocycle derivatives from five different datasets were generated to discover the relation between the chemical structures and the inhibition activity. Meanwhile, Structure Based Drug Design simulations as Interaction fields (MIF), molecular docking and ligand sites studies (LSI) from FAAH were performed using Autogrid software and FTmap/FTsite servers using both enzymes' monomers . Both studies' results were merged to propose predictive models. The constructed predictive model (HQSAR) using the full α-ketoheterocycle dataset had not good internal consistency and external predictivity, but the models built using the five sets, individually, had. The dataset 4 gave the best HQSAR model (fragment distinction A/B; fragment size 6-8, maximum compound 15 and best length 83). The most robust classification (kGCN) model (learning rate = 0.001 and batch size = 10) was constructed using the full data set. The quality of the best models with respect to internal and external predictiveness was evaluated by statistical parameters - such as leave-one-out cross-validation q^2 (0.857) and quality of test set predictions CCC (0.941) to the HQSAR model, and internal and external AUC-ROC (0.7922 and 0.7722, respectively) to kGCN model. The fragments contribution maps from both models were evaluated and compared (Fig. 1). From LBDD models' contribution maps and the generated probes using MIF and LSI, was observed that the oxazole ring, the ketone group and the apolar chain present in the structures of the inhibitors are important, besides the evidence of the Cys269 and Val270 residues importance for the potential interaction, confirmed by carried docking studies. These fragment and structural information evidence the potential ligand structural properties (Fig. 2) to the design of new FAAH inhibitors.

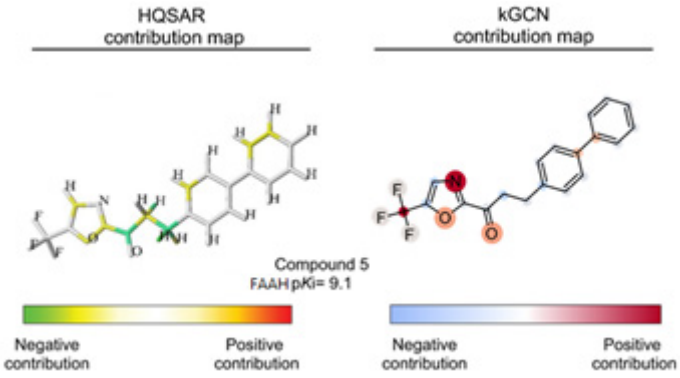

Figure 1. Fragments contribution maps from the best LBDD models.

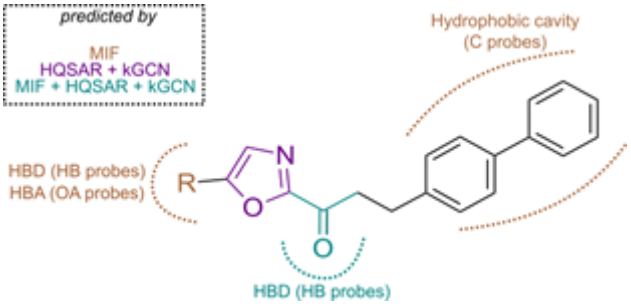

Figure 2. Potential structural properties of keto-oxazole FAAH inhibitors.

MOLECULAR DOCKING OF CHIRAL DRUGS ENANTIOMERS WITH DIFFERENT BIOACTIVITIES

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The human body is a chiral environment because it is composed of homochiral organic molecules that form the primary structures of biological macromolecules (amino acids, nucleic acids, lipids) [1]. It is the chiral environment that has a selective effect towards other enantiomers [2]. These sorts of interactions are most important for pharmacology because most of the currently used drugs are chiral. The interaction of two enantiomers of a drug with a biomacromolecule, such as an enzyme or receptor, is three-dimensional [3]. Because of this, biological molecules recognize enantiomers as different molecular entities due to their mirror three-dimensional structure, leading to different binding constants and different bioactivities of the enantiomers.

In the paper [4], based on the analysis of a set of one hundred chiral drugs, a correspondence between the chirality sign of the enantiomers and their bioactivity was established: most drugs in the set have a bioactive S-enantiomer, and R-enantiomers are more often responsible for the drug side effects.

There is an attempt to identify the reasons for the observed patterns of chiral specificity of drug enantiomers. To this end, the energetic aspect of the interaction of the opposite enantiomers with the target protein was considered. Docking of opposite enantiomers of the set drug into the active site of the target protein was performed, and quantum-chemical calculations of binding enthalpy for these enantiomers were made.

