BİRUNİ UNIVERSITY
"Future of Science"

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
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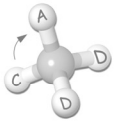
Computer-Aided Drug Design

Linking Design, Biology, Chemistry and Medicine



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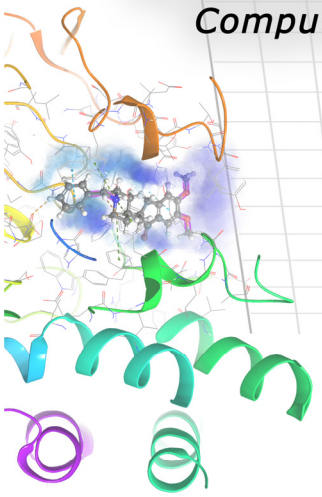
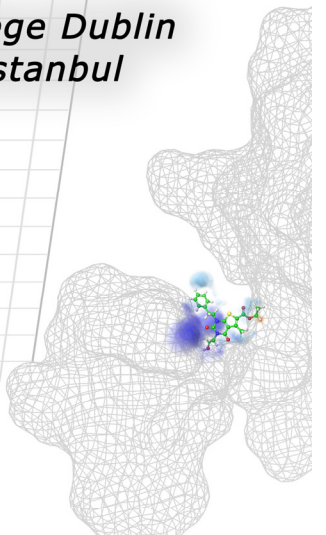
2. International Symposium and Workshop
Reyhan Conference Hall
Biruni University, İstanbul
11th - 12th May 2022

School of Pharmacy & Pharmaceutical Sciences, Trinity College Dublin
Computer-Aided Drug Design Center, Biruni University, Istanbul





Web: *http://www.caddsymposium.org*

Contact: *aece@biruni.edu.tr*

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ABSTRACT BOOK

School of Pharmacy & Pharmaceutical Sciences,

Trinity College Dublin

Computer-Aided Drug Design Center,

Biruni University, İstanbul

Web: http://www.caddsymposium.org/
Contact: aece@biruni.edu.tr

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Welcome

Dear Colleagues,

The focus of the symposium is to bring together academia and industry with an interest in the validation of novel biomolecule targets to treat disease with an unmet clinical need and in applying computational technologies towards the discovery and development of potential small molecule drugs. The main goal of the symposium is to forge interdisciplinary and trans-sectoral connections to foster novel drug discovery projects.

With this goal in mind we have a wide target audience spanning the fields of chemistry, biology, medicine, pharmacy, computational design and beyond. We wish to create an environment where large/ SME pharmaceutical and biotechnology companies, and academics can more readily appreciate how each sector contributes to drug discovery research and encourage closer collaboration.

While the scientific meeting will be guided by experts in the field of CADD, talks will be framed towards illustrating how chemistry – biology – design can synergistically interact with each other to bridge into the realm of medicine. We encourage early stage researchers who are not working on CADD projects to submit speaker/poster abstracts so that they can present their projects and stimulate discussion with other attendees. During the session discussions we expect the participants to find the answer to the question "how can computational drug design help me?"

CADD approaches are widely used in academia and by SMEs, pharmaceutical and biotechnology companies. A selection of successful applications of CADD includes the FDA approval of Captopril, Dorzolamide, Saquinavir, Zanamivir, Oseltamivir and Aliskiren. An aim of this symposium is to discover how these technologies can help with your project.

On behalf of the organising committee

Helen Sheridan
Trinity College Dublin
CO-CHAIR

Abdulilah Ece
Biruni University
CO-CHAIR

Speakers:

- **Helen Sheridan**
School of Pharmacy and Pharmaceutical Sciences - Trinity College Dublin, Ireland

- **Pedro Ballester**
Institut National de la Santé et de la Recherche Médicale (INSERM) Marseille, France

- **Mustafa Djamgoz**
Faculty of Natural Sciences - Imperial College London, UK

- **Ahmed Bourghida**
Clarivate Analytics - RMDM Group London, UK

- **Abdulilah Ece**
Computer-Aided Drug Design Center - Biruni University, Istanbul Turkey

- **Serdar Durdağı**
Department of Biophysics, School of Medicine - Bahcesehir University (BAU), Istanbul Turkey

- **Atilla Akdemir**
Faculty of Pharmacy, Computer-Aided Drug Discovery Laboratory
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- **Tao Zhang**
Technological University Dublin, Ireland

- **Mila Krämer**
Schrödinger GmbH, Germany

- **Junying Liu**
Trinity College Dublin, Ireland

- **Can Akçalı**,
Faculty of Medicine - Ankara University, Turkey

- **Klementyna Karlińska-Batres**
Clarivate, Germany

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- **Süleyman Selim,** *PhD Candidate Department of Biochemistry University of Oxford, UK*

Schrödinger Workshop:

- **Rita Podžuna,** *Executive Director, Schrödinger*
- **Mila Krämer,** *Schrödinger GmbH, Germany*

Clarivate Workshop:

- **Ahmed Bourghida,** *Clarivate Analytics - RMDM Group, London, UK*
- **Klementyna Karlinska-Batres,** *Clarivate, Berlin, Germany*

Program:

Symposium (Day I)

08:00 - 09:00 Registration and poster setup

09:00 - 09:10 Symposium opening *welcome*
by Professor Adnan Yüksel, Rector

Session 1: Chair: Helen Sheridan

09:10 - 09:15 Session introduction
by Prof Tuncer Değim, Dean of School of Pharmacy

09:15 - 09:45 Pedro Ballester – *Machine-learning scoring functions for structure-based virtual screening: where are we?*

09:50 - 10:20 Serdar Durdağı –*From "Molecule" to "Drug Candidate": A Sucessfull Example of Drug Repurposing Approach in COVID 19*

10:25 - 10:45 Coffee Break

Session 2: Chair: Serdar Durdağı

10:45 - 11:15 Helen Sheridan – *Natural Product Drug Discovery - from plants to clinical trials. The challenges and tools for revealing mechanism of action.*

11:20 - 11:50 Mila Krämer – *Enhancing Drug Discovery Using Modern Machine Learning Methods*
11:55-12:25 Atilla Akdemir – *A hierarchical VS campaign against Kinesin Eg5*

12:30 - 13:30 Lunch

Session 3: Chair: Nezih Hekim

13:30 - 14:00 Mustafa DJAMGOZ – *Neonatal ion channel expression in metastatic solid tumours: Multiple targeting strategies*

14:05 - 14:35 Junying Liu – *Network pharmacology provides new pharmacological data to ancient therapy*

14:40 - 15:10 Can Akçalı – *Combination of Biology and Computer Science: A Promising Therapeutic Tool For 21st Century Medicine*

15:10 – 15:30 Abdulilah Ece – *Computer-Aided Drug Design: methods, applications and challenges*

15:30 - 16:00 Coffee Break + Poster Sessions

Session 4: Chair: Junying Liu

16:05 - 16:20 Enes Seyfullah Kotil – *The atomic details of Griffithsin interaction with SARS-CoV-2's RBD*

16:20 - 16:35 Berna Doğan – *Applications of Molecular Modeling Approaches for the Identification of Novel Sars-Cov-2 Rdrp Inhibitors*

16:35 - 16:45 Abdullahi Ibrahim Uba – *Identification of Potential Antagonists of Crf1r Using Structure-Based Virtual Screening and Molecular Dynamics Simulation*

16:45 - 16:55 Nigar Çarşıbaşı – *Pharmacophore Model Accompanied by Conformational Dynamics Reveals New Anti-Cancer Drug Candidates*

16:55 - 17:05 Efe Doğukan Dincel – *Design, Synthesis, Characterization, Molecular Docking Studies and Anticancer Activity Evaluation of Novel Hydrazinecarbothioamide, 1,2,4-Triazole-3-Thione, 4-Thiazolidinone and 1,3,4-Oxadiazole Derivatives*

17:05 - 17:15 Mine Isaoglu – *Exploring the Potential of Natural Products As A-Glucosidase Inhibitors Through In Silico Studies*

17:15 - 17:25 Ismail Erol – *Unended Quest: In the Search of Dimerization Interfaces of AT1R-AT2R Heterodimer*

17:25 - 17:35 Mehreen Zaka - Fareed Asaad – *In silico and in vitro approaches for the identification of novel anti-cancer therapeutics against malignant glioma from ultra large libraries*

17:35 - 17:45 Pınar Siyah – *Discovery of New Malarial Targets and Identification of Potent Anti-Malarial Drugs*

Symposium (Day II)

Session 4: Chair: Abdulilah Ece

09:00 – 09:30 Tao Zhang – *Bioactive Indanes: Insight into The Bioactivity of Indane Dimers Related to the Lead Anti-Inflammatory Molecule Ph46a*

09:30 - 09:45 Cemal Köprülüoğlu – *Quantum Mechanics-Based Scoring Function for Structure-Based Drug Design*

09:45 - 09:55 Esra Nur Çakmak – *Investigation of Structure-Activity Relationships with Molecular Docking for Some Antiepileptic Drugs and Voltage-Gated Calcium (Cav) Channels*

09:55 - 10:05 Naz Mina Mert – *Identification of Potent and Selective Inhibitors Against Class IIb Histone Deacetylase Enzymes by Utilizing Virtual Screening Techniques of Known Compound Libraries*

10:05 - 10:15 Sergen Gül – *Oxime Ester-Based Di-Substituted Imidazole Derivatives for Inhibition of Acetylcholinesterase: Discovery and Structure-Activity Relationships*
10:15 - 10:35 Coffee Break

10:35 - 10:45 *Prize ceremony for best poster and best selected speaker*

Workshop

1. Schrödinger Workshop

Led by Dr. Mila Krämer and Dr. Abdulilah Ece

***10:45 - 12:30** – First Session*

***12:30 - 13:15** – Lunch*

***13:15 - 14:45** – Second Session*

***14:45 - 15:00** – Coffee Break*

- Introduction to the Maestro Interface
- AutoQSAR
- Ligand Designer
- Pharmacophore Modeling

2. Clarivate Analytics Workshop

Led by Dr. Ahmed Bourghida (Clarivate, Life Sciences Solution Consultant) &
Dr. Klementyna Karlinska-Batres (Clarivate, Regional Solution Consultant)

***15:30 - 17:30** – The Drug Discovery Journey from Early Discovery to Clinical Trials*
Led by Dr. Ahmed Bourghida (RMDM Group, Chief Scientific Officer) &
Dr. Klementyna Karlinska-Batres (Clarivate, Regional Solution Consultant)

- The Cortellis Suite: Drug Discovery and Clinical Trials
- Metacore: Biology and Early Discovery
- Decision Resources: Research Landscape and Epidemiology
- CMR: Clinical Trials Data Customized
A hands-on workshop with a demo. Complete understanding of how they can help your research.

***17:30 - 18:00** Discussion & Closing Talks + Certificate of Attendance*

MACHINE-LEARNING SCORING FUNCTIONS FOR STRUCTURE-BASED VIRTUAL SCREENING: WHERE ARE WE?

Pedro J. Ballester[a]

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Molecular docking usually predicts whether and how small molecules bind to a macromolecular target from one of its X-ray crystal structures. Scoring functions for structure-based virtual screening primarily aim at discovering which molecules bind to the considered target when these form part of a library with a much higher proportion of non-binders. Classical scoring functions are essentially models building a linear mapping between the features describing a protein–ligand complex and its binding/activity label. Alternatively, machine learning, a major subfield of artificial intelligence, can be used to build fast supervised learning models for this task. In this talk, we will provide an overview of such machine-learning scoring functions for structure-based virtual screening[1] and explain how are different from those intended for optimising a drug lead[2]. We will discuss what the shortcomings of current benchmarks really mean and what valid alternatives have been employed[3]. The latter retrospective studies observed that machine-learning scoring functions were substantially more accurate, in terms of higher hit rates and potencies, than the classical scoring functions they were compared to[3,6]. Several of these machine-learning scoring functions were also employed in prospective studies, in which mid-nanomolar binders with novel chemical structures were directly discovered without any potency optimization[4,6,7]. A discussion of prospects for future work completes this talk.

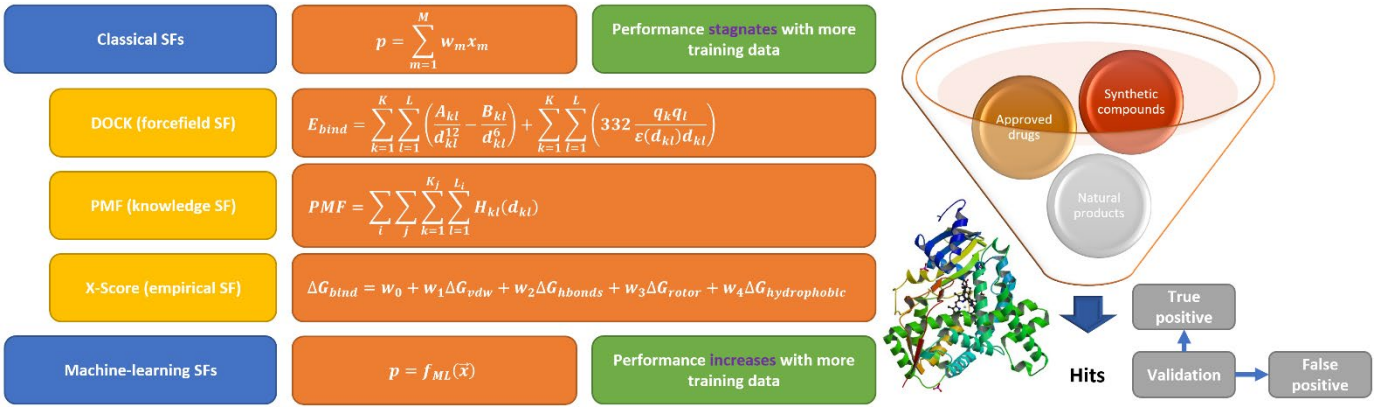

Figure 1. A schematic representation of different types of scoring functions.

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FROM "MOLECULE" TO "DRUG CANDIDATE": A SUCESSFULL EXAMPLE OF DRUG REPURPOSING APPROACH IN COVID 19

Serdar Durdağı

NATURAL PRODUCT DRUG DISCOVERY - FROM PLANTS TO CLINICAL TRIALS. THE CHALLENGES AND TOOLS FOR REVEALING MECHANISM OF ACTION

Helen Sheridan[a,b], Jinfan Wang [a,b], Tao Zhang[b,c], Gaia Scalabrino[a,b], Neil Frankish[a,b], Vilmar Bandero [a,b], Junying Liu, Shipra Nagar[a,b]

[a]*NatPro, Trinity Centre for Natural Products Research, Trinity College Dublin, Dublin 2, Ireland.*
[b]*School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin 2, Ireland.*
[c]*School of Food Science and Environmental Health, Technological University Dublin, Grangegorman, Dublin 7, Ireland.*
Presenting Author's E-mail: hsheridn@tcd.ie

The driving force behind my groups research is to find new therapeutic treatments for unmet clinical need and to finding meaningful uses for natural molecules. Our drug discovery focus has been informed by the natural world, global ethnomedical practice; molecular design, and the use of computer modelling and systems pharmacology to find natural molecules that target important receptors. This lecture will focus on two strands of our research. The first strand relates to the '*Houttuynia cordata*' decoction (HCD), a Traditional Medicine used therapeutically in large populations in Asia, and we have established therapeutic efficacy *in vivo* and *ex vivo* models of Inflammatory Bowel Disease. Secondly, I will present a first in class group of molecules, which incorporate the privileged 'indane moiety' that we have progressed to the clinic in both cases, we have been challenged to establish the mechanism of action. We have established that changing the chemical architecture of the indane scaffold changes the therapeutic and we see shifts from anti-inflammatory to anticancer activity, and molecular modelling has helped us identify optimised structures. In drug discovery funding is often dependent in understanding MOA, which can be very difficult to establish for 'naturally derived' molecules and extracts, and therefore we have had to use a range of approaches and techniques to build on our knowledge of biological fingerprints. Our approaches include *in vitro, in vivo,* and *ex-vivo* screening; use of arrays, *in silico* screening, and systems pharmacology (Figure 1). I have learned a lot about the journey from therapeutic drug discovery to human trials, and the challenges and obstacles that line the road. Experience led decision making about research is invaluable.

