ABSTRACT BOOK

8TH INTERNATIONAL BAU DRUG DESIGN CONGRESS

CONGRESS

NOVEL METHODS AND EMERGING TARGETS IN DRUG DISCOVERY & PATENTED DRUG DEVELOPMENT

İSTANBUL - TÜRKİYE

15-17 DECEMBER 2022

Prof. Dr. Canan ATILGAN

Short Biography
Canan Atılgan received her BS degree from the Department of Chemical Engineering of Boğaziçi University in 1991, and her PhD degree from the same institution in 1996. She was a postdoctoral research fellow at the Supercomputer Computations Research Institute of Florida State University through 1999. Since then, she has been a faculty member at the Faculty of Engineering and Natural Sciences of Sabancı University. She is the recipient of Boğaziçi University PhD Thesis (1996), TÜBİTAK Encouragement (2002), Turkish Academy of Sciences Young Scientist (2004), L'Oréal Turkey For Women in Science (2005) Awards. She is an elected member of the Science Academy and is its current President.

Dr. Atılgan's expertise is on the computational and theoretical investigation of complex molecules. Her focus is on disclosing dynamical features of soft matter systems that lead to unique behavior identified, but not explained, through experiments. Protein dynamics, manipulation of protein conformations, understanding the antibiotic resistance problem at the scale of the three-dimensional structure of single proteins, prediction and control of nanostructures formed by self-organizing oligomeric systems are areas of current interest for her. Dr. Atılgan has also contributed to the reflection of the new learning patterns to the teaching of science at the University level. She has been applying and disseminating new paradigms such as student-centered learning and flipped classroom techniques to the courses she teaches at all levels of the University. She is on the editorial board of the Turkish language popular science web site sarkac.org where she is also a regularcontributor.

http://people.sabanciuniv.edu/canan/

Abstract

Teaching Old Drugs New Tricks: Protein Dynamics in the Limelight

Drug design has been at the forefront of applications targeted by scientists working on molecular modelling. While the knowledge of the atomistic coordinates of the protein structure is a prerequisite for the design process, docking-based studies fall short of fulfilling the need for developing new drugs. This is primarily due to the fact that proteins exist in an environment, and many a times, the static picture does not take into account the conformations sampled by the proteins in the various niches of the cellular environment. Our group studies the dynamics of proteins via modelling and simulation, developing new approaches as the need arises. We are interested in understanding the role of allostery and environment on the conformational multiplicity of proteins. Here, I will present our work on the antibiotic resistance problem in the model system of dihydrofolate reductase in *E. coli*. I will discuss, using atomic scale dynamical information and very rewarding collaborations with experimental colleagues, how we can explain the way point mutations affect evolutionary paths, how such evolutionary trajectories may be steered using rational design, and how hidden allosteric sites may be utilized for alternative drug discovery strategies.

Prof. Dr. Thierry Langer

Short Biography

Prof. Langer holds an M.S. degree in Pharmacy and a Ph.D. in Pharmaceutical Chemistry from the University of Vienna, Austria. He began his career at Leopold-Franzens-University of Innsbruck in 1992 after completing a post doctoral fellowship at the Université Louis Pasteur, Strasbourg, France with Prof. C.-G. Wermuth. In 1993, he established the Computer Aided Molecular Design Group at Innsbruck University. In 1997, he was appointed Associate Professor of Pharmaceutical Chemistry, and served as Head of the Institute of Pharmaceutical Chemistry there in 1998 and 1999.

In 2003 he founded, together with two colleagues, the company Inte:Ligand GmbH, an Austrian based privately held software development and consulting organization, in which he served as CEO from 2003 to 2008.

In 2008, Prof. Langer was appointed CEO of Prestwick Chemical Inc., a world renown contract research organization specialized in medicinal chemistry services located in Strasbourg-Illkirch, France. Under his leadership, several drug discovery programs in different research target sectors successfully progressed into pre-clinical and clinical development.

In 2013, Prof. Langer was nominated Full Professor for Pharmaceutical Chemistry at University of Vienna, Austria, where since 2014 he also heads the Department of Pharmaceutical Chemistry at the Faculty of Life Sciences. Since March 2021, he heads the Department of Pharmaceutical Sciences, which has been created by merging all departments related to pharmaceutical research at University of Vienna, with a headcount of more than250.

His research interests range from medicinal chemistry, computer-assisted molecular design, to pharmacophore elucidation as well as machine learning based molecular modeling techniques. His expertise and scientific work have culminated in more than 250 original articles, book chapters, and invited reviews (scholar.google.com: h-index 62, more than 12300 citations; Scopus: h-index 55, more than 9000 citations), several patents, and more than 300 lectures and poster presentations at scientific meetings.