It was suggested that molecular docking can be used in the development of chiral drugs. It is known that the more efficiently an inhibitor binds to a protein, the higher the value of the binding constant and the lower the value of the free energy of protein-ligand binding. Thus, the bioactive enantiomer of the chiral drug was expected to have lower binding free energy and binding enthalpy compared to its antipode.

For 10 chiral drugs from a previously compiled set, the opposite enantiomers were docked into the active center of the target protein using the SOL program [5]. For the opposite enantiomers, the binding free energy to the protein and the binding enthalpy obtained using quantum-chemical methods in the MOPAC program were compared. The assumption was confirmed for most of the drugs reviewed (7 out of 10): the bioactive enantiomers have lower binding energy and binding enthalpy. Three drugs were exceptions. For these drugs, the discrepancies may be related to the method of adding hydrogen atoms to the protein model for docking, since it is known that the accuracy of docking depends on the protonation process.

Thus, one of the possible reasons for the observed patterns of chiral specificity of drug enantiomers may be the energetic aspect of the interaction of opposite enantiomers with the target protein. The results of this research can be used for developing application methods of molecular docking for the design of chiral drugs, which in turn can improve the process of creating new drugs.

This research was financially supported by the Russian Science Foundation, Agreement no. 21–71–20031.

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A BIOPHYSICAL APPROACH: ELUCIDATING THE BINDING INTERACTION MECHANISMS OF ROGINOLISIB (IOA-244) WITH TYROSINE PROTEIN KINASES (TPKS) AND HUMAN SERUM ALBUMIN (HSA)

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Tyrosine protein kinases (TPKs) plays a pivotal role in cellular signal transduction, and their dysregulation has been implicated in various diseases, including cancer. TPKs are a class of enzymes that play a crucial function in cellular signal transduction by transferring a phosphate group from ATP to the hydroxyl group of tyrosine residues on target proteins. In particular, overactive TPKs in cells contribute to uncontrolled cell growth and tumor formation, development of TPK inhibitors a promising strategy for cancer therapy. Roginolisib (IOA-244), a specific inhibitor of phosphatidylinositol 3-kinase (PI3K), which is an essential downstream effector of TPK signaling has shown potential in disrupting downstream signaling pathway is necessary for cancer cell proliferation and survival. Recently, IOA-244 has emerged as a promising candidate for inhibiting TPKs, that targets solid tumors and breaks immune tolerance. This study, focused to investigate the potential inhibitory activity of IOA-244 against Human Serum Albumin (HSA) and P13K through a computational approach that includes molecular docking, molecular dynamics simulations, to understand the binding interaction studies. Also, we calculate Density Functional Theory (DFT) to accurately predict and describe the electronic structure and properties of molecules. We will predict ADMET, to ensure safe and effective drug therapy. This biophysical approach, also opens up new and promising avenues for further research and potential therapeutic applications.

FROM MICELLE STABILIZATION TO DRUG DISCOVERY: STRUCTURAL STUDY OF MEMBRANOTROPIC ENZYME

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Trypanosoma cruzi (*T. cruzi*) is a parasitic protozoan responsible for Chagas disease, or *American trypanosomiasis*. This parasite is primarily transmitted through blood-sucking insects inhabiting rural regions of South America, and it can lead to fatal consequences if left untreated. Currently, two drugs, nifurtimox and benznidazole, are known to be effective against *T. cruzi*. However, their application is limited by severe side effects, debatable efficacy, and developed resistance.The final step of vitamin C biosynthesis in trypanosoma is catalyzed by the enzyme TcGAL, or L-galactonolactone dehydrogenase from *T. cruzi* (EC 1.3.2.3). Unlike humans, who get vitamin C with food, the parasite relies on vitamin C synthesized by TcGAL and is unable to uptake it from external sources. Therefore, TcGAL might be an attractive target for novel drugs. However, TcGAL is a membranotropic enzyme, and its inherent instability *in vitro* is a substantial challenge. To overcome this obstacle, in our group TcGAL was successfully stabilized within micelles, mimicking its natural membrane environment. This approach enables the exploration of TcGAL functions and kinetic properties using various substrates and inhibitors.