Through this lens of experience, the molecules my group is working on have real therapeutic potential and have been designed to address diseases with unmet clinical need and to eliminate some of the insurmountable obstacles to drug development.

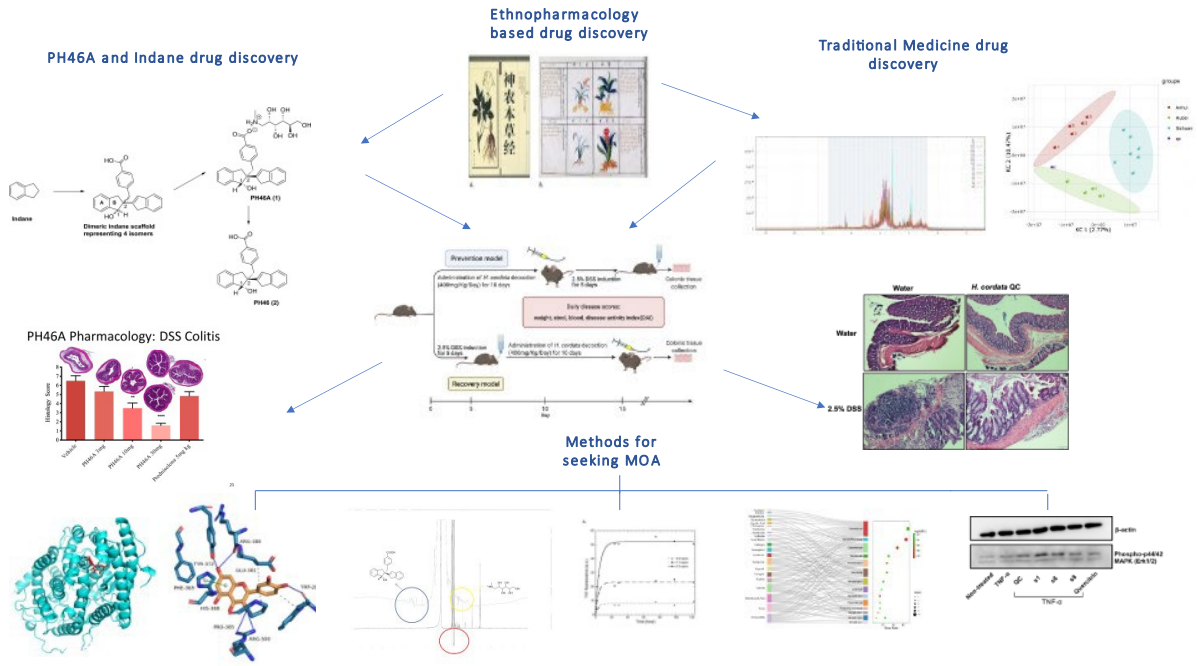

Figure 1: Drug discovery at TCD and tools for investigating mechanism of action of natural medicines.

ENHANCING DRUG DISCOVERY USING MODERN MACHINE LEARNING METHODS

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Exploring chemical space to find molecules which bind to a biological target is a "finding a needle-in-a-haystack" kind of task, making such molecular design endeavours challenging, time-consuming and expensive. This is compounded by the plethora of molecular properties which need to be considered additionally, e.g. off-target activity, physicochemical and ADMET properties, and synthetic accessibility. While a (virtual or real) high-throughput screen can provide good starting compounds, evaluating and optimising hits is difficult because the underlying structure-property relationships are complex and often not amenable to rigorous physics-based calculations.

To address this problem, simpler methods for structure-property prediction have been developed for decades. Classical QSAR models attempt to predict molecular properties for novel compounds from known data points, reducing the complexity of the system to a limited set of descriptors. Modern machine-learning methods build upon the same data-driven approach, but the automated and efficient training routines available today allow for arbitrarily flexible functions fitted to thousands (or millions) of data points. This can result in highly accurate models with an extended range of applicability across chemical space.

It is this flexibility and robustness which enable ML methods to improve or speed up many steps in the CADD pipeline. In the Schrödinger platform, ML models are used for applications as diverse as predicting pKa values, binding affinities, and other properties, as well as generating novel molecules, docking and improved force-fields. This presentation will demonstrate the value and ease of use of these techniques on selected examples.

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A HIERARCHICAL VS CAMPAIGN AGAINST KINESIN EG5

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Kinesin Eg5 motor proteins are homotetrameric proteins that are attached to two microtubules and play a role in the separation of centrosomes during cell division (Figure 1). Eg5 inhibitors block centrosome migration and thus lead to cell cycle arrest and apoptotic cell death. In addition, Eg5 selective inhibitors exhibit improved safety profiles compared to other antimitotic drugs that target microtubules. Therefore, Kinesin Eg5 proteins are accepted as target proteins for new generation anticancer drugs.[1, 2]

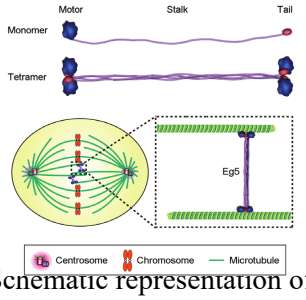

Figure 1. Schematic representation of Eg5[3]

Potent Eg5 inhibitors are available, but their numbers are limited. In addition, no Eg5 inhibitor has been approved for clinical use by the FDA or EMA to date. However, several drug candidates are currently being studied in clinical trials. Thus, there is still an urgent need for the development of new and selective Eg5 inhibitors.
In this ongoing project, we have set-up hierarchical virtual screening procedures that consists of pharmacophore screenings (successively Shape-GPU and Phase), HTVS docking studies followed by SP, XP and MM-GBSA rescorings and molecular dynamics simulations.
Complementary to our docking and rescoring procedure, we will also use active learning docking studies. Both techniques have been and will be applied to several large compound collections.

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NEONATAL ION CHANNEL EXPRESSION IN METASTATIC SOLID TUMOURS: MULTIPLE TARGETING STRATEGIES

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Cancer, particularly metastatic disease, is a major health problem and much unmet need remains in its clinical management. We have discovered that metastasis in carcinomas is promoted (may even be initiated) by de novo expression of functional voltage-gated sodium channels (VGSCs). Thus, cancer cells become electrically excitable upon (or prior to) becoming metastatic and it is this hyperactivity that is the root of the cancer aggressiveness. We called this phenomenon "Celex" (for cellular excitability). In several carcinomas the predominant VGSC subtype is Nav1.5. Where examined, as in human breast and colorectal cancers, the channel has been found to be the neonatal variant (nNav1.5), resulting from alternative splicing of exon 6. Metastatic progression can be suppressed by inhibiting the channel activity. This may be possible as follows.

1. Small-molecule inhibitors of nNav1.5. The channel can be pharmacologically distinguished from its 'nearest neighbour', adult Nav1.5 (aNav1.5), using spider toxins, and has a distinct pH sensitivity. This enables a high throughput strategy as well as design of a nNav15-specific peptide drug.
2. Monoclonal antibody for nNav1.5. A blocking polyclonal antibody has been produced with 100-fold selectivity for nNav1.5 over aNav1.5. The voltage and use dependencies of the antibody are ideal for cancer cells. A monoclonal antibody that has also been produced and sequenced is currently being validated.
3. Small-molecule inhibitors of the 'persistent current' (INaP). This develops under hypoxia, which occurs in growing tumours. INaP can be blocked selectively using drugs like ranolazine and this also significantly inhibits invasiveness and metastasis.
4. Combination therapies. Several combination therapy strategies are possible for increasing the effectiveness of therapy using modulators of ionic including VGSC mechanisms. This includes exiting therapeutic modalities such as chemotherapy and immunotherapy.

In conclusion, metastasis, the main cause of death from cancer, can be controlled using repurposed drugs as well as novel, selective inhibitors of nNav1.5 or INaP. This is possible as monotherapy as well as combination therapies. Such strategies could ultimately enable conversion of cancer into a chronic condition with which we can live!

NETWORK PHARMACOLOGY PROVIDES NEW PHARMACOLOGICAL DATA TO ANCIENT THERAPY

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Systems pharmacology is a new strategy to uncover the mechanism of action of natural products as drug candidates, providing a powerful way to identify novel mechanisms of potential natural products with therapeutic effect -. This approach has emerged as a powerful tool to overcome the limitations of traditional methods, such as the ability to predict the adverse effects of a drug and the likelihood of failure during clinical trials, by applying systems biology principles to the pharmacology field. This method combines the multi-omics dataset, computer modeling, and chemical biology to reveal pharmaceutical actions and guide drug discovery. Therefore, computational drug design (CADD) combined with systems pharmacology can be viewed as novel in-silico screening approach to drug discovery utilising chemoinformatics, bioinformatics, structure biology and chemical biology. This strategy includes target-based virtual screening—molecular docking, ligand similarity-based virtual screening and inverse screening (inver-dock), providing a powerful tool for target identification of drug candidate, multitarget discovery, and natural bioactive product profiling. It can be also used for selectivity profiling of drugs, drug repositioning, safety profiling and metabolism profiling prediction (ADMET).

Case study 1: New data on ancient remedies

COVID19 pandemic is a mass trauma to all the people around the world and it has remained an uncontained, worldwide pandemic. The discovery and clinical application of new or existing drugs or the potential use of traditional medicines against SARS-CoV-2 is important to assist in alleviating the current pandemic situation as the viruses are responsible for a growing economic, social and mortality burden. Naturally occurring antiviral agents acting against general coronaviruses can be explored via their mechanism of action as low toxic side effect therapies for COVID19. *Houttuynia cordata* Thumb. (Saururaceae, HC) is a traditional herbal medicine recognized for its favorable antiviral properties, particularly against clinically enveloped viruses which has found use in Asian countries, including China, Japan, and Thailand. As a potent folk therapy used to treat pulmonary infections, further research is required to fully elucidate the mechanisms of its pharmacological activities and investigate its therapeutic potential for treating pneumonia caused by SARS-CoV-2. The data suggests that HC exerts collective therapeutic effects against pneumonia caused by SARS-CoV-2 and thus affords a sound theoretical basis for further study of HC's active drug-like ingredients and mechanism in the treatment of pneumonia.

Case study 2: MOA of *Panax Notoginseng* against post-COVID-19 thromboembolism

The significant coagulopathy and hypercoagulability, which are the main hallmarks of the pathophysiology of coronavirus disease 2019 (COVID-19), include venous and arterial thromboembolism, as well as cardiovascular and lung diseases. In general terms, no clear benefit for acutely ill patients with extended pharmacological thromboprophylaxis can reduce the risk of venous thromboembolism without increasing the risk of bleeding. *Panax Notoginseng* (PNGS) is a potent folk therapy used to treat blood-related diseases.

However, further research is required to fully elucidate the mechanisms of its pharmacological activities and explore its therapeutic potential for treating thromboembolism caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The data suggest that PNGS exerts collective therapeutic effects against TE caused by SARS-CoV-2 and provides a theoretical basis for further laboratory study of the active drug-like ingredients and the mechanisms of PNGS in TE treatment options.

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2. Junying Liu, Shouyi Yuan, Tao Zhang, Ismael Obaidi, Helen Sheridan, Gaia Scalabrino, Maria Pigott. Network pharmacology reveals the mechanism of *Panax Notoginseng* against the post COVID19 thromboembolism. (In progress)

COMBINATION OF BIOLOGY AND COMPUTER SCIENCE: A PROMISING THERAPEUTIC TOOL FOR 21st CENTURY MEDICINE

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Recent developments in molecular biology and biotechnology are major elements of breaking old barriers to invent new cures for many pathophysiological conditions including cancer and infectious diseases. Innovation occurs when people face both terrible challenges and inspirational opportunities. There is no debate that if we decipher the biological mechanisms and apply this knowledge in computer aided drug discovery, it will be a powerful tool for humanity. We all benefit from developing this capacity to provide new treatment options in a shorter time period with less cost. Drug repurposing is an area of such combination. Often considered as a serendipitous approach, where repurposable drugs are discovered by chance, drug repurposing has heavily benefited from advances in human genomics and silico approaches. We were able to come up some candidates to be used in Covid-19 by using this approach specifically targeting corona virus and its action of mechanism[1]. In our studies, we also target to wider biological processes such as epigenetic modifiers, in order to fight against cancer. Epigenetic is the study of heritable phenotype changes that do not involve alterations in the DNA sequence, but yet have an effect on the transcription and activation of the genes including the ones that provide advantage for uncontrolled cell growth. In silico approaches enable us to find the molecules or compounds that may have an effect that regulate this activation and hence block this process.

Finding a molecule with this approach will play a central role in the control of physiological and pathological cellular functions, that makes it an ideal target for new therapeutic strategies in the epic fight against cancer[1].

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COMPUTER-AIDED DRUG DESIGN: METHODS, APPLICATIONS AND CHALLENGES

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Computer-aided drug design (CADD) has become an indispensable part of drug discovery owing to the fact that it not only speeds up the drug design and discovery process but also could reduce the cost by up to 50%.[1,2] CADD involves many scientific disciplines such as biochemistry, genetics, toxicology, biophysics etc., but most importantly, organic chemistry, pharmacology and physical chemistry plays vital roles.[3] Two main approaches used are structure-based and ligand-based drug design. Both quantum mechanics (more accurate) and molecular mechanics (faster) are used in molecular simulations depending on the aim and off course the size of the system under study.

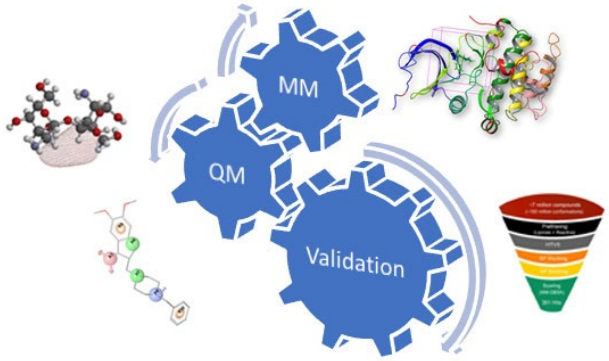

Figure 1. A graphical abstract for CADD tools & methods.

One can expect that the improvements in computer technologies and increasing number of software at the market should result in more effective and reliable outcomes, however, lack of proper training have resulted in many scientific flaws. Each of every step in computations should be validated before going further in calculations. To give some examples, but not limited to, correct selection of level of theory and basis set in QM calculations, evaluation of some statistical parameters such as cross validation, student t-test, fisher validation, enrichment factor, ROC, BEDROC etc. in QSAR and virtual screening, comparison of docked pose and experimental active confirmation in molecular docking should all be considered. if a model has not been validated, then the remaining parts will all be unsound.

Some successful applications of different methods used in CADD will be discussed. In addition, examples of failed models that were rejected by reviewers and editors will also be highlighted.