Abstract
Towards Next Generation Pharmacophore Modeling:
Concepts and Applications

Pharmacophore-based compound modeling, virtual screening, and bio-activity profiling has become a popular in silico technique for supporting medicinal chemists. The advanced molecular design tool LigandScout [1] has been developed to successfully address one of the most important issues in virtual screening: Enhancing early enrichment while maintaining high computational speed as well as ease of use, as shown by referencestudies. [2]

As an extension of the static pharmacophore approach, we lately have focused on incorporating dynamic effects of ligand protein binding into our automated interaction determination process. Our Common Hits Approach (CHA) [3] uses multiple coordinate sets saved during MD simulations. Pharmacophore models with the same pharmacophore features are pooled and virtual screening runs are then performed with every representative pharmacophore model resulting in a consensus hit list. The recently developed GRAIL (GRids of phArmacophore Interaction fieLds) [4] method combines the advantages of traditional grid-based approaches for the identification of interaction sites with the power of the pharmacophore concept: A reduced pharmacophore abstraction of the target system enables the computation of all relevant interaction grid maps in short amounts of time. This allows one to extend the utility of a grid-basedmethod for the analysis of large amounts of coordinate sets obtained by long-time MD simulations. In

this way it is possible to assess conformation dependent characteristics of key interactions over time.

In the NeuroDeRisk project [5], we utilize these new developments, together with machine learning methods for adding quantitative pharmacophore feature weighting [6] to predict potential neurotoxic effects of drug candidates.

[1] Wolber G, Langer T, *J Chem Inf Model.* **2005**; 45(1):160
[2] Karaboga AS, et al., *J Chem Inf Model.* **2013**; 53(3):1043
[3] Wieder M, et al., *J Chem Inf Model.* **2017**; 57(2):365
[4] Schuetz DA, et al., *J Chem Theory Comput.* **2018**; 14:4958
[5] NeuroDeRisk IMI2 JU (www.neuroderisk.eu) has received funding under grant agreement No 821528
[6] Kohlbacher SM, et al., *J Cheminform* **2021**; 13,57

Assist. Prof. Dr. Berna DOĞAN

Short Biography

Dr. Berna Doğan got her B.S. degree in Chemistry from Boğaziçi University. She spent a summer in Ghent, Belgium as an Erasmus internship trainee working at Center for Molecular Modeling, Ghent University. She got her M.Sc. degree in Chemistry also from Boğaziçi University while guided by Prof. Dr. Victoria Aviyente. After that she went to Munich, Germany to get her PhD degree in computational chemistry from Technical University of Munchen, TUM under the guidance of Prof. Dr. Karsten Reuter. She did a post-doc at Durdağı Lab, BahçeşehirUniversity after coming back to Turkey and started working on computational drug discovery. She become a faculty member after post-doc studies and working at Bahcesehir University as Assistant Prof. Nowadays, she is more focused on applying machine learning approaches for virtual screening and drug discovery.

Abstract

Machine learning approaches to quantitatively predict selectivity of compounds against hDAC1 and hDAC6 isoforms

Histone deacetylases (hDAC) are enzymes catalysis the removal of acetyl group from proteins with acetylated lysine residues. These enzymes are necessary for the normal body functions and disease conditions are observed when they are out of balance and/or overexpressed in the body. Inhibitors for these enzymes were already developed and in fact there are some approved drugs targeting this enzyme class. However, these drugs target more than one isoform of the enzyme, i.e., they are pan-inhibitors and as nonselective inhibitors could cause dose-dependent side effects in patients such as thrombocytopenia, cardiotoxicity, hematological toxicity, neutropenia, fatigue. The discovery and design of compounds selectively binding to specific isoforms of hDAC is ongoing research to reduce adverse side effects of compounds. Two of the most studied isoforms are hDAC1 and hDAC6, important targets for various disease conditions. Here, variousmachine learning approaches were tested with the aim of developing models to predict the bioactivity and selectivity towards specific isoforms. Selectivity models weredeveloped by directly training on the bioactivity differences of tested compounds against hDAC1 and hDAC6. Both classification and regression models were developed and compared to each other by using traditional evaluation metrics. The compounds mispredicted by different models were analysed and common structural features were determined in those molecules. The models developed are also tested against an external set. As a future work, the developed will utilized for screening of molecular libraries to discover selective inhibitors for targets.

Assist. Prof. Dr. Bircan Dinç

Short Biography
Assistant Prof. Dr. Bircan Dinç is a faculty member at Bahçeşehir University, Faculty of Medicine, Department of Biophysics. She completed her undergraduate degree in basic sciences and physics, and his graduate degree in biomedical engineering. The researcher completed her doctorate at Istanbul Medical Faculty, Department of Biophysics. She works on the analysis of molecules, biomaterials, and nanoparticles by microscopic, calorimetric, and spectroscopic methods. She works in the field of investigating the toxicity of molecules, biomaterials, and nanoparticles. In addition, she performs drug screening studies and toxicity experiments in different cell lines and with the model organism Caenorhabditis elegans.