The limited throughput of the experiment makes *in silico* screening essential. Since the experimental structure of TcGAL is unknown, we employed AlphaFold and classical homology modeling to construct a full holoenzyme structure, including the cofactor FAD. Subsequent preliminary molecular dynamics (MD) simulations revealed a tunnel inside the protein, and ensemble docking with known inhibitors demonstrated a correlation with experimental kinetic data. Specifically, competitive inhibitors, which are close analogs of vitamin C, bind in the active site, while other inhibitors (such as lycorine, apiol and its analogs, allylbenzenes, and chalcones) bind differently.

However, the stability and observed conformational diversity of the enzyme in bulk raised concerns. Therefore, the objective of this work is a more rigorous investigation of the dynamic properties of the enzyme.

We conducted several microsecond-scale MD simulations utilizing both conventional and accelerated approaches to gather comprehensive structural data. We took into account different protonation states. The resulting trajectories were characterized by a standard MD analysis framework. Additionally, we performed clustering of the trajectories to determine representative enzyme conformations and estimate their relative populations. The contacts between the cofactor and the protein were identified to understand the realizable protonation states.

We employed dimensionality reduction techniques to visualize a conformational space to compare conventional and accelerated MD exploration power. As a more advanced method, we trained a distance-preserving autoencoder neural network on the structural data in an effort to construct an interpretable low-dimensional space, and the results were compared to other methods to assess its efficacy.

The enzyme dynamics demonstrated that the model is stable and suitable for application in structure-based drug design. The representative protein conformations we obtained will be employed in comprehensive ensemble docking within a dataset of drug-like molecules.

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CREATION OF SAR MODELS FOR PREDICTION OF T-CELL EPITOPES BASED ON PROTEIN STRUCTURAL FORMULAS

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Prediction of interactions between T-cell receptors and their ligands called epitopes is one of the key tasks for immunoinformatics. An epitope for T-cells is a linear protein fragment presented on a major histocompatibility complex (MHC). Epitopes are produced by cells in the complicated cascade of reactions. Viral epitopes and neoepitopes are usually presented on MHC I. Antigen processing for MHC I consists of three stages: ubiquitin-dependent protein degradation, fragment translocation into endoplasmatic reticulum via transporter associated with antigen processing (TAP) and fragment binding with MHC I. Models of antigen processing and presentation make vaccine development cheaper, simpler and faster. The COVID-19 pandemic demonstrates the necessity of rapid vaccine development for global risk minimization. These models can be also used to protein drug safety evaluation and cellular immunotherapy development. The existing programs convert proteins to the vectors of numbers or work with protein sequences as letter sequences models for prediction and don`t use information about chemical structures.

This work is intended to present the structure–activity relationship (SAR) analysis of antigen processing stages. We used the IEDB data for modelling ubiquitin-dependent protein degradation and prediction of binding epitopes with MHC [1]. The TAPPRED dataset was used for TAP affinity prediction [2]. It contains 613 peptides and almost all have length 9 residues. Also, MHCflurry 2.0 dataset was used for MHC binding prediction [3]. The dataset for protein degradation prediction contains 313,811 peptides from 56,187 proteins. The source protein sequences were divided into fragments with lengths 5, 7 and 9 residues using a sliding window. The central residue was marked as “active”. The TAP dataset was divided on “high-active” and “low-active” classes by 100 nM threshold. The dataset for MHC binding prediction contained 416,084 peptides and 193 alleles of human MHC. Peptides binding with certain allelic variant marked as “active” and other marked as “inactive”. The datasets were converted to Structure-Data files, which employ a representation of structural formulas in MOL V3000 format with molecule properties [4]. The SAR models were created and validated by the modified version of Prediction of Activity Spectra for Substances (MultiPASS) software which allows using different levels of multilevel neighborhoods of atoms (MNA) descriptors to describe the peptide’s structural formula [5, 6]which should reflect physicochemical features of site-surrounding regions. We have evaluated the reasonability of this approach by applying molecular descriptors (MNA. All models were estimated using 5-fold cross-validation.

According to values of invariant accuracy of prediction (IAP) we chose SAR models with optimal levels of MNA descriptors and peptide length. The protein degradation model has IAP equal 0.875 (0.874; 0.876). The prediction affinity to TAP model has IAP 0.855 (0.802; 0.895). The MHC binding model predicts binding with 171 allelic variants and half of this have IAP 0.927 (0.911; 0.950). The 95% confidence intervals presented in the round brackets. We combined these models to pipeline using Python language.