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THE ATOMIC DETAILS OF GRIFFITHSIN INTERACTION WITH SARS-COV-2'S RBD

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Griffithsin (GRFT), a 121-aminoacid (AA) sequence lectin protein that isolated from the red algae Griffithsia. Previously, GRFT binding to glycoproteins of different types of virus families were shown[1,2]. Recently, SARS-CoV-2 entry blocking ability of GRFT was shown with in vitro and in vivo experiments [3,4]. However the atomic details of the interactions between GRFT and the spike protein of SARS-CoV-2 is not known. In this study, we utilized protein-protein docking and molecular dynamics simulations to reveal, how GRFT binds and inhibits spike proteins Receptor Binding Domain (RBD). This study uses the "computational microscope" to validate the inhibitory capacity of GRFT on RBD. RBD and GRFT obtained from rcsb.org with PDB IDs; 6LZG and 3LL2, respectively. Omicron variant mutations and GRFT mutants were introduced using PyMol. HADDOCK 2.4 webserver used for the protein-protein docking, PRODIGY server used to calculate predicted binding free energy of obtained docking complexes. Two docking procedure were applied, in first one, all AAs in GRFT defined as active. In the second approach, only the residues 30, 69, 70, 111, 112, and 114 selected as active residues [5]. Top docking poses in terms of HADDOCK score downloaded and prepared with Maestro Molecular Modelling Package. Prepared structures were used in MD simulations. 1 microsecond (μs) long MD simulations were conducted with Desmond MD code. Our results shed light into binding mode of GRFT to the spike's RBD.

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APPLICATIONS OF MOLECULAR MODELING APPROACHES FOR THE IDENTIFICATION OF NOVEL SARS-COV-2 RDRP INHIBITORS

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The coronavirus infection (SARS-CoV-2) has spread to more than 170 nations around the world and has influenced over 500 million people with over 6 million confirmed deaths.[1] Development of vaccines have assisted in hindering the effects of the spread and reducing the hospitalization and mortality rate. However, there is still requirement for the design of optimal therapeutics to help patients suffering due to the infection. Additionally, some fast-spreading variants of the virus could decrease the effectivity of developed vaccines. As such, there is ongoing research to develop antiviral therapeutic compounds that will oppose the disease by targeting the SARS-COV-2. One such target protein is RNA dependent RNA polymerase (RdRp), an essential SARS-COV-2 enzyme involved in RNA replication for the elongation of the viral RNA entry.[2] Here, our aim was to identify possible inhibitors for RdRp of SARS-COV-2 by targeting the druggable sites in the RdRp complex using *in silico* drug discovery methods. We have utilised SiteMap module of Maestro and identified two allosteric sites of RdRp complex that were also reported as possible druggable sites by other researchers.[3] In this study, we considered two different compound libraries DrugBank (https://go.drugbank.com) and Specs SC (https://www.specs.net/) for the *in silico* exploration of allosteric and catalytic site which in total accounts around 300 thousand compounds. Specially molecules from DrugBank could advance to clinical stage after in vitro testing as they are already approved molecules. We employed molecular docking initially to form the complexes between RdRp and potential molecules. However, docking could only provide a static picture and could lead to false positive compounds to be identified. Hence, we have also performed short (1 ns) molecular dynamics simulations to select potential compounds as this approach in our previous studies provided effective in identification of potential inhibitor compounds against different targets.[4,5]

At the end, we have identified eight compounds that could potentially display inhibitory effect against RdRp complex and four of these compounds were approved drug molecules. These suggested molecules should be tested with in vitro experiments to display their potential inhibitory effects.

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IDENTIFICATION OF POTENTIAL ANTAGONISTS OF CRF1R USING STRUCTURE-BASED VIRTUAL SCREENING AND MOLECULAR DYNAMICS SIMULATION

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The corticotropin-releasing factor receptor type 1 (CRF1R) is a member of class B GPCRs that is predominantly found in the central nervous system, where it plays a key role in stress-related neuro-disorders[1]. To date, no drug targeting this receptor has been approved, partly due to inadequate understanding of its activation mechanism of class. Previously, using MD simulation, we demonstrated that the CRF1R complexed with a small-molecule antagonist CP-376395 maintains a conformation of its transmembrane domain (TMD)[2]. Here, using the most abundant structures derived from those simulations, we carried out a structure-based virtual screening of ZINC "Druglike" library containing approximately 17 million compounds. The docking complexes of the CRF1R with the top 30 hits were submitted to MD simulation to examine the stability of ligand binding mode, and MM/GBSA binding energy calculations were performed on all the complexes to rank them with improving accuracy.

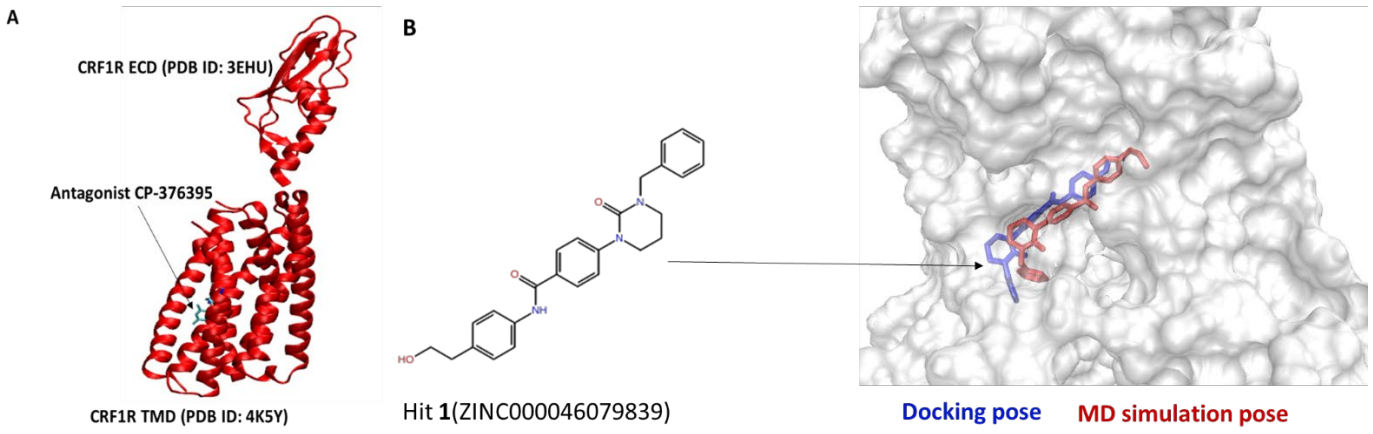

Figure 1. A. Crystal structures of the N-terminal extracellular domain (ECD) (PDB ID: 4KBY) and transmembrane domain (TMD) of CRF1R. **B.** Superimposition of the docking and MD simulation poses of the top hit (ZINC000046079839) identified by structure-based virtual screening.

Eleven compounds demonstrate potential to be CRF1R antagonists, from which ZINC000046079839 and ZINC000032907937 span the allosteric site of the CRF1R, persistently forming interactions with transmembrane

helices 3 and 6. These interactions are likely to keep the receptor in an inactive state since both transmembrane helices play a critical role in the activation of the receptor.

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PHARMACOPHORE MODEL ACCOMPANIED BY CONFORMATIONAL DYNAMICS REVEALS NEW ANTI-CANCER DRUGS

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Targeting the interaction between tumor suppressor p53 and murine double minute 2 (MDM2) protein has been an attractive therapeutic strategy of recent cancer research. There are a few number of MDM2-targeted anticancer drug molecules undergoing clinical trials right now, however none of them have been approved so far. In this study, a new approach in which global dynamics of MDM2 obtained by elastic network models are used as a guide in the generation and validation of the ligand-based pharmacophore model prior to virtual screening was employed in order to search for novel MDM2 inhibitors. We recently explored the conformational transitions and global motions of MDM2 and alterations brought about by the existence of its native inhibitor p53 and other small molecule inhibitors undergoing clinical trials, using high efficiency low resolution elastic network modeling technique.[1] Using our recent findings about the global dynamics and binding mechanism of MDM2 obtained by ENM, we conducted a simulation strategy in which we incorporated protein dynamics for generation and validation of the pharmacophore model. Virtual screening, rigid and induced-fit molecular docking strategies were then conducted to account for the very flexible and intrinsically disordered nature of MDM2, so as to capture several hit molecules exhibiting high affinity. Application of a rigorous molecular mechanics-generalized born surface area (MM-GBSA) method provided a more accurate prediction of the binding free energy values. Two leading hit molecules which have shown better docking scores, binding free energy values and drug-like molecular properties as compared to seven clinical trial MDM2 inhibitor molecules were identified by screening the drug libraries with this methodology. It was worth noting that besides their high docking scores, the two leading hits obtained have extra intermolecular interactions with MDM2 which indicates a stable complex formation as compared to the clinical trial MDM2 inhibitors. Having molecular properties in suitable ranges contributes positively for the hit compounds to be drug-like. Therefore, combined computational strategy employed in generating a pharmacophore model based on the active available ligands undergoing clinical trials and validating the model by the conformational dynamics background to screen libraries can be a promising tool in the initial stage of computational drug design.

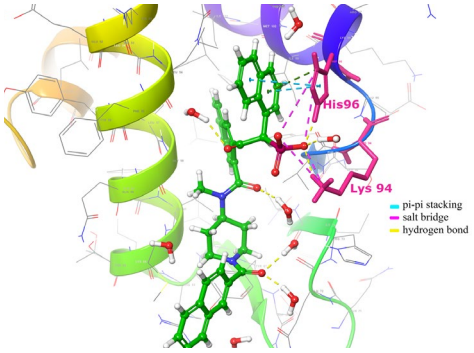

Figure 1. A schematic representation of the interactions between the hit drug molecule and MDM2 protein

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DESIGN, SYNTHESIS, CHARACTERIZATION, MOLECULAR DOCKING STUDIES AND ANTICANCER ACTIVITY EVALUATION OF NOVEL HYDRAZINECARBOTHIOAMIDE, 1,2,4-TRIAZOLE-3-THIONE, 4-THIAZOLIDINONE AND 1,3,4-OXADIAZOLE DERIVATIVES

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A series of novel hydrazinecarbothioamide, 1,2,4-triazole-3-thione, 4-thiazolidinone and 1,3,4-oxadiazole derivatives were synthesized and evaluated for their cytotoxic activity against A549 lung adenocarcinoma cells and L929 normal mouse fibroblast cell line. The structural elucidation of the compounds was performed and verified by IR spectroscopy, ^{1}H-NMR, ^{13}C-NMR, mass and elemental analysis. Compound **3a**, **3b**, **3c**, **3d**, **3e**, **3g** and **3i** displayed the best anticancer activity against A-549 cell line. The anticancer activities of **3a**, **3c**, **3d**, **3e**, **3g** and **3i** were determined as better than the positive control **Cisplatin**. In addition to the in vitro analysis, molecular docking studies were employed to explore the possible binding interactions of the title compounds with cyclooxygenase-2 (PDB ID: 4COX).[1] Structure-activity relationships, as well as virtual ADME studies, were carried out and a relationship between biological, electronic, and physicochemical qualifcations of the target compounds was determined. Consequently, these derivatives present a leading structure for future drug development due to their straightforward synthesis and relevant bioactivity.

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EXPLORING THE POTENTIAL OF NATURAL PRODUCTS AS α-GLUCOSIDASE INHIBITORS THROUGH *IN SILICO* ANALYSIS AND MOLECULAR DOCKING STUDIES

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Diabetes Mellitus (DM) is a chronic, metabolic disease characterized by elevated levels of blood sugar and is a major public health concern worldwide today[1]. According to a report issued by International Diabetes Federation (IDF), the prevalence of diabetes in the world reached 422 million people and is expected to reach 693 million in 2045[2]. Besides, World Health Organization (WHO) has reported that diabetes ranks seventh among the causes of death that will occur globally by 2030[1]. Overall, Type 2 diabetes (T2DM) is the most common type of diabetes, accounting for approximately 90-95% of all diabetic cases[3]. Insulin receptors or insulin-responsive cells in the cell membrane of T2DM patients cannot respond to insulin normally, and therefore their blood sugar levels increase[4]. Thus, the importance of effective management of high blood sugar comes to the fore in the prevention of complications arising from hyperosmotic stress that may cause hyperglycemia and other related diseases[1].

Alpha (α)-glucosidase inhibitors (AGIs), which are a class of oral antidiabetic drugs (OADs), have an important role in the control of postprandial blood glucose levels of diabetics, as well as keeping blood sugar levels in a normal range by delaying the digestion of carbohydrates and reducing the absorption of monosaccharides[5]. However, the oral bioavailability of OADs such as Acarbose and Voglibose, which are used clinically for the inhibition of α-glucosidase, is quite low and they have some known side effects on the organs in the gastrointestinal tract[6]. These challenges faced by researchers encourage them to continually conduct new research to access novel antihyperglycemic agents that are safer and pharmacologically more active. At this point, natural products provide a good starting point for drug research, with a wide range of bioactivity potential and relatively safer toxicological profiles[7].

The present study aims to identify novel hit compounds of natural origin with potential antidiabetic properties to inhibit intestinal α-glucosidase activity. For this purpose, the 1,60 Å crystal structure of isomaltase in complex with α-*D*-glucose (PDB ID: 3A4A) was downloaded from the Protein

Data Bank (PDB)[8]. The National Cancer Institute (NCI) database (422 natural compounds) was used as a ligand source. Structure-based virtual screening (SBVS) was performed using AutoDock Vina implicated in the PyRx 0.8 tool. Firstly, the grid box dimensions of the active site of the protein were set as 20x20x25 Å (x, y and z respectively) and the center was located at X: 20.886 Å, Y: -8.710 Å and Z: 23.205 Å. The compounds with a score equal to or greater than Vina score of the reference ligand (α-*D*-glucose) were then submitted to molecular docking studies with AutoDock suite for further analysis. The docking results in terms of binding energies and intermolecular interactions were visualized and analysed using Discovery Studio Visualizer software. In addition to molecular docking studies, some drug-like properties of newly selected AGI candidates were estimated using the SwissADME web tool[9]. The same procedure was also applied for Acarbose, an oral AGI.

The results revealed that 3 out of a total of 296 compounds recorded as Vina output (NSC123977, NSC107067 and NSC349155) had good potential as inhibitors of the α-glucosidase enzyme. These compounds had a lower binding energy, in the range of -10.40 to -7.85 kcal/mol, compared to Acarbose (-6.97 kcal/mol) and formed hydrogen bonds with some of the key residues (D69, H112, R213, D215, H351 and D352) in the catalytic site pocket of α-glucosidase (Figure 1)[10]. Furthermore, the three natural compounds were estimated to have approximately 3-fold greater bioavailability score than Acarbose and, unlike Acarbose, to have high absorption rates in the gastrointestinal tract.

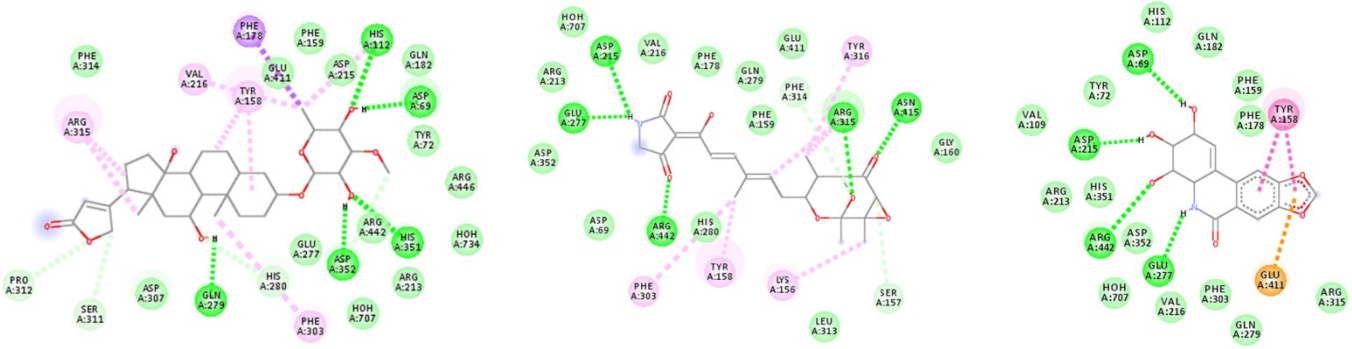

Figure 1. Two-dimensional (2D) interaction diagrams between α-glucosidase enzyme and NSC123977 (left), NSC107067 (middle) and NSC349155 (right).