Abstract

The Effects of Monoamine Oxidase-B Inhibitors in *C. elegans* Models of Parkinson's Disease

Background: With the use of Monoamine Oxidase B (MAO-B) inhibitors in Parkinson's disease (PD), it is possible to improve motor symptoms and provide neuroprotection by elevating high dopamine levels in the striatum. *Caenorhabditis elegans (C. elegans)* offers many advantages for PD research due to a simple, well-mapped, and accessible neuronal system. Several transgenic worm strains exhibiting multiple PD-related phenotypes have been developed to perform neuronal and behavioral experiments and drug screening (1). A53T and alpha-synuclein (α-syn) strains were used in the study.

Methods:

Experiments were performed using two MOA-B inhibitors for A53T and α-syn strains by forming experimental groups as in **Table 1**. Its effect on reproduction, alpha-synuclein accumulation, and the mobility of nematodes was evaluated. Standard nematode growth medium (NGM) was used at 20 °C (2) by adding 40 µM 5-fluorouracil to the NGM to inhibit reproduction (3).

MAO-B Inhibitors	A53T	α-syn	Experimental Groups
IZ080 : 3-(1-(1-((2 bromophenyl)ethynyl)cyclohexyl)pyrrolidin 2-yl)pyridine ($C_{23}H_{25}BrN_2$)	**500 µM**	**500 µM**	**Reproductive- Control**
			Reproductive- Inhibited-Control
			Reproductive- Dose
			Reproductive- Inhibited- Dose
IZ081: 3-(1-(1-((4-chlorophenyl)ethynyl)cyclohexyl)pyrrolidin-2-yl)pyridine ($C_{23}H_{25}ClN_2$)	**1000 mM**	**1000 mM**	**Reproductive- Control**
			Reproductive- Inhibited-Control
			Reproductive- Dose
			Reproductive- Inhibited- Dose

Table 1: Inhibitors, concentrations, and experimental groups.

Results:

Inhibitor-IZ081 caused an increase in mobility in α-syn strain reproduction-inhibited and uninhibited groups. This increase was 27.5% in uninhibited groups. The rate of increase in mobility was less in the inhibited groups, due to the effects of 5FU. The mobility of the A53T strain was two times higher in the control groups than in α-syn. An increase in mobility was observed in the groups that were administered inhibitors for the first 3 days. The IZ080 inhibitor did not elicit as much increased mobility in the α-syn strain as the IZ081 inhibitor. However, there is an increase in the measurements taken compared to the control. No significant differences emerged in the A53T strain for this inhibitor. The decrease in α-synuclein protein expression in body muscle cells of the A53T strain of the IZ081 inhibitor is clearly observed in the microscope image (40x) in **Figure 1**.

Figure 1: Microscope images of A53T strains. Control(A) and IZ081 inhibitor applied group (B)

References:

1. Boos, J. R., Shubbar, A., & Geldenhuys, W. J. (2021). Dual monoamine oxidase B and acetylcholine esterase inhibitors for treating movement and cognition deficits in a C. elegans model of Parkinson's disease. *Medicinal Chemistry Research*, *30*(5), 1166-1174.
2. Perni, M., Van der Goot, A., Limbocker, R., Van Ham, T. J., Aprile, F. A., Xu, C. K., ... & Dobson, C. M. (2021). Comparative Studies in the A30P and A53T α-Synuclein C. elegans Strains to Investigate the Molecular Origins of Parkinson's Disease. *Frontiers in cell and developmental biology*, *9*, 552549.
3. Kumar, S., Aninat, C., Michaux, G., & Morel, F. (2010). Anticancer drug 5-fluorouracil induces reproductive and developmental defects in Caenorhabditis elegans. *Reproductive Toxicology*, *29*(4), 415-420.

Assoc. Prof. Dr. Kader ŞAHİN
Short Biography
Dr. Şahin received her bachelor's degree in Ankara Univ in Science and Enginering faculty and PhD degree in Erciyes Univ in 2011. During her PhD, she developed a new method called electron conformational-genetic algorithm (EC-GA) as an alternative to commercial programs. With this method developed, pharmacophore determination and biological activity prediction are performed. Her PhD studies is supported by The Scientific and Technological Research Council of Turkey-TUBITAK. Dr. Şahin carried out a few national projects so far (TUBITAK, Scientific Research Project (BAP)). Dr. Şahin worked as senior researcher (2019-2022) in Molecular Modeling and Simulation Laboratory, School of Medicine, Bahçeşehir University with research Lab of Prof. Durdağı. Dr. Şahin applies computational chemistry methods to biological systems. Her studies focus on protein modeling and dynamics, ligand- and structure-based drug design, investigation of molecular mechanisms of protein/drug, protein/protein, protein/DNA interactions and optimizations protocols for rational drug design. For this aim, Dr. Şahin also develops programing codes for several biological problems together with research Lab of Prof. Durdağı.