This work was supported by the framework of the Program for Basic Research in the Russian Federation for a long-term period (2021-2030) (no. 122030100170-5).

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DESIGN OF IMPRINTED PROTEINS BASED ON BOVINE SERUM ALBUMIN FOR DETECTION OF ZEARALENONE

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Specific molecular recognition is a fundamental feature of natural systems on which various biological processes rely. It is therefore not surprising that scientists have invested huge amounts of time and effort into harnessing, and more recently mimicking, biological function. Many synthetic approaches have been developed and one of the most interesting of these is molecular imprinting. Creation of molecularly imprinted polymers as supramolecular systems with tailor-made binding sites complementary to template molecules in shape, size and functional groups have already been widely used. Generally, it have been used, as robust and effective synthetic molecular receptors, in various technologies. The same procedure could also be applied for generation of specific sites in natural occurring proteins, when proteins are used instead of synthetic polymers as a matrix for imprinting.

Imprinting of bovine serum albumin by foodborne toxin, zearalenone, is one such prominent example [1]. Screening of this compound in maize and wheat have shown the prospects of using imprinted proteins as a recognition element in ELISA. It is well known that the procedure of imprinting contain a few basic steps [2]: (1) partial unfolding of a protein at low pH value and (2) adding of template molecules and self-assembling with the unfolded protein. However, the knowledge available on the theoretical study of imprinted proteins as ligand-receptor recognition systems is poor. Generally, the researchers prefer to study only the final analytical parameters of imprinted proteins without focusing on the causes of successful or unsuccessful synthesis results. At the same time, today computational modelling is a powerful tool for studying of mechanisms behind the imprinting process that provides enormous opportunities for the rational design of imprinted proteins.

Our work aims to explain the mechanism behind the imprinting of protein. In this work, we adopted comprehensive and fundamental approach to the imprinting of proteins, using a broad array of quantitative techniques that yield a more exhaustive characterization of the structural changes of the protein matrix. We carried out molecular dynamics simulation of bovine serum albumin (to simulate the first step of imprinting process) to understand how its conformation changes at low pH value just prior to addition of template molecules (zearalenone). Molecular modelling showed that the process by which bovine serum albumin change their conformational state is associated with displacements of molecular domains relative to each other. We hypothesized that imprinting occurs by binding in the several different regions located on the protein surface. In order to examine the binding mechanism in detail we considered interaction zearalenone with obtained bovine serum albumin structure via molecular docking method. We performed blind docking in the presence of multiple zearalenone ligands to identify and characterize potential binding sites. It was shown that there are at least seven potential binding sites for zearalenone molecules on bovine serum albumin surface. We hope that our theoretical studies and availability of computational methods will help in the rational design of imprinted proteins.

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IMPLEMENTATION OF CATBOOST CLASSIFIER PROTOCOL TO PREDICT THE HETEROGENEOUS HYDROLYSIS REACTION PROPERTIES OF ORGANOPHOSPHORUS SUBSTRATES USING QTAIM DESCRIPTORS

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While quantitative structure-activity relationship (QSAR) descriptors have proven effective in evaluating fundamental physicochemical properties, such as enthalpy of formation, water solubility, and lipophilicity (logP), as well as the efficacy of protein-ligand non-covalent interactions, predicting chemical reaction efficiency, even within the context of homogeneous catalysis, remains challenging. Traditional QSAR descriptors often overlook the critical aspect of electron density distribution, which is essential for an accurate description of reaction kinetics. In this regard, the Quantum Theory of Atoms In Molecules (QTAIM) analysis, rooted in the Bader theory postulates, provides a potential solution.[1]