Our study will provide considerable support for the development of promising new therapeutic agents with maximum efficacy and optimal side effect profile for the treatment of T2DM through the strategy of targeting the α-glucosidase active site with natural compounds.

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UNENDED QUEST: IN THE SEARCH OF DIMERIZATION INTERFACES OF AT1R-AT2R HETERODIMER

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G protein-coupled receptors (GPCRs) are the membrane proteins that play a wide variety of roles in cellular signalling. They consist of seven membrane-spanning helices and intra- and extracellular loops that connect these transmembrane helices. Ligand binding to the GPCR causes a conformational change to couple with intracellular effectors[1]. Coupling to these proteins either activates the G protein or beta-arrestin signaling[1]. Each of these two effectors signal through different pathways. GPCRs can act as monomers[2]. They can also function as either dimer or higher order oligomers[3]. The renin-angiotensin system (RAS)'s main effector, angiotensin II (AII), is an octapeptide (DRVYIHPF) hormone. AII can bind to two different membrane receptors, Angiotensin II type 1 (AT1) and type 2 (AT2) receptors[7]. AII binding to AT1R initiates G protein coupling. AT1R can couple and signal through several G proteins (G_q, G_i, $G_{11,12,13}$ and G_o), scaffolding proteins (such as beta arrestins 1/2), and protein kinases (RTKs and non-RTKs)[8]. Overactivation of AT1R by AII can cause hypertension, stroke, diabetic nephropathy, metabolic disorders and cardiac arrhythmia[9]. AT2R does not signal through classical G protein pathways and its physiological role is unclear. AT2R is believed to inhibit AT1R mediated signals. AT1R and AT2R can form heterodimer and because of dimerization, AT1R specific signalling is decreased, and this inhibition is shown through protein kinase C-dependent pathway. However, the exact heterodimerization interface is not known clearly. This work aimed to perform a detailed study of possible heterodimerization interfaces of the AT1R-AT2R system. As of 25.11.2019, we collected 352 GPCR structures. All possible dimerization interfaces are created. Generated AT1R-AT2R heterodimers were first oriented using OPM server, then submitted to CHARMM-GUI membrane simulation builder server to obtain systems for the molecular dynamics (MD) simulations. TIP3P water and POPC membrane models were used. First, coarse-grained (CG) simulations were run with the elastic network for the protein, Martini 2.0 for the lipids and water. MD simulations were repeated at least three times and ran for 10 μs (each system simulated for 30 μs). 11 systems were selected and converted to all-atom (AA) representation based on the distances between, 3.50 – 6.34[6], and ((2.41 – 6.38) – (3.44 – 7.52)) - GPCRdb distance[7]. 8 of the 11 systems were selected based on 3.50 – 6.34 distance, and the other 3 were based on GPCRdb distance. The backward algorithm was used to convert system CG to AA. The converted systems run with AA representation for 1 μs, each system repeated at least two times. According to preliminary results, two interfaces were distinct from others, and AT1R inactivation was observed in these interfaces.

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IN SILICO AND *IN VITRO* APPROACHES FOR THE IDENTIFICATION OF NOVEL ANTI-CANCER THERAPEUTICS AGAINST MALIGNANT GLIOMA FROM ULTRA LARGE LIBRARIES

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Gliomas are common primary brain tumors of glial origin (representing 40-50% of all brain tumors) with highly aggressive and invasive properties (Arora and Somasundaram, 2019). The World Health Organization (WHO) classifies them from I to IV according to their aggressiveness. However, its biological behavior, prognosis, and response to treatment vary, even within the same histological category (Louis et al., 2007). IDH1 mutant protein is a promising therapeutic target for glioblastoma and many small molecule inhibitors are identified and tested against IDH1 mutant (Rohle et al., 2013; Davis et al., 2014). In this study, we combined machine learning algorithms and molecular modeling techniques for the identification of novel IDH1 mutant inhibitors against glioblastoma multiforme (GBM). Ligand-based and structure-based models were constructed with the aim of screening ultra large-small molecular databases (SPECS_SC, SPECS_NP, NPC, and ZINC20). Docking analysis with IDH1 mutant was done for the compounds that passed the decided criteria after the initial screening with the constructed models. Molecular dynamic simulations, molecular mechanics/generalized Born surface area (MM/GBSA), root mean square deviation (RMSD) and root mean square fluctuation (RMSF) calculations were performed for selected hits to check the stability of the ligand within the binding pocket. The hits selected after each virtual screening were submitted to toxicity QSAR and cancer QSAR model screenings, and the hits that survived the criteria were ordered for *in vitro* proliferation/toxicity assays by cell proliferation, spheroid formation assay, ECAR, and OCR.

Among 11 tested hit compounds 10 of them were found to be significantly inhibiting cell proliferation at 100 μM in cell proliferation assay. Moreover, all hits retrieved from all aforementioned libraries showed either partial or potential suppression against GBM cell lines U87 and U251, two of them were predicted to pass the blood-brain barrier (BBB) which makes them potential candidates for GBM cancer therapy.

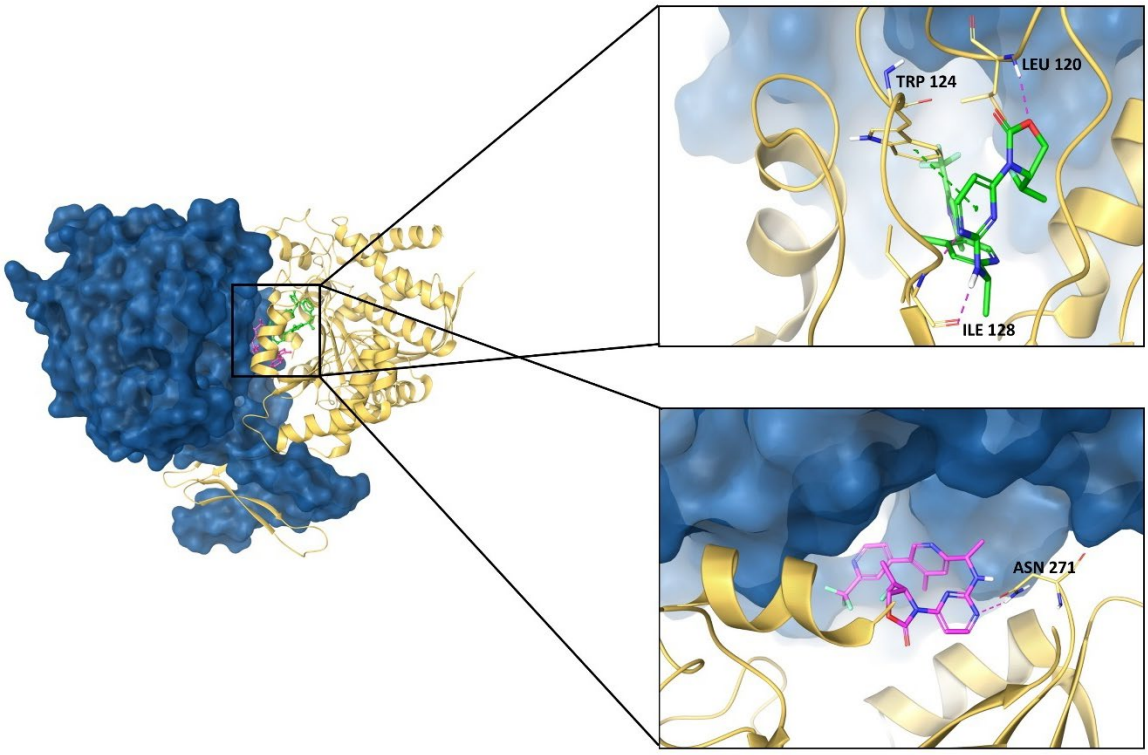

Figure 1: Illustration of 502 (green) and 504 (pink) ligand binding sites of co-crystallized ligand (IDH305)

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DISCOVERY OF NEW MALARIAL TARGETS AND IDENTIFICATION OF POTENT ANTI-MALARIAL DRUGS

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About half of the world's population lives in areas at risk of contracting malaria. Parasites acquire high resistance to available drugs. There is a need for an effective treatment. The survival of viruses as mandatory intracellular parasites such as Crimean Congo Hemorrhagic Fever Virus, depends on the invasion of the host cell after antagonizing the NF-κB signaling pathways. CCHFV performs intracellular invasion using viral OTU deubiquitinase with extensive deconjugation activity. Inhibition of this viral OTU protein is associated with the Y89-W99 pocket. Interestingly, same aminoacids which correspond to OTU domain were highly conserved in malaria parasites. It was suggested that malaria parasites can perform their activities by antagonizing the NF-κB pathway using the deconjugation feature of OTU proteins similar to CCHFV. Thus, we hypothesized that OTU proteins could be a key target in malaria and it was aimed to discover inhibitors targeting these OTU proteins as candidate drugs in malaria. The project contains both computational and wet-lab studies. Here for the first time, novel OTU deubiquitinases of three different malaria strains were 1) modeled three-dimensionally, 2) produced recombinantly, 3) characterized and their DUB activities were proved in vitro and in vivo. Moreover, it was shown how the new OTU proteins manipulate both the innate immune pathways and the cell mono-Ub and polyUb levels. A small molecule library was prepared and all the compounds in the library were targeted against OTU DUBs. Based on docking scores, druggabilities, ADME-tox features, IC50 values, DUB inhibitory characteristics even at micro level concentrations, effects of the molecule treatments on expression in both RNA and protein level, four molecules were discovered. In conclusion, best candidate drug molecules against malaria disease were identified.

Keywords: anti-malarial, OTU-like DUBs, parasites, computer aided drug discovery, small molecules, recombinant DNA technology, Plasmodium

BIOACTIVE INDANES: INSIGHT INTO THE BIOACTIVITY OF INDANE DIMERS RELATED TO THE LEAD ANTI-INFLAMMATORY MOLECULE PH46A

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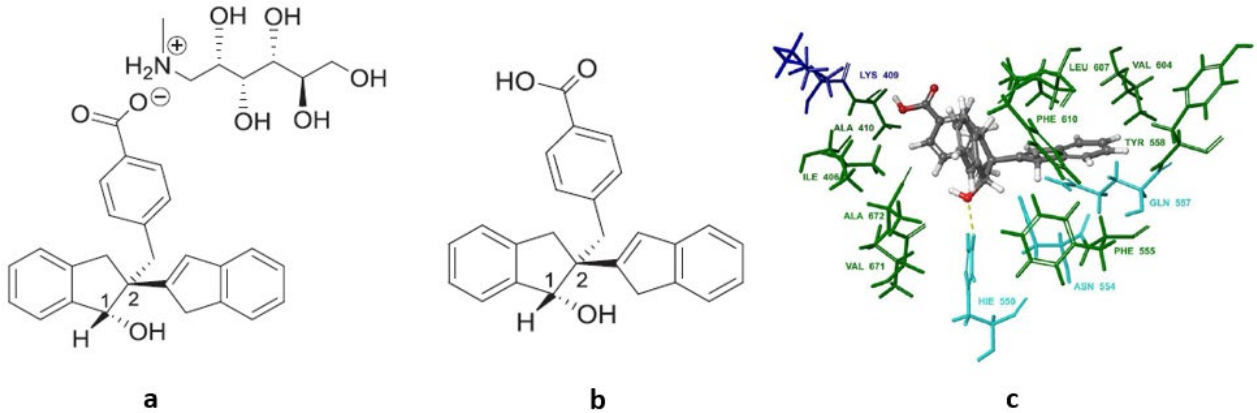
The indane skeleton is found in many natural molecules as well as being embedded in several synthetic molecules used clinically. A new class of bioactive 1, 2-indane dimers has been developed by our research group as a potential therapeutic agent for the treatment of inflammatory and autoimmune conditions. The lead molecule, PH46A (a) which has recently progressed to Phase 1 human clinical trials, demonstrates significant anti-inflammatory activity in phenotypic models[1], but its mechanism and site of action still proves elusive. Recent studies have focused on the characterising the biological fingerprint of PH46 (the free base) (b) and related novel indane dimers to determine the impact of changes in substitution and stereochemistry at the C-1 and C-2 positions of the PH46 scaffold. Cytotoxicity and cytokine profiles of the compounds were established using THP-1 macrophages and SW480 cells. The inhibitory effects of 5-lipoxygenase (LOX), 15-LOX and nitric oxide (NO) released from LPS-induced SW480 cells were then investigated. 5-LOX binding was evaluated *in silico* against nordihydroguaiaretic acid. PH46 and compound 7 cause a statistically significant reduction in NO, inhibition of 5-LOX with high binding energy and no cytotoxicity effects in THP-1 macrophages and SW480 cell lines (up to 50 μM). The cytokine profiling of the series demonstrated inhibition of IL-6 and TNF-α in THP-1 macrophages together with IL-8 in SW480 cells. The observed profile of cytokine modulation (IL-6, TNF-a, IL-8) and inhibition of release of NO and 5-LOX may contribute to the *in vivo* effects demonstrated by indane dimers and PH46A in murine models of colitis.



a b c

Figure 1. Chemical structures of PH46A (a), PH46 (b) and calculated 3D binding interactions of PH46 with 5-LOX.

Studies using Human Proteome Microarrays suggest the involvement of a known protein, which has not received much investigation. In the absence of commercial ELISA protein kits to facilitate studying binding, the protein interaction with PH46 was further investigated by ligand based nuclear magnetic resonance experiments: WaterLOGSY and Saturation Transfer Difference was investigated and will be presented in this lecture. This target is still under investigation and now that the protein has been crystallised, we hope to explore its interaction with PH46A further, using *in silico* methods. to develop a deeper understanding of the pharmacological fingerprint to identify potential development of more potent anti-inflammatory therapeutic agents.

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QUANTUM MECHANICS-BASED SCORING FUNCTION FOR STRUCTURE-BASED DRUG DESIGN

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Reliable pose and affinity prediction of Protein-Ligand (P-L) complexes is one of the main challenges for academic and industrial areas. In the structure-based methods, there is no single docking/scoring function which would give correct solutions for diverse protein targets[1]. Ligands are bound in the active site of the protein by non-covalent interactions which have been studied in our laboratory for decades. Accurate description of non-covalent interaction is crucial in P-L complexes. We have repeatedly shown the importance of quantum effects being the case of protein-ligand complexes as well. This has prompted us to introduce a semi-empirical quantum mechanics-based scoring function (SQM/COSMO).

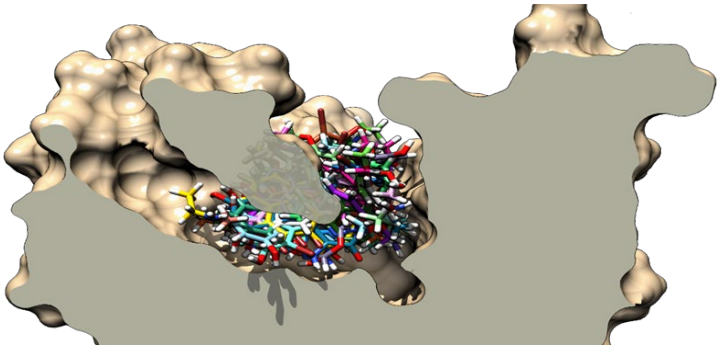

Figure 1. A schematic representation of a protein-ligand docking in the binding site.

The SQM/COSMO, coupled with an implicit solvent method, which parametrized against high level QM data. The newly introduced SQM SF has achieved far better performance in sampling and ranking power against the widely used scoring functions (such as Glide, AD4, Vina). Undoubtably, the impressive enrichment performance[2] of SQM/COSMO was the biggest success. An impressive enrichment increase was achieved when protein-ligand structure was optimised and score determined at the quantum mechanical level. As a final conclusion, the SQM/COSMO is proposed as an efficient tool in structure-based drug design[3].