Abstract
Hybrid In Silico and TR-FRET-Guided Discovery of Novel BCL2 Inhibitors
B-Cell lymphoma 2 (BCL-2) proteins are vital in controlling cell death. Overexpression of BCL-2 proteins is usually directly related to various types of cancer. We used the latest state-of-the-art computational molecular modeling and dynamics approaches, which include advanced integrated text mining, virtual screening, and hybrid molecular modeling techniques, combined with in vitro binding and cell culture studies to identify the small-molecule inhibitors targeted to the BCL-2 binding site. We used a small-molecule library with about 210 000 molecules. The binary cancer quantitative structure-activity relationships (QSAR) model was used to calculate the predicted therapeutic activity value (TAV) of the compounds in this library. The molecules with a high calculated TAV were used in 26 individual toxicity QSAR models. As a result of this screening protocol, 288 nontoxic molecules with high predicted TAV were identified. MD simulations were initiated for the top recorded docking pose for each of the 288 molecules and 2 known BCL-2 inhibitors (venetoclax and navitoclax analog). Moreover, a five-site (AHRRR) structure-based pharmacophore model was constructed, and this model was used in the screening of the same database. On the basis of docking scores and interaction diagrams throughout the 100 ns MD simulations, 15 hit compounds (with high therapeutic activity and no toxicity) were identified. TR-FRET experiment results represented that hit compounds identified by the epharmacophore modeling has a high power for the correct identification of bioactive ligands from a large ligand database. The selected ligands were further evaluated in the U87-MG cell line, and among them three compounds were shown to be significantly effective on glioma cells by inhibiting and/or reducing cell proliferation. Consideration of these fingerprints together with indole analogs within the scaffolds of the designing of new compounds may improve activity against BCL-2. The identification of potent and safe small molecules as potential inhibitors of BCL-2 is a step closer to finding appropriate effective therapies for cancer. Our lead ligands identified from in silico guided screening can be used as a scaffold for further structural optimization and development, enabling further research in this promising field.

KEYWORDS: binary QSAR modeling, virtual screening, BCL-2, text mining, colorimetric biochemical in vitro assay, TR-FRET assay

IS-6

Malgorzata Poczopko

Short Biography

Gosia is a Sales and Application Specialist at NanoTemper Technologies where she prides herself on bringing cutting-edge protein analysis tools to the customers both, in academia and industry. Since 2018, Gosia has been working globally with customers and stakeholders, to pave the path to making every disease treatable. Prior to joining NanoTemper, Gosia worked at Max Plank Institute of Biochemistry in Martinsried, Germany, in the lab of Prof. Petra Schwille. Gosia was applying a range of biochemical and biophysical methods, including fluorescence correlation spectroscopy (FCS), to study molecular mechanisms underpinning interleukinsignalling.

Abstract

Small Molecule Effectors of The MYC/MAX Oncogene

MYC is a commonly amplified oncogene in human cancers. Inhibition of the obligatory homodimerization of MYC with MAX is one of the possible molecular strategies to suppress downstream transcription of MYC targets. However, intrinsically disordered structure of MYC and the lack of defined binding pockets make development of small molecule inhibitors challenging and gave MYC the label of an "undruggable" target.

Here we present a new biophysical technology, Spectral Shift1, that enables easy in-solution investigation of MYC/MAX interactions with various molecular partners, reversible and covalent small molecule binders, and a nucleic acid consensus binding sequence. Spectral Shift enables direct binding and competition assays for characterization of Kd and EC50 values, respectively.

Spectral Shift is based on a well-known observation that organic fluorophores react to changes in their chemical microenvironment with slight modifications of their emission spectrum. The method exploits this observation by performing ratiometric measurements at two distinct emission wavelengths of a labeled target molecule in the presence of various concentrations of an unlabeled ligand to derive the affinity constant (Kd) for the interaction. The method is highly robust against sample impurities and aggregates and provides high quality data with minimal assay development time. The Spectral Shift technology is amenable for both, a flexible capillary-based set up, as well as high-throughput, 384 well plate-based screening campaigns.

References :
1)   Langer A. et al. ASSAY and Drug Dev Tech. 2022, 20, 83.