In our study, we assessed the capacity of 63 organophosphorus pesticides to modify the A17 L47K catalytic antibody (abzyme). Extensive examination of this abzyme and its various mutants has been conducted in prior research. [2,3] For our investigation, we deliberately selected the most reactive mutant, L47K, which exhibits slow covalent inhibition by Paraoxon. The experimentally measured k2 value for this mutant is 1.3 ± 0.07 · 103 s–1. [3] We conducted 132 short 10 ps well-tempered ab initio metadynamics simulations (with 4 trials for each compound) and identified 18 pesticides that could be hydrolyzed by the abzyme, alongside 45 ‘inactive’ compounds. Our aim was to predict the reaction direction using the QTAIM descriptors matrix for all 63 examined pesticides. An inherent challenge arose due to the relatively limited number of entries in the acquired dataset, which might be insufficient for comprehensive description using certain machine learning (ML) protocols. To tackle this issue, we assessed the efficiency of the CatBoost Classifier algorithm [4], known for its promising results with small datasets. Consequently, our study investigated the suitability of QTAIM descriptors as a feature matrix for the selected supervised ML protocol. Despite the challenges and peculiarities of our ML input dataset, the CatBoost Classifier effectively distinguished 18 ‘active’ compounds from 45 ‘inactive’ compounds. It’s important to note that during ML cross-tests, certain polyhalogeno-substituted phenyl ‘active’ pesticides were occasionally misclassified as ‘inactive’. In most instances, the desired covalent product emerged in just 1 out of 4 trajectories, with approximate Δ‡G°298 values exceeding 22 kcal/mol. Furthermore, it should be emphasized that actual reaction barriers could potentially be even higher, considering that all trajectories originated from pre-activated geometries. As a result, in wet experiments, some of these compounds may be categorized as non-active.

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PITFALLS IN A (Q)SAR MODEL BUILDING TO PREDICT DRUG-DRUG INTERACTION INDUCED ADVERSE DRUG REACTIONS

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Drug co-administration is used for therapy improvement, decreasing of adverse drug reaction (ADR) rates, and in cases of co-morbidity. However, it may lead to a drug-drug interactions (DDIs), followed by an ADRs. The ADRs induced by DDIs vary from mild to severe, e.g., cardiovascular events leading to death. As DDI investigations are usually not conducted due to high financial and time costs, they become known *a posteriori*. There is a need for *a priori* knowledge about DDI risk. To solve this problem, (Q)SAR modeling can be used; however, the modeling for drug combinations has some pitfalls making it more difficult comparing to (Q)SAR analysis for single drug-like compounds starting with drug pairs description and finishing with model assesment.

In this study, we used two types of chemical descriptors, Random Forest method and "both-compound-out" cross-validation to create the models, but there was an unexplainable difference between sensibility and specificity of models trained on balanced sets.

Drug pairs are difficult to explore, and it's become obviously that it's not enough to just have balanced training sets to access potential of computer models to predict DDI risks. Such models show decreased sensitivity to the positive classes, which is lower than specificity. The first reason is a lack of negative control data, and the second is the low quality of the available data. The first problem was successfully overcome by using spontaneous messages response system analysis data as a negative sample. The second problem was successfully overcome using several methods.

Our work has succeeded in solving the unbalanced results of prediction and improving the results due to separated pair analysis. As a result, we were able to correctly access balanced accuracy, obtain balanced estimations, and propose a method to estimate drug pair samples using the Uniform Manifold Approximation and Projection (UMAP) method. The samples unbalance has been uncovered by the features of separate compounds. The unbalance of previously used samples according to the features of individual compounds was revealed. We found that the sensitivity of the prediction was significantly decreased due to the drugs that are associated with both positive and negative examples in the training set.

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COMPUTER MODEL FOR PREDICTION OF DRUG-DRUG INTERACTIONS MECHANISMS

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The combined use of drugs, which has become considerably more prevalent in recent years, can have a versatile effect on the human body: it can cause beneficial effects or lead to undesirable, possibly life-threatening Drug-Drug Interactions (DDIs). Many *in vitro* and *in vivo* studies have been carried out to identify the mechanisms that cause DDI, on the basis of which more successful and safe pharmacotherapeutic protocols are proposed. In some cases such experiments cannot be conducted (e.g. limitations of laboratory methods, high cost of research). Therefore, it is especially important to develop and improve computer-based methods for prediction and/or classification of potential DDIs.

Our work aims to introduce a model for predicting and classifying drug interactions based on the mechanism of their occurrence utilizing PASS (Prediction of Activity Spectra for Substances) algorithms [1]. The training dataset was extracted from MecDDI web resource [2], which hosts clear mechanistic clarifications for a large number of existing DDIs. Subsequently, a dictionary of terms describing mechanism of DDIs (which are referred to as "biological activity types" in PASS) predicated on the exact same resource was developed. The hierarchical structure of this dictionary is as follows: (1) two classes of DDI, which are pharmacokinetic (PK) or pharmacodynamic (PD); (2) seven Effects of DDI which are based on Class of DDI (for example, Affected intra/extra-hepatic metabolism in PK and Pharmacodynamic additive effects in PD) and (3) 109 Subeffects of DDI which are derived from Effect of DDI (CYP450 enzyme inhibition in Affected intra/extra-hepatic metabolism or Additive CNS depression effects in Pharmacodynamic additive effects). One out of three Severity Levels is assigned to each entry: Minor, Moderate or Major. The input data are the structural formulas of a pair of substances from which PoSMNA (Pairs of Substances Multilevel Neighborhoods of Atoms) molecular descriptors [3] are generated.