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INVESTIGATION OF STRUCTURE-ACTIVITY RELATIONSHIPS WITH MOLECULAR DOCKING FOR SOME ANTIEPILEPTIC DRUGS AND VOLTAGE-GATED CALCIUM (CAV) CHANNELS

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In the study, the active drugs molecules used in the treatment of convulsive seizures occurring in epilepsy disease were used. These molecules; Vigabatrin, Lacosamide, Zonisamide, Oxcarbazepine, Levetiracetam, Tiagabine, Topiramate, Lamotrigine, Gabapentin, Felbamate, Ethosuximide, Valproic Acid, Mesuximide, Ethotoin, Primidone, Trimethadione, Phenytoin, Remacemide, Mephenytoin. These molecules have been selected considering the physiopathological mechanisms of action of epilepsy. Since the selected molecules are used as a potential antiepileptic agent, they were deemed suitable for molecular insertion studies. In addition, voltage-gated calcium channels, which play an important role in epilepsy, are emphasized. Voltage-gated calcium channels (CaV) act by providing the flow of Ca^{+} ions during the action potential that triggers seizure formation, and among the ten subtypes of voltage-gated calcium (CaV) channels, CaV3.1- CaV3.3, T-type or abnormal activities are associated with epilepsy, psychiatric form the associated low-voltage-activated subfamily[1]. For this reason, the PDB ID: 6KZP receptor, which acts as an antagonist according to its activity on the channel in the formation of epileptic seizures, was chosen for the molecular insertion study. Molecular docking study was performed using BIOVIA Discovery Studio and Autodock Vina program[2].

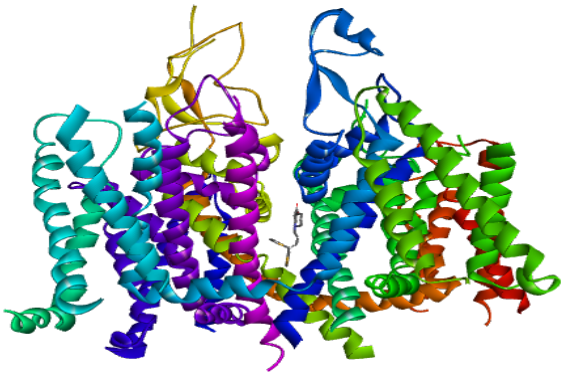

Figure 1. A schematic representation of a ligand-protein (6KZP-Tiagabine) complex and binding site.

As a result of molecular placement studies; Oxcarbazepine and Phenytoin gave the best binding affinity for 6KZP with a value of -7.5 kcal/mol. Other results are in descending order (in kcal/mol); Tiagabine (-7.4), Mesuximide (-7.3), Primidone (-7.1), Remacemide (-7.0), Topiramate (-6.9) Mephenytoin (-6.7), Lomotrigine and Ethotoin (-6.4), Lacosamide and Zonisamide (-6.1), Felbamate (-6.0), Levetiracetam and Gabapentin (-5.4), Ethosuximide (-5.1), Valproic Acid (-4.9), Trimethadione (-4.7), Vigabatrin (-4.4) determined as.

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IDENTIFICATION OF POTENT AND SELECTIVE INHIBITORS AGAINST CLASS IIB HISTONE DEACETYLASE ENZYMES BY UTILIZING VIRTUAL SCREENING TECHNIQUES OF KNOWN COMPOUND LIBRARIES

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HDACs are the class of enzymes involved in epigenetic modification of histone proteins by removing the acetyl groups of ε-N-acetyl lysine residues, inducing chromatin condensation and regulating the expression of tumor suppressor genes. Lysine deacetylation is a crucial regulatory pathway for various cellular processes, such as cell cycle, transcription, and cellular metabolism.
HDACs enzymes are grouped into four classes based on their homology to their respective yeast orthologous. HDACs 1, 2, 3, and 8 are grouped in Class I. Class IIa includes HDACs 4, 5, 7, and 9, while Class IIb includes HDAC6 and HDAC10. Class IV has only HDAC11. Recently, a few inhibitors of histone deacetylation drugs have received regulatory approval as anticancer agents. However, currently, there is no clinically approved inhibitor for Class IIb yet. Designing selective and potent inhibitors for various HDAC enzymes are a challenging task for researches. Therefore, Class IIb HDACs are considered a promising therapeutic target for anticancer drug discovery. In this study, utilizing structure-based virtual screening and molecular modeling techniques, numerous small molecule databanks showing possible anticancer potency were *in silico* screened for selective and potent drug candidates against HDAC6 and HDAC10 isozymes.The top inhibitors with the best binding affinity and selectivity were subjected to molecular dynamics simulation studies to observe their stability and dynamic behaviors in the binding pockets of these enzymes. Additionally, drug-likeness properties of these compounds, such as absorption, distribution, metabolism, elimination, and toxicity (ADMET) were estimated computationally.

Keywords: Class IIb HDACs, HDAC6, HDAC10, cancer, drug, *in silico* screening, docking, HDAC inhibitors.

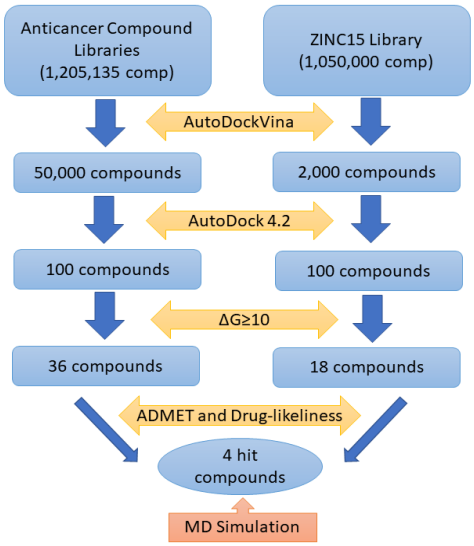

Figure 1. A schematic representation of virtual screening workflow for the identification of selective and potent lead compounds for HDAC6 and HDAC10.

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OXIME ESTER-BASED DI-SUBSTITUTED IMIDAZOLE DERIVATIVES FOR INHIBITION OF ACETYLCHOLINESTERASE: DISCOVERY AND STRUCTURE-ACTIVITY RELATIONSHIPS

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Alzheimer's is a brain disorder characterised by the gradual decline of memory, thinking skills, and the ability to perform simple tasks.[1] Decreased levels of acetylcholine (ACh) in the brain can cause memory and learning problems. Inhibiting acetylcholinesterase (AChE) is one way to enhance cholinergic neurotransmission by increasing ACh availability.[2] Our previous study investigated mono- or di-substituted imidazole derivatives for their ability to inhibit both BChE and AChE.[3] Our findings indicated BChE IC_{50} values ranging from 27.02 to 151.2 nM, and those for AChE ranged from 17.3 to 120.9 nM. Results of that study were comparable to donepezil and higher than tacrine. In addition to our previous study, we discovered from the literature that imidazole groups having an oxime ester could improve ACh activity.[4] For this reason, these studies prompted us to search for substituted C-2 and C-4 imidazole derivatives with oxime ester moiety to inhibit AChE.

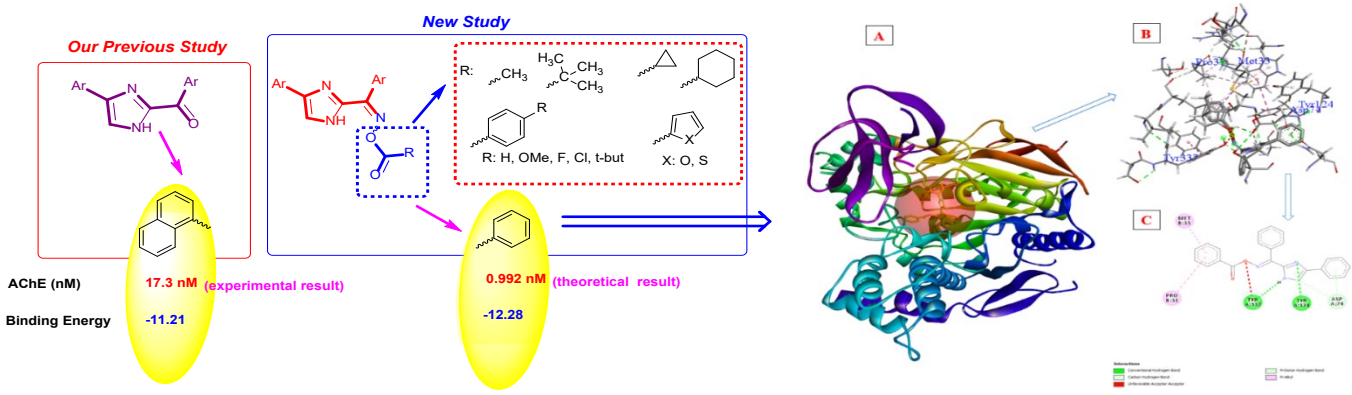

Figure 1. Our studies and a schematic representation of the ligand-protein complex and binding site.

As a result of our approach, which took into account previous results and literature data, we have *in silico* developed 11 imidazole molecules for the purpose of increasing the AChE inhibition. In this study, we designed imidazole compounds containing oxime ester modifications, focusing on the compound that we found the most active in our previous study. Imidazole molecules with an oxime ester group exhibited inhibition between 49.18 nM and 0.992 nm. The clinically used reference drug tacrine displayed inhibition at 698.6 nM, whereas donepezil exhibited inhibition at 32.9 nM. Comparing the best active imidazole molecule that was reported in this study to the clinically used reference drug, we see that the reported molecule showed approximately 703-fold higher activity than tacrine and 33-fold higher activity than donepezil. In summary, in this study, we have reported previously unknown imidazole molecules that might be the next drug for Alzheimer's diseases, which are powerful inhibitors of AChEs at nanomolar concentrations. Additional studies, including *in vivo* and *in vitro* studies, are underway.

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APPLICATION OF INTERCRITERIA ANALYSIS TO COMPARE DOCKING SCORING FUNCTIONS IN MOE SOFTWARE ON A SET OF PROTEIN-LIGAND COMPLEXES FROM PDBBIND DATABASE

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As a key element in the protocols for molecular docking of bioactive compounds, the scoring functions available in Molecular Operating Environment (MOE)[1] are in the focus of this investigation. The performance of MOE scoring functions London dG, Affinity dG, Alpha HB, ASE and GBVI/WSA dG has been explored on a set of protein-ligand complexes from the Comparative Assessment of Scoring Functions benchmark subset (CASF-2013)[2] of PDBbind database[3]. This benchmarking set is a comprehensive collection of 195 protein-ligand complexes with collected binding affinity data.

In this investigation the performance of the scoring functions has been compared using the multi-criterion decision-making approach of InterCriteria analysis (ICrA)[4]. It has been elaborated to detect possible relations of pairs of criteria when multiple objects are considered. ICrA relies on the mathematical concepts of index matrices and intuitionistic fuzzy sets and allows for identification of intercriteria relations in terms of consonance or dissonance, thus differentiating from the classical correlation analysis. For the CASF-2013 dataset, re-docking of the ligands in the protein-ligand complexes has been performed. For each ligand 30 poses per ligand have been generated and the following data have been extracted: i) best docking scores; ii) lowest root-mean-square deviations (*RMSDs*); iii) RMSDs of the best docking scores; iv) docking scores of the lowest RMSDs; v) ranks of the best RMSDs. The collected information has been processed employing the free ICrAData software (https://intercriteria.net/software/). The ICrA results have been analyzed to reveal any relations between the results produced by the scoring functions. For most of the cases no significant consonance, neither positive, nor negative, has been observed. This comparison suggests that the scoring functions do not produce equivalent results and consensus docking studies using more than one scoring function are recommended.

Acknowledgment: This investigation is supported by the National Science Fund of Bulgaria, grant № DN-17/6 "A New Approach, Based on an Intercriteria Data Analysis, to Support Decision Making in *in silico* Studies of Complex Biomolecular Systems".

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A DENSITY FUNCTIONAL STUDY ON THE FLUORESCENCE QUENCHING

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Studying on the interaction between small molecules and plasma proteins is an interesting area of research in chemistry and pharmaceutical chemistry. Human serum albumin (HSA) is one of the most studied plasma protein. HSA is a globular protein consisting of a single polypeptide chain with 585 amino acids and it is composed of three structurally homologous domains (I, II and III) each of which contains two subdomains (A and B) and is stabilized by 17 disulfide bridges. Crystal structure analyses have revealed that the drug binding sites are located in subdomains IIA and IIIA. HSA has been widely used as a model protein for many biochemical studies using fluorescence quenching. The fluorescence of HSA is originated by tryptophan alone.[1-2] Acridine derivatives are widely used as antibacterial, antiprotozoal, antimalarial agents and anticancer drugs.[3] Aminoacridines such as proflavine is well known and used for the synthesis of several dyes and drugs.[4] In this study, binding and fluorescence quenching of proflavin and tryptophane side of HSA has been calculated.

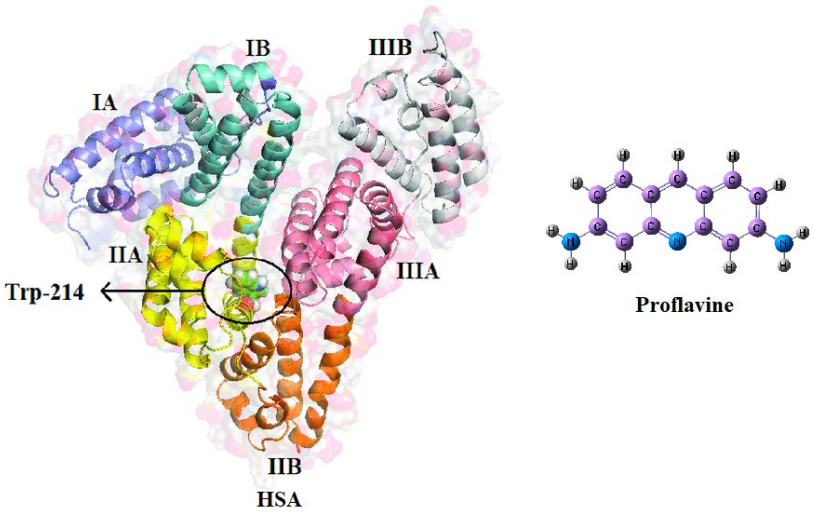

Figure 1. Structures of HSA and Proflavine molecule.

Fluorescence quenching is a powerful and simple method to study the interaction of small molecules with protein because of its high sensitivity, rapidity and convenience. The fluorescence quenching of the interaction of tryptophan side of HSA with the ploflavine was investigated using density functional theory (DFT). The absorption and emission spectra of tryptophan, ploflavine and interacted tryptophane and ploflavine were calculated at B3LYP, PBE0, TPSSH and M06 hybrid functional and triple zeta quality 6-311G(d,p) basis set. The theoretical spectral data matched the experimental absorption and emission bands. The calculations showed that ploflavine quenched the fluorescence of HSA, which is consisted with the experimental result.

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IN SILICO SCREENING OF THYMOQUINONE AGAINST TARGET OF GLP-1

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In the treatment of Type 2 Diabetes Mellitus (T2DM), Glucagon like peptide-1 receptor agonist (GLP-1 RA) is also included in the class of incretin-based drugs. GLP-1 receptor agonists stimulate insulin secretion and inhibition of glucagon release by the pancreas[1].

In this study, the interaction of GLP-1 with thymoquinone[2] which one of the important bioactive compounds of black cumin (Nigella sativa L.), which has been shown to be effective in the treatment of many diseases, was investigated.