Prof. Dr. Gebhard F.X. Schertler

Short Biography
Prof. Dr. Gebhard Schertler heads the PSI Division of Biology and Chemistry (BIO) and is Professor emeritus of Structural Biology at the ETH Zürich (D-BIOL). He joined PSI in 2010 and became a member of the directorial board of PSI in 2011. He received his PhD at the University of Munich where he built his expertise in structural biology of membrane proteins and molecular pharmacology. He was at the MRC-LMB in Cambridge, UK, as a group leader until 2009. His research focus are G protein coupled receptors (GPCRs) and retinal proteins. He is a world-leading structural biologist of membrane proteins with expertise in biophysical methods, electron microscopy, and X-ray crystallography including time-resolved measurements at Synchrotrons and Free Electron Lasers. He initiated the Free Electron Laser biology research program at PSI. He is a member of the electron detector consortium headed by Richard Henderson and he was on the Scientific Advisory Committee of MAX IV Laboratory, Sweden. His experience with translating research resulted into business opportunities. He is a scientific founder of MRC-LMB Spin-Off Heptares Ltd., and he co-founded InterAx AG and leadXpro AG, two Biotech companies at the PSI in 2015 and 2016 in context with Park InnovAare. In 2021 he obtained and coordinates an ERC Synergy Grant on Switchable rhodOpsins in Life Sciences (SOL). OptoGPCRs will open new opportunities in life sciences and medical research.

Abstract
Title: GPCR signaling in vision and molecular pharmacology

Vertebrate and invertebrate rhodopsins are very suitable to study the paradigm of GPCR cascades. The retinal chromophore allows for many biophysical studies which are harder to execute with other ligand binding GPCRs. Insights from optical spectroscopy, DEER spectroscopy, NMR, infrared and Raman spectroscopy can be obtained with relative ease. The 11-cis to all-trans isomerization of retinal converts the strong antagonist 11-cis retinal (inverse agonist) to an all-trans retinal agonist. This reaction is a natural photo trigger that enables vision. In addition, it offers the possibility to carry out pump-probe experiments in spectroscopy and room-temperature crystallography. I will present the newest results in this area. Cryo-electron microscopy has enabled the study of the signaling complex of rhodopsin and other GPCRs with the G protein. I will present the rhodopsin-transducin complex and the CCR5 chemokine signaling complex. On the example of the HIV Co-receptor G protein complex I will discuss the selectivity of the receptor for different G proteins. The target of the visual cascade is a cyclic GMP gated non-selective cation channel. We have been able to obtain the structure of this hetero oligomeric CNG channel directly isolated from retinas. This is an example of an effector of a G protein coupled receptor cascade that is modulating the neurotransmitter release at the synapse of the photo receptor cell. The impact of structural biology on molecular pharmacology and the progress with modelling GPCR cascades will be discussed. Both approaches are highly relevant to drug discovery.

REFERENCES:

Cryo-EM structure of the rhodopsin-Gαi-βγ complex reveals binding of the rhodopsin C-terminal tail to the gβ subunit
CJ Tsai, J Marino, R Adaixo, F Pamula, J Muehle, S Maeda, T Flock, N Taylor, I Mohammed, H Matile, R Dawson, X Deupi, H Stahlberg, GFX Schertler.
Elife 8, e46041

Structural basis of the activation of the CC chemokine receptor 5 by a chemokine agonist
P Isaikina, CJ Tsai, N Dietz, F Pamula, A Grahl, KN Goldie, R Guixà-González, C Branco, M Paolini-Bertrand, N Calo, F Cerini, GFX Schertler, O Hartley, H Stahlberg, T Maier, X Deupi and S Grzesiek.
Science Advances, 7(25), p. eabg8685. 10.1126/sciadv.abg8685.

Ultrafast structural changes direct the first molecular events of vision
T Gruhl, T Weinert, M Rodrigues, CJ Milne, G Ortolani, K Nass, E Nango, S Sen, P Johnson, C Cirelli, A Furrer, S Mous, P Skopintsev, D James, F Dworkowski, P Bath, D Kekilli, D Ozerov, R Tanaka, H Glover, C Bacellar, S Brunle, C Casadei, A Diethelm, D Gashi, G Gotthard, R Guixa-Gonzalez, Y Joti, V Kabanova, G Knopp, E Lesca, P Ma, I Martiel, J Muhle, S Owada, F Pamula, D Sarabi, O Tejero, CJ Tsai, N Varma, A Wach, S Boutet, K Tono, P Nogly, X Deupi, S Iwata, R Neutze, J Standfuss, GFX Schertler, V Panneels
bioRxiv

The structure of the native CNGA1/CNGB1 CNG channel from bovine retinal rods
DCA Barret, GFX Schertler, U Benjamin Kaupp, J Marino
Nature Structural & Molecular Biology 29 (1), 32-39

Assist. Prof. Dr. Hasan DEMİRCİ

Short Biography
I completed my B.Sc. at Bosphorus University in 2002 and later obtained a Ph.D., in Molecular Biology, Cell Biology, and Biochemistry at Brown University in 2007. Before joining Koc University in August 2019, I was a member of the Biosciences Division at SLAC National Accelerator Laboratory and affiliated with the Non-Periodic Imaging group at Stanford PULSE Institute. My research focuses on the structural biology of mutant prokaryotic ribosomes, where I am interested in characterizing the function and dynamics of these mutants, with an eye toward answering questions in the structure and dynamics of ribosomes resistant to some of today's commonly-used antibiotics. My current research efforts also include methods development for time-resolved ambient-temperature X-ray crystallography of large and challenging biomacromolecules at 4th-generation light sources like the Linac Coherent Light Source at SLAC.