The result of prediction is a list of activity types exhibited by the selected pair as a result of specific DDI. An Invariant Accuracy Prediction (IAP) criterion, which is similar to AUC (Area Under ROC Curve), was calculated in Leave-One-Out Cross Validation (LOO-CV) procedure to assess the predictive power of PASS algorithms. To increase IAP values for Severity Level term, which were initially low due to high heterogeneity of the chemical structures, we created «multiplicative» terms which combine Severity Level with Class of DDI and Effect of DDI. The following mean IAP values were obtained: 0.76 for (Class x Severity Score) and 0.77 for (Effect x Severity Score) multiplicative terms, and 0.87 for all non-multiplicative terms (0.84 for Class, 0.71 for Severity score, 0.84 for Effect and 0.78 for Subeffect respectively).

The obtained IAP values indicate the applicability of the developed models for predicting and classifying DDIs with relatively high accuracy and can be used for practical tasks to predict mechanisms of known DDIs events as well as to predict DDIs for virtual pairs of substances that have not yet been synthesized. The use of multiplicative terms can increase the accuracy of prediction, which is crucial for determining the severity of DDIs.

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COMHT_PREDICT: ONLINE HDAC6 ACTIVITY AND ACUTE TOXICITY PREDICTIONS BY QSAR MODELS

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Some pan-HDAC inhibitors, for example, vorinostat (SAHA), panobinostat, have been approved by FDA for the treatment of hematological malignancies. However, the efficacy of pan-HDAC inhibitors in solid tumours has not been satisfactory partially due to their side effects and toxicity. Overexpression of HDAC6 is associated with the development of multiple cancers. The role of HDAC6 in the development of neurodegenerative diseases, in particular, Alzheimer's disease and multiple sclerosis, is also known. In addition, inhibiting HDAC6 can enhance the effect of the leptin hormone, which suppresses appetite. In this regard, considerable attention is paid to the development of selective HDAC6 inhibitors [1].

The existing QSAR models of HDAC6 inhibitors consider a molecular structure from various points of view using various methodological approaches [2, 3]. Unfortunately, most QSAR models have not been implemented in the form of a software product, which allows on-line virtual screening of libraries of chemical compounds in order to search for highly active HDAC6 inhibitor. When developing a strategy for the synthesis and testing of physiologically active compounds, in addition to the target property, it is extremely important to be able to assess toxicity. Therefore, the purposes of this work were as follows: (1) to develop regression QSAR models for HDAC6 inhibitors and acute toxicity (LD_{50}, rat, oral); (2) to integrate the developed QSAR models into a web application in order to conduct virtual screening of non-toxic HDAC6 inhibitors.

At the first stage, we processed the ChEMBL database (Target ChEMBL ID: CHEMBL1865, Standard Type: IC_{50}) with a total number of 6287 records. Polymers, mixtures, and compounds in salt form were not included in the set. Experimental activities expressed using the semi-maximal inhibition concentration (IC_{50}, nM) were converted into the negative decimal logarithm of this quantity (pIC_{50}) Multiple measurements for the same compound were averaged if their standard deviation was less than 0.5 logarithmic units; otherwise, they were discarded. The size of the formed set was 3854 compounds. A sample of compounds with experimental LD_{50} values when administered orally to rats was exported from the publication [4]. To evaluate the predictive ability of the models, the total sets of compounds was divided into training (80%) and test sets (20%). To describe a molecular structure, we used Morgan fingerprint descriptors 2 bits in radius and 1024 bits in length (RDKit library). The scikit-learn library and gradient boosting method were used to build models. At the second stage, adequate QSAR models (Q^2_{test}=0.66-0.72) of HDAC6 inhibitors and acute toxicity were developed. They were integrated into the developed web site *HT_PREDICT*, which is freely available at https://htpredict.streamlit.app/. The *HT_PREDICT* was created using the Streamlit framework. Information about the chemical structure of a certain compound in the *HT_PREDICT* application can be entered using linear SMILES notation or *sdf , *csv files. The *HT_PREDICT* is automatic verification and standardization of chemical structures using the MolVS library. When the user introduces the chemical structure of the compound to be studied, the *HT_PREDICT* web application initially checks for the experimental IC_{50} values of HDAC6 and LD_{50} for this compound. If this compound has experimental data, the average value of the experimental values of IC_{50} or (and) LD_{50}, the standard deviation, and the identifier of this substance in the ChEMBL (CAS number) database are displayed in the web application, and activity is not predicted. Our results will decrease the financial, time, and labour costs for discovery of new medicines.