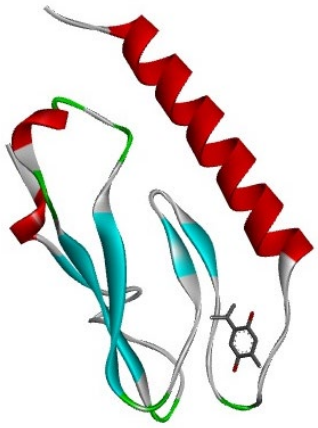

Figure 1. Molecular Docking Analysis results using Discovery Studio Visualizer

According to analysis thymoquinone and GLP-1 bind at PRO73, PRO54, PRO56, PHE61, ALA57, ASP53 points. These binding sites show similar binding sites to the GLP-1 interaction with Rifabutin. The reason why Rifabutin was referenced for the significance of our binding sites was that its interaction with lixisenatide (one of the GLP-1 RA drugs) was studied[3]. Finally; since our study is based only on data analysis, we think that it should be examined in more detail with in vitro and in vivo experiments.

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REPURPOSING STATINS IN BREAST CANCER THERAPY

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Statins are fungal-derived compounds that inhibit the hydroxymethylglutaryl-CoA (HMG-CoA) reductase enzyme. Because of their demonstrated effectiveness and safety profile, statins are used for hypercholesterolemia control. Numerous preclinical researches show statins' anticancer properties in a variety of tumor types, including liquid cancers such as myeloma and leukemia, as well as solid tumors, like breast cancer[1]. Statins have been shown to directly influence tumor cells in four distinct ways: growth inhibition, induction of apoptosis, anti-invasive metastatic effects, and anti-angiogenic effects.

Statins selectively inhibit the mevalonate pathway which coincides with some cancer pathway and leads to cell death due to depletion of GGPP[2]. So, the statins may be used in cancer therapy beside its cholesterol lowering feature[3]. In this work, a set of statins are chosen to check their potential in breast cancer therapy by using Molecular Docking method. After geometry optimization of the statins, molecular docking performed with AutoDock Vina by using p53 and HER2 proteins as target proteins. As a result of this study, we aim to find out a candidate that already approved as drug for treatment of breast cancer.

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IN SILICO INVESTIGATION OF NEW MULTI-TARGET UREA/THIOUREA AND CARBAMATE/THIOCARBAMATE DERIVATIVES FOR ALZHEIMER'S TREATMENT

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Alzheimer's disease (AD) is chronic neurodegenerative disorder and common cause of several dementia. It can cause cognitive disfunction (memory loss, language difficulties etc.), non-cognitive symptoms (depression, hallucinations etc.) and difficulties performing daily tasks.[1] Due to the complex patophisicology of AD and insufficent drugs with various side effects for treatment, studies exploring new potential drug compounds exhibiting multi-target inhibitory properties have gained interest in recent years. Drugs used to treat the disease generally target Acetyl cholinesterase (AChE) enzyme which has major role in cholinergic system in the brain.[2] It is known that Monoamine oxidase B (MAO-B) enzyme is also associated with AD by causing oxidative stress and increasing amyloid-β fibril formation.[3] Besides these, amiloid-binding alcohol dehydrogenase (ABAD) enzyme in the neuronal mitochondria binds to amyloid-β plaques and show toxic effects in the cell.[4] Thus, the purpose of this project is to develop new lead compounds having multi-target (AChE/MAO-B/ABAD) inhibitory potentials.

For this purpose, 109 new compounds containing urea/thiourea, carbamate/thiocarbamate scaffolds and pharmacophore groups of known AChE/MAO-B/ABAD inhibitors were designed. Their geometries were optimized with density functional theory M06-2X/6-31G(d,p) method. They were screened with their AChE/MAO-B/ABAD binding energies calculated from molecular docking using AutodockVina software. ADME properties (absorption, distribution, metabolism, elimination) and blood-brain barrier permeability were predicted as well.

Potential lead compounds that can show good inhibitory effect to AChE/MAO-B/ABAD enzymes and cross the blood-brain barrier were determined. In the light of these findings, *in vitro* experiments are still in progress in our group.

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QM/MM COMPUTATIONS ON THE BINDING ENERGY OF IRON WITH THE TERNARY COMPLEX OF HUMAN TRANSFERRIN PROTEIN AND *NEISSERIA MENINGITIDIS* BACTERIA

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Neisseria meningitidis, called meningococcus, is a Gram-negative bacterium that causes meningitis and meningococcemia, which threatens human life. *Neisseria* needs the iron (Fe^{3+}) ion for survival and virulence[1]. Unlike most Gram-negative bacteria, *Neisseria* does not transport Fe^{3+} but instead directly uptakes the Fe^{3+} ion from the C-lobe of human transferrin (hTf) via its transport system consisting of Tf-binding protein A (TbpA) and Tf-binding protein B (TbpB). Thus, understanding the molecular mechanism of Fe^{3+} release upon binding of this pathogen to its host via transmembrane protein complex, TbpA-TbpB is important in designing new therapeutic agents for meningitis. In the literature, the information about the Fe^{3+} ion binding/release mechanism in the C-lobe is quite limited[2]. Therefore the aim of this study is to explore how Fe^{3+} release from C-lobe is initiated upon TbpA-TbpB binding to hTf by utilizing hybrid QM/MM calculations.

ONIOM QM/MM approach[3] was employed to calculate the binding energy of Fe^{3+} to the TbpA –TpbB- hTf ternary enzyme complex using the Gaussian 09 program. QM and MM regions were treated by M06/6-31G(d,p) and AMBER metodologies, respectively. Solvent effect calculations showed that the aqueous environment increases the binding energy leading to more favorable release of Fe^{3+} from the ternary complex. Additional binding energy calculations on Lys359Ala mutation will provide insight into the Fe^{3+} ion release mechanism.

Acknowledgements: This work is supported by TUBITAK (Project no: 118Z353)

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COMPUTATIONAL INVESTIGATION OF THE MONOMER RATIO AND SOLVENT ENVIRONMENT FOR THE COMPLEX FORMED BETWEEN SULFAMETHOXAZOLE AND FUNCTIONAL MONOMER METHACRYLIC ACID

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In this study, the MIPs (Molecullarly Imprinted Polymers) that will be formed by the antibiotic sulfamethoxazole (SMX) molecule and methacrylic acid (MAA) molecule were examined theoretically. In this direction the most stable interaction region between the two molecules was determined, then solvent environments (ethanol, acetonitrile, dimethylsufoxide) and monomer ratios (SMX:MAA; 1:1, 1:2, 1:3) were examined in order to form the most stable complex. The number and length of the hydrogen bonds formed between the template molecule and the functional monomer and the interaction between atoms were determined. Geometry optimizations and single point energies of the molecules were calculated by the B2PLYP-D3 method ccpvtz basis set. In addition to the theoretical studies, the experimental Fourier-transform infrared spectroscopy (FTIR) spectrum of the complex formed between SMX and MAA was compared with the theoretical FTIR spectrum. As a result of the studies, the monomer ratio and solvent environment in which the stable complex was formed were determined in the MIP studies to be carried out with the SMX template molecule and MAA monomer. The most stable template molecule-monomer ratio of the complex between SMX and MAA was determined as 1:3, and the solvent medium in which the most stable complex was formed was determined as dimethylsulfoxide (DMSO).

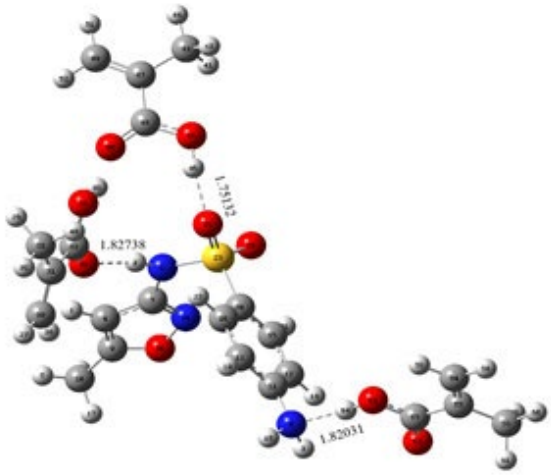

Figure 1. Most Stable Complex Formed Between SMX and MAA molecules.

NEW BIOACTIVE SEMI-SYNTHESIS GYPSOGENIN COMPOUNDS

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Gypsogenin compound, used as a starting material, is obtained by boiling *Gypsophila arrostii* plant roots in water. This natural saponin has various biological properties such as antiviral, antitumor, anti-carcinogen, antioxidant, and anti-cancer.[1] On the other hand, semi-synthesis gypsogenin compounds, combined with different substituted derivatives, have higher activity than gypsogenin aglycon.[2] So, we targeted to synthesize new more bioactive semi-synthesis gypsogenin compounds. The starting material gypsogenin aglycone was combined with different amines compounds by using sodium triacetoxyborohydride in DCE at room temperature. Purification was carried out using chromatographic methods.The synthesized compounds were determined by IR, UV, ^{1}H NMR, APT, and LCMS analysis. The biological activities of new compounds were employed very important pharmaceutical properties against HeLa (human cervix adenocarcinoma), MCF-7 (human metastatic breast adenocarcinoma), Jurkat (human lymphocytic cancer cell), and K562 (human erythroleukemic cell).

Acknowledgements: This work is supported by TUBITAK (Project no: 117R034).

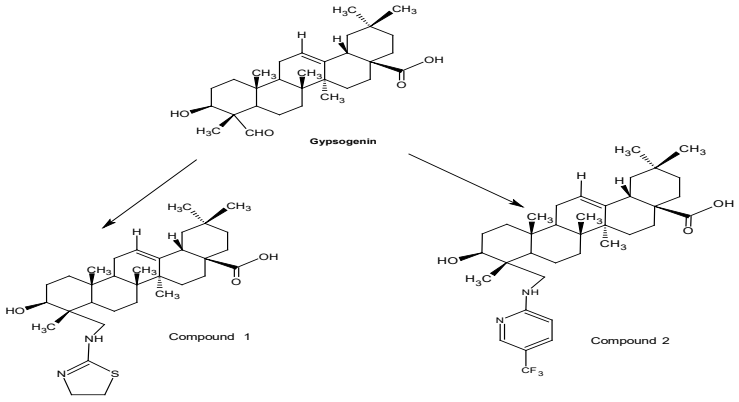

Figure 1. General synthetic route for compounds **1-2**

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A NEW APPROACH TO SMA THERAPEUTICS WITH MOLECULAR MODELLING METHODS

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Spinal Muscular Atrophy (SMA), an autosomal recessive inherited neuromuscular disease, is caused by homozygous loss of survival motor neuron gene 1 (SMN1)[1]. Symmetrical weakness and wasting of the voluntary muscles in the body and decreased mobility, different body structure and regression in respiration are among its many symptoms[2]. In addition to the high cost of existing treatments, only some countries' health insurances cover the cost of medications. Therefore, there is a need for cost-effective and easily accessible alternative therapies that can improve the neuromuscular function of SMA patients and help maintain general health throughout their lives[3].

In order to propose alternative SMA treatments in our project, macromolecules from the symptom-exacerbating Rho/ROCK pathway were selected and ligands that could inhibit this mechanism were investigated by the means of molecular modelling[4]. In order to apply molecular modeling techniques with different approaches, PyRx and UCSF Chimera using AutoDock Vina and Schrödinger Maestro using the Glide module were utilized. A total of 2 macromolecules and 8.854 ligands were docked, and possible drug candidates, which showed much higher binding affinity compared to their known inhibitors, were proposed for the inhibition of Rho/ROCK pathway. It has been seen that among the candidate drugs, there are multiple novel molecules, and those that have been already approved for different diseases can also be potential cures for SMA. In our project, candidate drug molecules with high binding affinity values, which can contribute to alleviating the long and costly drug development processes through molecular modeling methods, are presented in an available and low-cost manner.

Keywords: SMA, Molecular Modeling, Docking, SMN protein, ROCK I

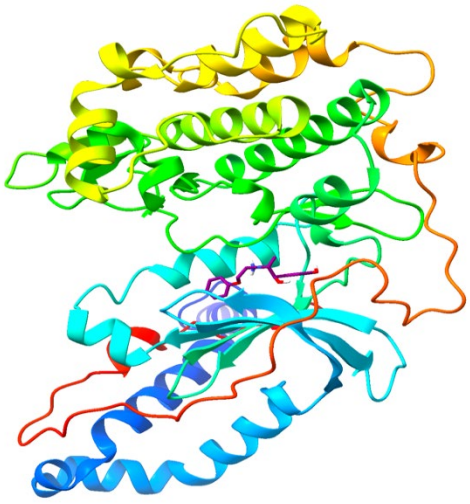

Figure 1. 4-[(1R,2R)-1-hydroxy-2-[[(2R)-1-phenoxypropan-2-yl]amino]propyl]phenol in complex with the ROCK-I kinase enzyme.

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COMPUTATIONAL MODELING ON THE LYSINE-TARGETTED COVALENT INHIBITION OF PHOSPHOINOSITIDE 3-KINASE (PI3K) ENZYME BY P-FLOROPHENYL ESTER INHIBITOR

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Phosphoinositide 3-kinase (PI3K) enzymes are important drug targets, especially in oncology and cancer treatment. Recently, Dalton et al.[1] developed new highly selective irreversible inhibitors of PI3Kδ bearing an ester functional group as warhead which targets the conserved lysine residue in the active site. The x-ray crystal structure (PDB: 6EYZ) of p-fluorophenyl ester derivative of the inhibitor proved that it is covalently linked to the enzyme via Lys779. However, the mechanism of this reaction and the role of the enzyme active site residues are unknown.

In this study, as a continuation of our recent article[2], the amine acetylation reaction shown below between the enzyme's Lys779 and the p-fluorophenyl ester inhibitor (I) was modeled using a cluster structure representing the PI3Kδ enzyme active site. Potential energy surfaces of four mechanistic schemes (Path A-B-C-D involving the tetrahedral zwitterion intermediate were obtained from the geometry optimizations at the M06-2X/6-31+G(d,p):PM6 level using the ONIOM method in Gaussian09 program. Asp782, Asp911 and water molecules are involved in these mechanisms via H-bond network. We found that Path C is the most plausible pathway where the zwitterion NH_2 proton is transferred to the negatively charged oxygen to form a neutral intermediate, and then the same hydrogen is transported to Asp911 while dissociation of p-F phenoxide occurs at the same time. Although the zwitterion formation step is endergonic and reversible, overall reaction is exergonic and irreversible. Our results explain why an irreversible covalent inhibition was observed with this inhibitor and pave the way for designing more promising new covalent inhibitors of PI3Kδ enzyme.

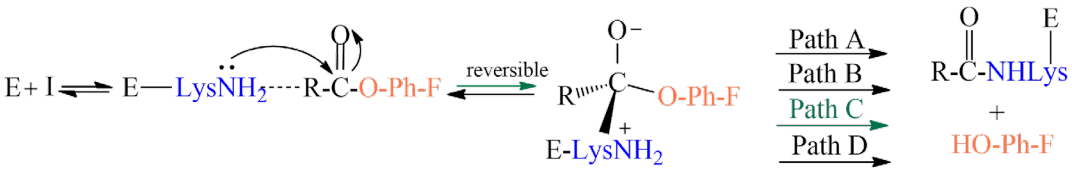

Figure 1. A schematic representation of a ligand-protein complex and binding site.

Acknowledgement: The authors thank to French-Turkish Bosphorous program (Project number 44738WL) and TUBITAK (Project number 119N133)

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IDENTIFYING PROTEINS IN CANCER CELL SECRETION THAT ARE ACTIVE IN THE TUMOR MACROENVIRONMENT

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Cancer cachexia is a wasting syndrome characterized by loss of body weight, with specific loss in skeletal muscle and adipose tissue, in addition to the loss of homeostatic control of energy and protein balance[1]. The pathogenicity of this syndrome is multifactorial, due to a complex interaction of tumour and host factors. The signs and symptoms of cachexia are considered as the prognostic parameters in cancer patients[2]. Tumours secrete molecules which directly result in catabolism of skeletal muscle and adipose tissue. White adipose tissue has the major role of storing lipids as energy reservoir and has the capacity to adopt physiological similarities to brown fat through a process known as browning. The physiological role of brown fat tissue is to burn lipids to generate heat through adaptive thermogenesis which involves the uncoupling of mitochondrial respiration by Uncoupling Protein 1 (UCP1). Tumor-driven increase in thermogenic activity of adipose tissue contributes to energy wasting and the loss of fat mass as seen in cancer cachexia. Here we aim to identify novel secretion factors or proteins which activate the browning of white adipose tissue.