Abstract

"Bright Future of New Generation Drug Design in Turkiye"
High-resolution ribosome structures determined by cryo X-ray crystallography have provided important insights into the mechanism of translation. Such studies have thus far relied on large ribosome crystals kept at cryogenic temperatures to reduce radiation damage. We use serial femtosecond X-ray crystallography (SFX) with an X-ray free-electron laser (XFEL) to obtain diffraction data from ribosome microcrystals in liquid suspension at ambient temperature. Small 30S ribosomal subunit microcrystals programmed with decoding complexes and bound to either antibiotic compounds or their next-generation derivatives diffracted to high resolution. Our results demonstrate the feasibility of using SFX to better understand the structural mechanisms underpinning the interactions between ribosomes and other substrates such as antibiotics and decoding complexes. We have determined the structure of large (50S) ribosomal subunit in record-short time by using record-low amount of sample during and XFEL beamtime. This structure is the largest one solved to date by any FEL source to near atomic resolution (3 MDa). We expect that these results will enable routine structural studies, at near-physiological temperatures, of the large ribosomal subunit bound to clinically-relevant classes of antibiotics targeting it, e.g. macrolides and ketolides, also with the goal of aiding development of the next generation of these classes of antibiotics. Overall, the ability to collect diffraction data at near- physiological temperatures promises to provide new fundamental insights into the structural dynamics of the ribosome and other medically important drug targets with their functional and inhibitor complexes.

Prof. Dr. Bülent ÖZPOLAT

Short Biography

Dr. Ozpolat has expertise in Immunology, Cancer biology, Gene therapy, Experimental Therapeutics, Nanotechnology, and development of targeted cancer therapeutics. After getting his M.D. degree Dokuz Eylul University, Izmir, Turkey, Dr. Ozpolat received his Ph.D. degree in Immunology from The University of Texas- MD Anderson Cancer Center Houston, TX, USA and completed post-doctoral training on Cancer biology, cancer genetics, nanotechnology, targeted cancer therapeutics.at MD Anderson Cancer. After serving as a faculty for more than 15 years at MD Anderson Cancer Center and Dr. Ozpolat currently works as a Professor at Houston Methodist Research institute Houston, USA and at Neil cancer Center where he leads Innovative Cancer Therapeutics. Dr. Ozpolat's translational research focuses on 1) identification of novel molecular targets and oncogenic pathways in highly aggressive cancers such as triple-negative breast cancer, drug-resistant ER+ and HER2+ breast cancer, pancreatic, lung and ovarian cancers, melanoma 2) Development of highly targeted therapeutics for oncogenic survival pathways including EF2K, AXL, FOXM1, KRAS and FOXM1, and non-coding oncogenic RNAs (microRNAs and long-noncoding RNAs) as potential targets using gene silencing therapies and small molecule inhibitors. Dr. Ozpolat has 5 patents for development of targeted therapeutics and published more than 137 publications (H-index 39) (90 research papers, 20 book chapter sand 24 reviewarticles) in peer-reviewed high impact journals.

Abstract

Development of Targeted Therapeutics for Breast and Solid Cancers Breast cancer the most common cancer in women and the second leading cause of cancer related deaths. Triple negative breast cancer (TNBC) is highly aggressive, metastatic and the deadliest and incurable type of breast cancer. Significant heterogeneity with 6 genetically defined subtype has prevented development of targeted therapeutics for TNBC. The chemotherapy remains as a mainstay treatment, however only 30% of the patients achieve remission and most patients develop resistance and relapse. To develop highly effective targeted therapeutics and prolong patient survival novel molecular targets needed to be identified. After a decade of research our studies identified an oncogenic atypical kinase, Elongation Factor-2 kinase (EF2K) as major oncogenic driver in TNBC and validated it as a novel therapeutic target in triple negative breast cancer. To specifically target, we developed tumor-targeting microRNA-based nanotherapeutics. We demonstrated that single lipid or albumin-based nanoparticles can effectively deliver EF2K-targeting microRNA therapeutics into TNBC tumors in mice, inhibit EF2K gene and suppresses tumor growth with no toxic or side effects in mice, suggesting that this technology may be used clinical translation to patients for Phase 1 clinical trials. Overall, the talk will focus the current state of targeted therapies and development of successful novel RNA-based nanotherapeutics which is considered a novel era of targeted therapeutics in treatment of human cancers and diseases.