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CATECHOL-DERIVED SCHIFF BASES: SYNTHESIS AND ANTIOXIDANT ACTIVITY

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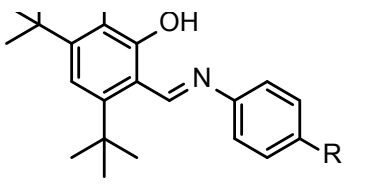
Reactive oxygen and nitrogen species (ROS and RNS) are implicated in several physiological processes, including host-defense against invading pathogens and signal transmission. Overproduction of ROS and RNS plays a major role in several pathophysiological conditions, such as atherosclerosis, cardiovascular diseases, neurodegenerative diseases and cancer [1]. Both naturally occurring and synthetic phenolic compounds find application as food preservatives and antioxidants to preserve appealing food odour, colour and flavour by attenuating the processes of lipid peroxidation associated with free radicals [2]. Mechanistic investigation of the reactions between free radicals and phenolic compounds as well as prediction of their reactivity on the basis of physicochemical descriptors may be of interest for the development of novel antioxidants with improved characteristics. The derivatives of 3,5-di-*tert*-butylbenzene-1,2-diol were synthesized as described in the previous paper [3]. The descriptors (dipole moment μ, polarizability α, refractivity R_M, hydration energy E_{hydr}, volume *V*) have been calculated using Hyperchem 8.0.9. The geometries were fully optimized using the B3LYP functional combined with the 6-311++G** basis.



1: R = H, **2:** R = CH_3, **3:** R = NO_2

Descriptor	Compound		
	1	**2**	**3**
μ, D	2.30	3.37	5.57
α, Å^3	38.82	40.65	40.66
R_M, Å^3	100.1	105.14	107.43
E_{hydr}, kcal/mol	-7.85	-6.61	-12.7
V, Å^3	1005.06	1058.58	1061.8

The compounds under study have been shown to posess IC_{50} values in the range of 13.3–39.7 μM when tested against DPPH free radical. The results obtained indicate that the antioxidant activity significantly depends on the nature of the substituent.

The work was carried out within the framework of the task 2.2.01.05 SRP “Chemical processes, reagents and technologies, bioregulators and bioorgchemistry”.

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APPLICATION OF GENERATIVE NEURAL NETWORKS FOR DE NOVO DESIGN OF POTENTIAL HIV-1 INHIBITORS

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Nowadays, the task of searching for new drugs is a highly demanded and important problem for society. At the same time, the use of generative neural networks makes it possible to obtain compounds that are not present in existing databases of chemical compounds, but which would be more effective in the task of inhibiting a given molecular target than currently known drugs.

In this work, a training sample of 94661 low molecular weight compounds was formed, relying on the inhibitor NBD-14204 in complex with the GP120 HIV-1 protein (PDB ID: 8F9Z) [1], to train a selected LSTM autoencoder model [2] using the following virtual screening methods: pharmacophore modeling and pharmacophore screening (Pharmit; https://pharmit.csb.pitt.edu), and molecular docking (AutoDock Vina; https://vina.scripps.edu). Using the LSTM autoencoder model, 46846 new compounds were generated, from which for a random sample of 7023 compounds the bound dissociation energies [3] was evaluated against protein GP120 of the human immunodeficiency virus type 1. According to molecular docking results for 7023 generated compounds, 527 conpounds showed bond dissociation energies equal to or better than the reference inhibitor NBD-14204 (-8.3 kcal/mol). The results of the LSTM autoencoder were obtained as linear SMILES representations. These representations were cleaned from duplicates, checked for validity and interpretability using the RDKit module (http://www.rdkit.org/), and converted from SMILES representations to 2D and 3D chemical structures of molecules (Fig.).