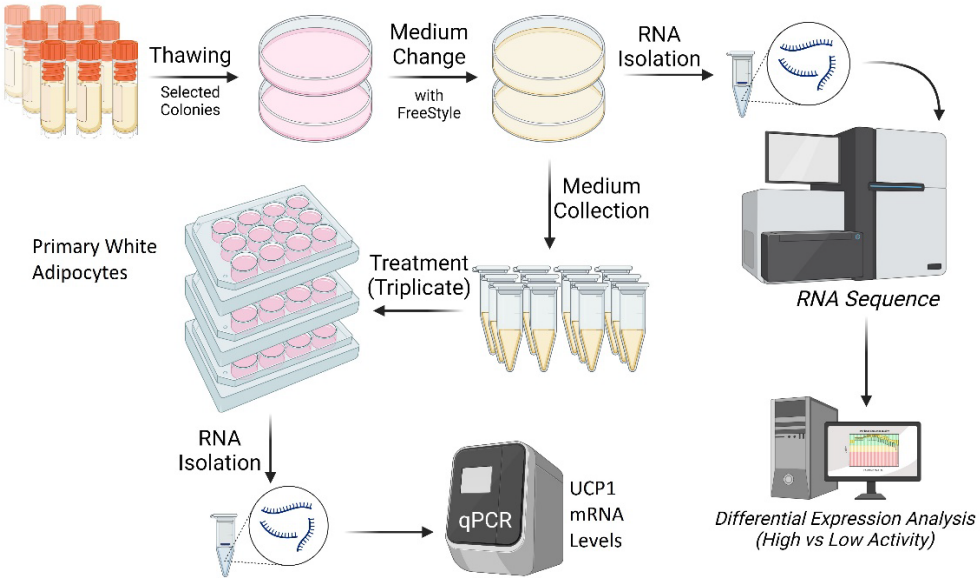

Figure 1. Experimental design of the first set of experiments. *UCP1; Uncoupling Protein1*

Here we have generated Lewis Lung Carcinoma cell (LLC) colonies and have tested the effect of their conditioned medium on relative UCP1 expression in primary white adipocytes. We aim to identify differentially expressed genes

in these LLC colonies through RNA sequencing to identify the factors involved in mediating this browning process. Our future experiments may involve designing target molecules against these identified factors to look at the effect of their inhibition on the browning of adipose tissue in animal models. This may lead to the development of a novel agent which can be further investigated and modified to be used clinically to prevent the development of cachexia in cancer patients.

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MOLECULAR DOCKING APPROACH TO ENLIGHTEN PHOTODYNAMIC THERAPY APPLICABILITY OF THE TAILORED D-A *OR* D-A-D TYPES' AIEGENS

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Fluorescence imaging-assisted photodynamic therapy (PDT) allows accurate tumor visualization in addition to preventing long-term side effects. Therefore, developing photosensitizers emitting light in the near-infrared region (NIR) is crucial. Creating a complex between an organic dye and a macromolecule improves fluorescence efficiency by stabilizing the luminogens inside the complex[1].

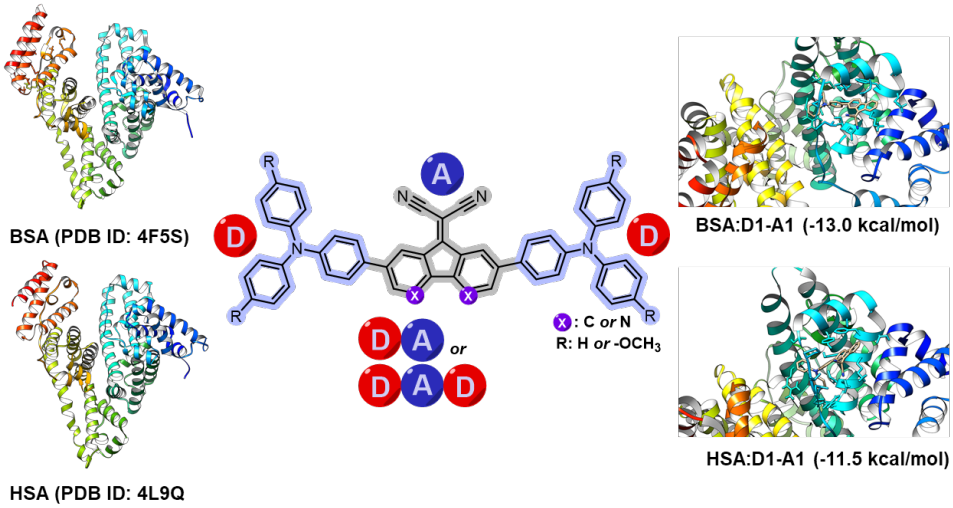

Figure 1. Scope of the investigated AIEgen candidates and blood proteins

In this scope, we have performed a molecular docking study of D-A *or* D-A-D type luminogens with blood proteins; namely bovine serum albumin (BSA), and human serum albumin (HSA) (Figure 1) which are appeared as a robust carrier of several pharmaceuticals against preliminary cancer diseases[2]. Geometry optimization studies were performed with the Gaussian 09, whereas molecular docking simulation and visualization of the dye-albumin complexes were carried out utilizing UCSF-Chimera and Discovery Studio Visualizer, respectively. Our results revealed that the binding scores of the dye: BSA complexes ranged from -8.6 to -13.0 kcal/mol while dye: HSA complexes showed scores varying from -9.9 to -11.5 kcal/mol.

Keywords: Organic luminogens, FLI, AIEgen, BSA, HSA.

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IMIDAZOLE DERIVATIVES: SAR, ADME, AND MOLECULAR DOCKING AS ANTIFUNGAL AGENTS

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The purpose of this study was in silico investigation of the affinities of the previously synthesized imidazole and triazole derivatives that exhibited considerable antifungal activity and show no activity on *candida albicans*, against 14-alpha-sterol demethylase. In this study, the chosen imidazole and triazole derivatives were investigated using Maestro Schrödinger 2021-4 package program. The synthesized molecules and . A high resolution (2.05 Å) X-ray crystal structures of cytochrome p450 14-alpha-sterol demethylase (cyp51) from mycobacterıum tuberculosıs ın ferrıc low-spın state in complex with HEM, native ligand[1-3] were prepared using LigPrep and Protein Preparation Wizard in Maestro of Schrödinger-2021 software package, respectively[4-6]. The docking calculations were performed using the Glide SP (standard precision) module of Schrödinger Suite. Additionally, some selected physicochemical properties of the synthesized compounds were also calculated[7]. Molecular docking studies were achieved to see possible binding modes of the synthesized compounds with 14-alpha-sterol demethylase and it was observed that the considerable active compound 3 makes hydrogen bond with CYS394 amino acid residue and pi-pi interaction with TYR76, that is believed to be critical in activities.

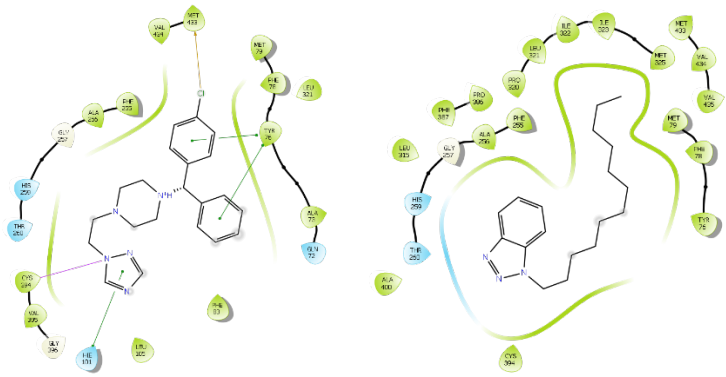

Figure 1. 2D ligand interaction diagram for active compound 13 (left), and inactive compound 30 (right).

Consequently, the results obtained from both experimental and *in silico* agreed well with one other. Thus, these results can shed light on the design and synthesis of potential drug molecules in the future.

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A FACILE SYNTHESIS OF NOVEL PYRIDINE N-OXIDE CONTAINING 5-AMINO-ISOXAZOLES

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Diseases caused by thrombosis are still the source of morbidity for many people in the world. Pulmonary embolism, deep vein thrombosis and thromboembolic stroke are just a few examples of this condition.[1] There are still limitations associated with available treatments, studies have been initiated that the small molecules have the potential to directly inhibit the related enzymes.[2] Over the years, thrombin inhibitors have attracted considerable attention. In a recent study, it was reported that a molecule with a pyrazinone skeleton retains the classical hydrogen bond when oxidized to the N-oxide form of pyridine which is a direct analog of pyrazinone [3]The efficient and straightforward synthesis of novel pyridine N-oxide containing 5-aminoisoxazoles by reacting 2-(cyanomethyl)pyridine 1-oxide and α-chloro oximes in the presence of a base at reflux temperature and the effects of the obtained compounds on the thrombin protein were evaluated using autodock with important data such as binding energy, inhibition constant and bond interactions[4].

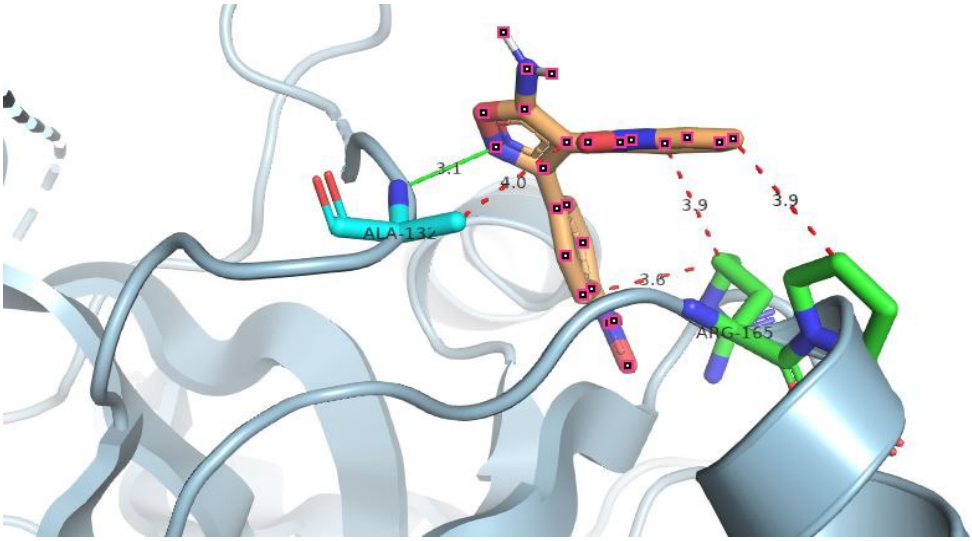

Figure 1. A schematic representation of a ligand-protein complex and binding site of molecule 4-b and thrombin.

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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF UREAS DERIVED FROM SULFONAMIDES

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Ureas are important pharmacophoric structures that play an important role in drug design process. Belonging to their capacity to form multiple hydrogen bonds with biological targets, urea nucleus is associated with several biological activities such as antibacterial, antifungal, anticancer, anti-inflammatory and antioxidant. In addition, there are clinically approved urea derivatives which play active role at the treatment of several diseases[1,2].

Sulfonamides are an important class of biologically active molecules which are commonly known for their antimicrobial activity. However, with recent studies they came to the forefront with their diverse biological activities[2].

Within this context, we synthesized a new series of urea-sulfonamide hybrid compounds and characterized their structure by IR, ^{1}H-NMR, ^{13}C-NMR, MS and elemental analysis. The antimicrobial activity of the compounds were tested on a strain of bacteria and yeast like fungi by using agar well diffusion method[3]. Also, their *in vitro* anti-inflammatory activity was evaluated by the method of Phosrithong and Nuchtavorn[4] with slight modifications described by Yıldırım et al.[5] Among the tested compounds, Y10 with IC_{50} value of 19,93 µg/mL displayed a strong anti-inflammatory activity compared with standard Indomethacin (IC_{50}=18,05 µg/mL).

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MOLECULAR DOCKING STUDY OF NOVEL QUERCETIN DERIVATIVES

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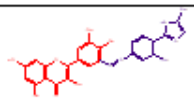
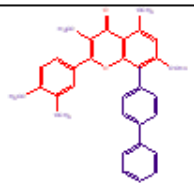
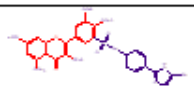
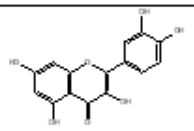
Three novel quercetin derivatives, ZC-1, ZC-2 and ZC-3 were designed and their CCRP5 antagonist[1] effects have been investigated with molecular docking studies[2]. All compounds confirmed appropriate binding free energies towards 4MSB, CCRP5 receptors. Data show that all compounds have higher energy scores than quercetin. As shown in the figures 1 and 2, compounds bonded to the active site and overlapped with reference compound quercetin.

Comp No.	Structure	Docked aminoacid residues (vdW interactions)	Energy Score	RMSD Value	H bond (distance Å)
ZC-1		TYE37, TRP86, PHE109,	-11.68	1.34	H of SH with O of LYS191 (2.068)
ZC-2		TRP86, THR284, MET287	-13.12	0.17	O of OCH3 with OH of SER179 (2.168)
ZC-3		TRP86, SER180, ILE198	-11.00	1.15	H of SH with O of THR284 (2.235)
Quercetin		TRP86, THR105, TYR108	-10.45	0.14	H of OH with O of THR284 (2.062)

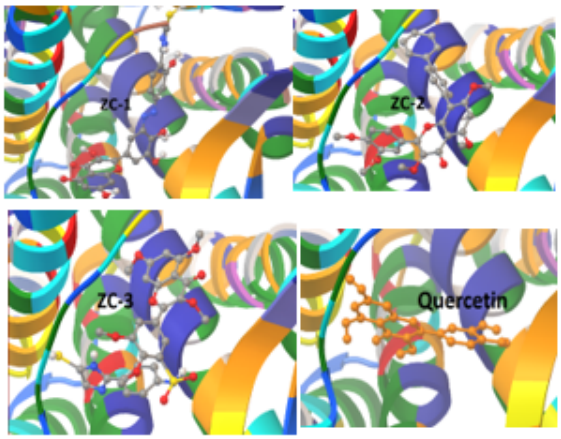


Figure 1. Interaction of the best-docked poses of compounds **ZC-1, ZC-2, ZC-3** and reference drug **Quercetin** to 4MSB target protein.

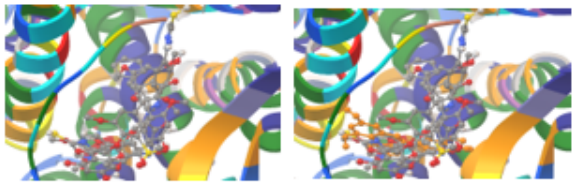


Figure 2. Superimposing poses of best scored compounds with and without reference drug Quercetin against 4MSB

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SCREENING OF JAK-2 INHIBITORS WITH MACHINE LEARNING

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Janus Kinases (JAKs) are a family of intracellular non-receptor protein tyrosine kinases that play crucial roles in the JAK-STAT signaling pathway. JAK family has four sub enzymes, JAK1, JAK2, JAK,3, and TYK2. Among the four JAK subtypes, JAK2 emerged in recent years as a potential therapeutic target for myeloproliferative neoplasm. In this study, based on ECFP4 and Deep Neural Network (DNN), we developed a classification machine learning model for JAK2 inhibitors. Dataset obtained from ChEMBL (release 30, Feb 2022). IC_{50} values on the dataset converted pIC_{50} values to decrease the range of distribution. We set a threshold of 7.5 pIC_{50} to label molecules active or inactive. Dataset split training and test set by DeepChem's scaffold splitting. Training set were split into 5 equal parts with 5-fold cross-validation to reach the validation set. DNN model contains 3 hidden dense, dropout, and batch normalization layers and the activation function is ReLu, the output layer activation function is sigmoid. The performance of the model was evaluated by ROC-AUC score, accuracy score, F1 score, and Matthew's correlation coefficient (MCC). [1,2] In conclusion, we have a machine learning tool capable of classifying molecules such as active or inactive for JAK2.