Prof. Dr. Uğur BOZKAYA

Short Biography

Dr. Uğur Bozkaya was born in Kars on 21st September 1982. He started his chemistry education in Gazi University in 1999. He continued his education as a TUBITAK Undergraduate Fellow (2001-2003) and graduated from the Department of Chemistry in 2003 with the 1st rank.

He started his graduated studies as a Faculty Development Program Fellow in Middle East Technical University (METU) in 2004. He continued his graduate studies as a TUBITAK Fellow (BIDEB-2211). He spent one year of his graduate studies (2009-2010) in University of Georgia with Prof. H. Fritz Schaefer as a TUBITAK Fellow (BIDEB-2214). He obtained his Ph.D. degree from Department of Chemistry, METU under supervision of Prof. İlker Özkan in 2011.

Dr. Bozkaya joined to Department of Chemistry, Atatürk University as a Faculty member in 2011. Then, he continued his researches in Prof. C. David Sherrill group, in Georgia Institute of Technology, as a National Science Foundation (NFS) Fellow during 2012-2013. In 2014, he appointed as an associate professor in Atatürk University. In 2015, Dr. Bozkaya moved to Hacettepe University where he continues his scientific studies.

Dr. Bozkaya's PhD studies were on the theoretical studies of thermal rearrangement reactions of biradical systems. During his Ph.D. Dr. Bozkaya interested in electronic structure theories and ab initio programming in addition to his thesis studies. After Ph.D., Dr. Bozkaya's research has been focused on the development of new electronic structure theoreties, their efficient programming, and applications of the developed methods to interestingchemical systems.

In 2012, Dr. Bozkaya was invited to join the development team of open-source Psi4 quantum chemistry package (http://www.psicode.org) by Prof. Sherrill. Since 2012, he contributes the Psi4 package as one of the primary developers. In 2022, Dr. Bozkaya and his research group release the MacroQC software (https://macroqc.hacettepe.edu.tr).

In 2016, Dr. Bozkaya has been elected as a new member of Editorial Board of Turkish Journal of Chemistry. He acts as a reviewer in scientific journals such as Journal of Chemical Theory and Computation, Journal of Chemical Physics, Journal of Physical Chemistry, Physical Chemistry Chemical Physics, International Journal of Quantum Chemistry, ChemPhysChem, and Molecular Physics. Dr. Bozkaya manages several research projects supported by TUBITAK, COST, and BAP.

In 2019, Dr. Bozkaya was awarded by TÜBİTAK for his studies in Theoretical Chemistry field. In 2015, Dr. Bozkaya was awarded for Outstanding Young Scientists Award by Turkish Academy of Sciences (TÜBA GEBİP-2015) and The Science Academy (BAGEP-2015), and Research Incentive Award by METU Prof. Dr. Mustafa N. Parlar Foundation. In 2013, 2014, and 2015, He has also been awarded for Scientific Incentive Award for Articles in Natural Sciences by Atatürk University.

Dr. Bozkaya is author of 65 scientific papers, and his studies has been cited more than 2600 times so far. Dr. Bozkaya has delivered about 30 invited talks in national and international conferences.

Abstract

Linear-Scaling Systematic Molecular Fragmentation Molecular Fragmentation Approach for High-Level Coupled-Cluster Methods: Applications to Protein-Ligand Interactions

The accurate computation of the protein-ligand interaction energies is one of the most challenging problems in modern computational chemistry. The coupled-cluster (CC) singles and doubles with perturbative triples method [CCSD(T)] is generally referred as the "gold standard" of computational chemistry. However, high computational costs of CC methods limit their applications to medium sized molecules. To address this problem, efficient implementations of linear-scaling coupled-cluster methods, which employ the systematic molecular fragmentation (SMF) approach (LSSMF-CC), are reported. Performances of the fragment-based linear-scaled CC approaches are investigated for several sets of molecular systems in comparison with their canonical versions. In addition, preliminary applications of the LSSMF-CC approaches to protein-ligand interactions are presented. We conclude that the fragment-based CC methods are promising for studying large-scale chemical systems, where the conventional methods are computationally prohibitive.