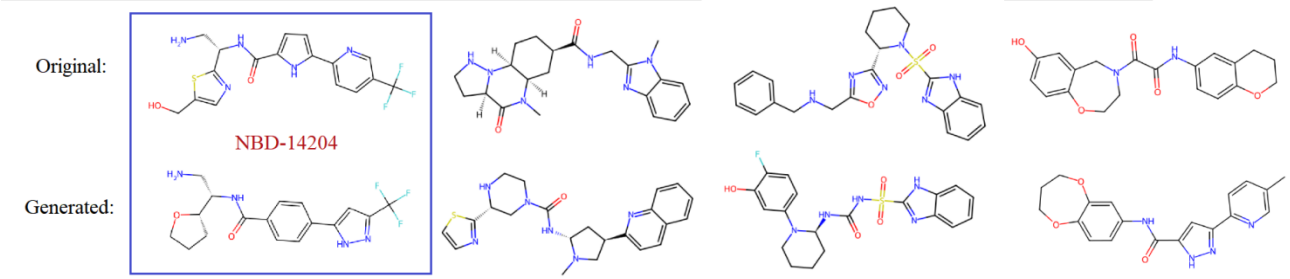

Figure. Examples of generation

For the 100 generated compounds with the best bound dissociation energy, were evaluated the aqueous solubility, synthetic accessibility and toxicity using the SwissADME program (http://swissadme.ch). After being tested for SwissADME 84 compounds showed themselves as potential drugs.

Future studies consider the prospect of improving the existing LSTM model of autoencoder by switching to reinforcement learning to achieve lower bond dissociation energies, and plan to evaluate the binding efficiency of the generated compounds by molecular dynamics methods.

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STRUCTURE AND DYNAMICS OF LATERAL HETEROGENEITY IN TWO-COMPONENT DOPC/DOPS LIPID BILAYERS: RESULTS OF COMPUTATIONAL EXPERIMENTS

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Lateral heterogeneity of cell membranes is an inhomogeneous dynamic lipid distribution on the bilayer surface. It occurs on a wide range of spatiotemporal features: from microdomains, like rafts, to nanodomains (NDs) existing in micro- and nanoseconds, respectively. Nanoscale lateral heterogeneity is known to be a key participant in the mutual dynamic adaptation of membranes to different biomolecular agents like receptors [1] and membrane-binding peptides [2]. However, despite the progress in super-resolution techniques, the experimental study of NDs remains challenging due to their small size and short lifetime. Therefore, they are often studied by computational methods supported by available experimental data.

In the present work, NDs in model bilayers consisting of a 512-lipid mixture of zwitterionic dioleoylphosphatidylcholine (DOPC) and negatively charged dioleoylphosphatidylserine (DOPS) were studied by molecular dynamics (MD) modeling. To numerically characterize the nanoscale lateral heterogeneity, we proposed a new method of NDs identification based on the attribution of lipid heads to tightly (TPH) and loosely (LPH) packed depending on the presence or absence of an excess of density of neighboring heads as compared with the average lipid density. Then, TPH located at a distance between their centers of mass less than 8.1 A for DOPC and 7.3 A for DOPS were united in groups named clusters.

Our analysis shows that 55-60% of the lipid heads can be classified as TPH for any considered system composition. The structure and dynamics of the identified clusters are found to be significantly different for DOPC and DOPS: DOPS clusters are characterized by a smaller average size (8 lipids for DOPC and 6 for DOPS) and a longer lifetime ($\tau = 4.0 \pm 0.1$ ns) compared to DOPC ($\tau = 0.3 \pm 0.1$ ns). The observed differences in the nature of the lateral heterogeneity are explained by more efficient lipid-lipid interactions (hydrogen bonds and lipid-ion-lipid bonds) in DOPS, formed predominantly between lipids in clusters. While DOPC clustering is caused by the “packing” effect of randomly distributed weekly interacting lipid heads. More importantly, this effect correlates with a more pronounced heterogeneity in the distribution of hydrophilic/hydrophobic properties of the DOPS membrane surface compared to the DOPC one. The obtained results can be used to study the molecular mechanisms of membrane surface adaptation to different biomolecules and also suggest further development with the inclusion of a larger number of components in the model systems.

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