	ROC-AUC	ACCURACY	F1 SCORE	MCC
Validation set	0.88	0.81	0.75	0.61
Test set	0.89	0.82	0.76	0.62

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AN *IN-SILICO* STUDY OF CHIRALITY OF BENZIMIDAZOLE AMINE HYBRIDS ON THE INHIBITION EFFECTS ON HUMAN CARBONIC ANHYDRASE ISOENZYMES AND ACETYLCHOLINE ESTERASES

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Benzimidazole-hybrid have a unique chemical structure which show tremendous pharmacological activity such as anti-inflammatory, antiviral, anti-histaminic, antimicrobial [1,2]. Due to their biological and therapeutic activity they have been studied extensively in recent years. For instance, Richards et.al. showed that the main benzimidazole structure has good efficacy in treating allergy and asthma [3]. Carbonic anhydrase (CA) regulates the acidity of the chemical environment in the body and prevents body functions from being damaged. Due to these vital physiological properties extensive studies have been performed on CA enzymes. Anti-acetylcholineesterases (anti-AChE) are used as anti-Alzheimer drugs to treat moderate Alzheimer disease because of their enhanced cognitive connectivity cholinergic neurotransmission in clinic applications. There are many CA and AChE inhibitiors identified and used in clinic treatments [4].

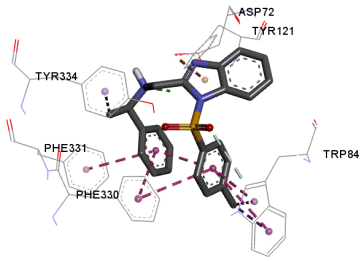

Figure 1. Representation of Ligand 4a -AChE (1EEA) protein complex and binding sites.

In this study, efficacy of novel chiral benzimidazole amine hybrids as CA and AChE inhibitors have been studied *in silico* and compared with the *in vitro* results. The binding energies (scoring based) were obtained as negative scores which proves that all compounds were successfully docked at the active sites of CA isoenzymes and AChE. The highest binding energies were observed in the case of AChE and these results are in consistent with the experimental data since all of the compounds have shown very good inhibition activity by means of IC_{50} values. The ADME (adsorption, distribution, metabolism and excretion) were also showed that these compounds could be recognised as drug like potential towards AChE and CA proteins

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SPR AND MOLECULAR MODELLING STUDY OF BOVINE SERUM ALBUMIN INTERACTION WITH DIPYRIDAMOLE

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Abstract Especially in order to evaluation of the pharmacokinetic profiles properties, serum concentration and physiological activity of drugs, determining the drug-serum protein interactions is very important issue in drug design and development studies. Albumin is the most abundant protein in the blood and responsible for transportation of small molecules such as drugs. The aim of this study was to investigate the interaction of a hydrophobic drug molecule Diprydamole with albumin by using surface plasmon resonance (SPR) and molecular docking methods. Diprydamole is vasodilator and inhibitor of platelet aggregation which is widely used to decrease the risk of thromboembolic complications due to its anti-platelet and anti-viral properties (It is lastly used Covid -19 patients). In the experiments, BSA was used because it is very similar structure to the serum Albumin protein (76%) (HSA) and it is cheap and available. In order to measuring Dip-BSA affinity of the interactions and binding kinetics, SPR spectroscopy was used. Surface plasmon Resonance (SPR) spectroscopy is a powerful label-free analytical technique that relies on changes in the refractive index at the surface of a gold. This technique offers valuable information about affinity of molecular interactions and reaction kinetics. All SPR measurements were performed with SPR-mini produced by the company Nanodev Scientific (Ankara, TR).

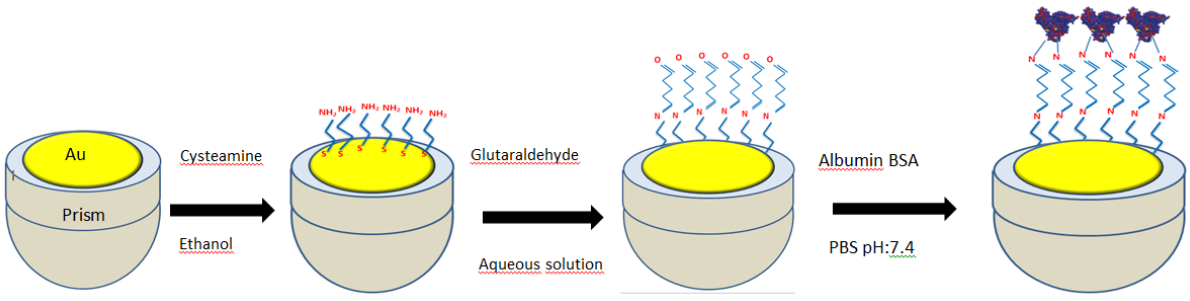

Figure 1. Schematic illustration of BSA immobilization on the bare gold SPR cips surface

After the bare gold SPR chip was activated with Cysteamine by forming a self-assembled monolayer (SAM), the Albumin molecule was covalently bound using 2.5% Glutaraldehyde. DIP-BSA interactions were performed at physiological pH (7.4) in different concentrations (5-80 µL) of DIP solution (10% DMSO/Ethanol) of PBS buffer with a flow rate of 50 µm/min.

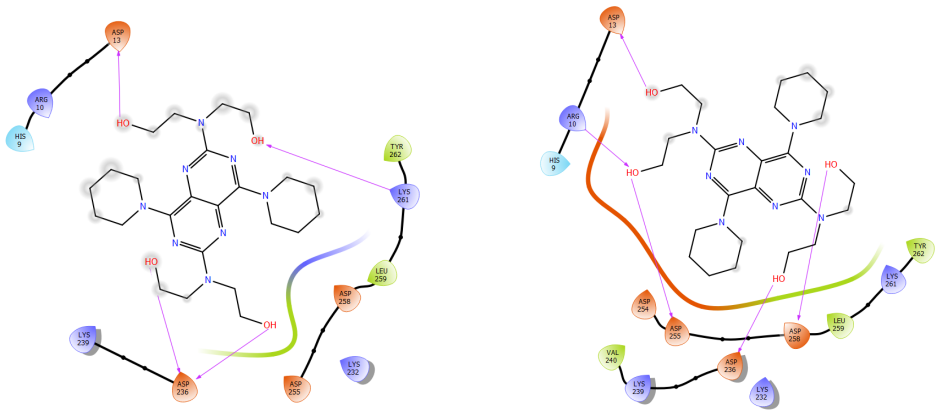

Figure 2. Amino acids that contacted with rifampicin from the analyzing of all runs of each docking procedure and the number and type of amino acids that join together in formation of H-bond in the selected binding site of BSA. Glide SP docking (left), Glide XP docking (right)

Molecular docking simulations employed revealed that dipyridamole successfully binds to BSA by making a number of hydrogen bonds with the amino acid residues of BSA.The docking study of BSA with dipyrimadole was carried out by Schrödinger Maestro 2021-4 package programme. The molecular docking studies were performed using a high resolution (2.47 Å) X-ray crystal structure of Crystal Structure of Bovine Serum Albumin. Molecular docking calculations successfully predicted binding mode of dipyridamole which reveals a number of hydrogen bonds with the amino acid residues of BSA.

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IDENTIFICATION OF NOVEL PARP1 INHIBITORS BASED ON STRUCTURAL SIMILARITIES OF FDA APPROVED DRUGS

***Haneen Ammuri*, Serdar Durdagi**

VIRTUAL SCREENING OF FDA APPROVED COMPOUNDS AND ULTRA LARGE LIGAND LIBRARIES AGAINST PARP1

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ABSTRACT

Under normal conditions, BRCA1 and BRCA2 genes are involved in DNA damage repair, and they act as tumor suppressors. When a deleterious mutation occurs in either of these genes, or a mutated copy is inherited from either one of the parents, it can result in cancer formation. Approximately, 10% to 15% of all ovarian and breast cancer are hereditary, while the mutations in the BRCA1 and BRCA2 genes are responsible for roughly 30% of all ovarian and breast cancer. Thankfully, scientist have identified an effective method for the treatment of cancers caused by BRCA1 and BRCA2 mutations, synthetic lethality. According to National Cancer Institute, synthetic lethality is a situation in which a mutation in one gene does not cause cell death, while mutations in two genes causes cell death. In the case of BRCA1 and BRCA2 mutations alone, cell death does not occur while if mutations occur in both BRCA genes and PARP-1, cell death occurs since they have synthetic lethal interaction. If a PARP inhibitor is introduced to BRCA mutated cancer cells, it will result in toxic DNA double-strand breaks, converted from single-strand breaks during replication, leading to cancer cell's death. Currently, niraparib, talazoparib, olaparib, and rucaparib are the only available FDA-approved PARP inhibitors for clinical use. In this study, 2360 promising hit FDA-approved molecules in Drugbank database and 1.569.617 ligands from Chembridge database are going to be screened and examined by virtual screening approaches to detect selective and effective promising drug candidates for the inhibition of PARP to cause cell death in BRCA mutated cancer cells. For this purpose, docking, Molecular Dynamics (MD) simulations and Molecular Mechanics Generalized Born Surface Area (MM/GBSA) methods are going to be applied on the protein-ligand complexes.

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DRUG REPURPOSING FOR M. TUBERCULOSIS BY TARGETING TRYPTOPHANYL-TRNA SYNTHETASE

Neslihan Demirci*, *Serdar Durdagi

SCANNING FDA APPROVED DRUG LIBRARIES FOR IDENTIFICATION OF ERCC1-XPF PPI INHIBITING POTENTIAL ANTICANCER DRUGS

Salma Ghazy*, *Serdar Durdagi

MOLECULAR DOCKING SIMULATIONS FOR THE DISCOVERY OF ANTAGONISTS TO KNOCKDOWN OF AXL – GAS6 OVEREXPRESSION

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ABSTRACT

Axl is one protein of the receptor tyrosine kinase (RTK) pathways which promote cancer development, progression, and metastasis. Axl is present in almost all tissues and cell membranes and is mainly concerned in cell proliferation and migration. Axl belongs to the Tyro3, Axl, and Mer (TAM) subfamily. They all play an important role in immunity, but Axl has also partaken in cancer. Hence, until recently, targeting Axl seems to have become popular because of increasing evidence of its significant association with poor prognosis and drug resistance. Growth arrest specific 6 (Gas6) is the major high affinity ligand for the activation of TAM subfamily proteins. Overexpression of TAMs and Gas6 is correlated with more aggressive cancer stages, poorer presumed patient survival, metastasis, and acquired drug resistance. [1-3] Hence, the Gas6 and Axl complex has been indicated as a trigger for abnormal cell growth and metastatic process in many cancer types, especially kidney cancer. In this study, it is planned to examine the status of therapeutics targeting the Gas6 and Axl pathway in cancer and to take it further with using chemicals wherein FDA and Specs libraries. We propose that a drug that suppresses the overexpression of the Gas6 and Axl complex would play an important role in inhibiting cancer development and metastasis.

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CONSTRUCTION OF MACHINE LEARNING MODELS FOR VIRTUAL SCREENING STUDIES AGAINST GLIOBLASTOMA MULTIFORME

Asena Himmetoglu*, *Seyma Calis, Timucin Avsar, Turker Kilic, Serdar Durdagi

DISCOVERY OF PAXLOVID ANALOGSAS SARS-COV2 MAIN PROTEASE INHIBITORS

Ezgi Sambur*, *Serdar Durdagi

AN *IN SILICO* DRUG REPURPOSING STUDY TARGETING FULL-LENGTH MODELED P62 STRUCTURE

Lalehan Oktay*, *Serdar Durdagi

GENE EXPRESSION PROFILE ANALYSIS IN C57BL/6 (B6) AND BALB/C MODELS OF CYSTIC FIBROSIS WITH LUNG DEFORMATION

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Introduction: Cystic fibrosis (CF) is a disease caused by mutations in the cystic fibrosis transmembrane conductivity regulator (CFTR) gene, affecting many organs such as the lung, intestines, liver, pancreas, and causing various symptoms. CF, also known as mucovisidosis, is an autosomal recessive inherited disease. CF lung disease consists of damage cycles that cause inflammation and infection (usually by Pseudomonas aeruginosa) due to high neutrophils, destroying the airway, preventing gas exchange, and resulting in death. Data from mice with null mutations in the Cftr gene (BALB/c and C57BL/6) were evaluated.

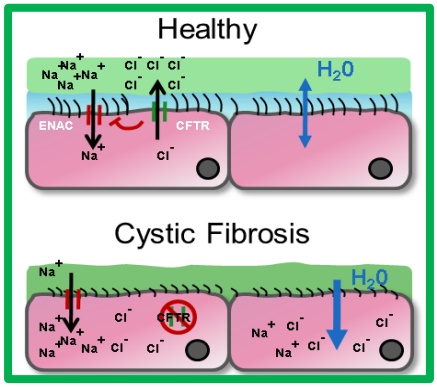

Figure 1: Function of CFTR gene in healthy and cystic fibrosis cell (Paul J.)

Objective: It was aimed to evaluate the gene expression profiles for the dysfunctional Cftr gene in C57BL/6 (B6) and BALB/c models and to reveal the direct or indirect effects of the relationships between the genes.

Method: In our study, BALB/c and C57BL/6 mice were compared for 100 genes known to be associated with the disease for the two models using the GenBank Overview-NCBI-NIH database. 12 BALB/c (5 controls 7 patients); 11 C57BL/6 (5 controls 6 patients) were included in the study. The relationship between genes was evaluated using the software we developed and the R database. Log-fold change (LogFC) values were taken into account while determining the expression levels. logFC −2.4, $p<0.05$ in determining low expression levels; logFC 2,382 , $p<0.05$ values were taken as criteria in determining high expression levels.

Result: While 36 genes show up regulation on the models; 64 genes were downregulated. The pyridoxal-dependent decarboxylase domain containing 1 (Pdxdc1) again shows both up-regulation and down-regulation for the two models.

Arsk, Rab6b, Vnn1 genes were down-regulated for 5 BALB/c mice; 7 showed up-regulation for BALB/c mice (Figure 2).

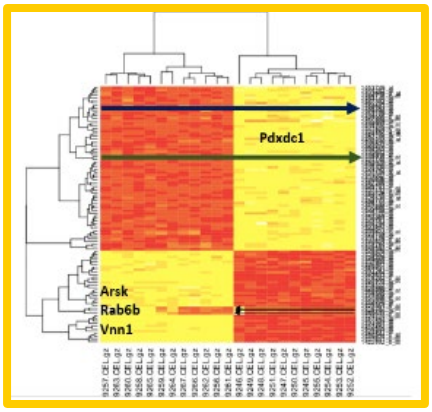

Figure 2: Evaluation of relationships between genes

Discussion: Contrary to the literature, Pdxdc1 gene, which is frequently studied in BALB/c and C57BL/6 mice, was not found to be distinctive for CF disease. More detailed studies are needed for the place of Arsk, Rab6b, Vnn1 genes in CF disease.

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