Assoc. Prof. Dr. Abdulkadir KOÇAK

Short Biography
I graduated from Ondokuz Mayis University in 2004 with B.Sc degree in Chemistry. I have started to carry out my M.Sc. studies in the following year at the same university. After I was awarded a scholarship by the Turkish Ministry of of Education, I started my graduate studies in the department of chemistry at the University of Massachusetts (UMASS), Amherst, USA. I have completed my MS and PhD studies between 2008 and 2014 in the field of photodissociation spectroscopy in Physical Chemistry at UMASS. I have published 7 articles about transition metal ion small ligand non-covalent interactions. Upon completion of my PhD, I returned to Gebze Technical University. I have been doing my research at the computational chemistry laboratory in Chemistry Department. Throughout my studies, I mostly carried out Molecular Dynamics simulations and Quantum Mechanical calculations for the host-guest non-covalently interacting systems. I have been authored to several publications fort he past 7 years in the field. One of my last studies is a TUBITAK Project in which we applied machine learning potentials to the host-guest systems to accurately and rapidly calculation of free energychanges.

Abstract
Application of ANI-ML potentials in drug discovery

Artificial intelligence tools, which have started to be widely used in the field of chemistry in recent years, can make it possible to calculate at the quantum mechanical (QM) level to systems containing tens of thousands of atoms, which are nearly impossible to calculate by known QM methods. In particular, ML potentials with their great capability of learning multidimensional potential energy surfaces (PES) at the DFT level are promising due to their efficiency and scalability to large systems. Recent studies showed that ML methods such as "Accurate NeurAl networK engINe for Molecular Energies" (ANAKIN-ME or shortly ANI) can be used to predict QM energy at a given non-equilibrium geometry for small organic compounds with millions times faster than conventional QM methods. We explore the potential use of ANI in drug discovery so as to calculate binding/solvation free energies from molecular dynamics (MD) trajectories or rescoring molecular docking and quick estimation of the lowest energy conformer of a given small organic compounds/drugs. We find ANI potentials can be used to accurately predict solvation free energies of small organic compounds and the binding free energies of drug-like molecules to proteins using linear interaction energy formalism. In addition, we can use ANI potentials as a rescoring function in molecular docking. We further utilize ANI potentials to calculate all possible conformers of a given drug like compound at the DFT accuracy. In conclusion, ANI can be utilized to solve several problems in drugdiscovery.

References:
1) Accurate Binding Free Energy Method from End-State MD Simulations, *Journal of Chemical Information and Modeling* **2022** *62* (17), 4095-4106,
2) The performance of ANI-ML potentials for ligand n(H2O) interaction energies and estimation of hydration free energies from end-point MD simulations, *Journal of Computational Chemistry, ASAP*
3) ANI-ML potentials as a rescoring function in molecular docking, *under review*
4) QM accurate conformer generation by ANI potentials, *to be submitted*
5) ANI-1: an extensible neural network potential with DFT accuracy at force field computational cost, *Chemical Sciences*, 2017,**8**, 3192-3203

Assist. Prof. Dr. Enes Seyfullah KOTİL

Short Biography

Abstract
The drug-isolate-fold change-based artificial neural network model predicts the resistance profiles of the HIV-1 protease inhibitors

Drug resistance is a primary barrier to effective treatments of HIV/AIDS. Calculating quantitative relations between genotype and phenotype observations for each inhibitor with cell-based assays requires time and money-consuming experiments. Machine learning models are good options for tackling these problems by generalizing the available data with suitable linear or nonlinear mappings. The main aim of this paper is to construct drug isolate fold (DIF) change-based artificial neural network (ANN) models for estimating the resistance potential of molecules inhibiting the HIV-1 protease (PR) enzyme. Throughout the study, seven of eight protease inhibitors (PIs) have been included in the training set, and the remaining ones in the test set. Using the leave-one-out (LVO) procedure, eight ANN models have been produced to measure the learning capacity of models from the descriptors of the inhibitors. Mean R-square value of eight ANN models for unseen inhibitors is 0.732, and 95% confidence interval (CI) is [0.613,0.850]. Predicting the fold change resistance for hundreds of isolates allowed a robust comparison of drug pairs. These eight models have predicted the drug resistance tendencies of each inhibitor pair with the mean 2D correlation coefficient of 0.933 and 95% CI [0.930,0.938]. A classification problem has been created to predict the ordered relationship of the PIs, and the mean accuracy, sensitivity, specificity, and Matthews correlation coefficient (MCC) values are calculated as 0.954, 0.791, 0.791, and 0.688, respectively. Furthermore, we have created an external test dataset consisting of 51 unique known HIV-1 PR inhibitors and 87 genotype-phenotype relations. Our developed ANN model has accuracy and area under the curve (AUC) values of 0.749 and 0.818 to predict the ordered relationships of molecules on the same strain for the external dataset. The currently derived ANN models can accurately predict the drug resistance tendencies of PI pairs. This observation could help test new inhibitors with variousisolates.

Assoc. Prof. Dr. Abdulilah ECE

Short Biography
Dr. Ece is associate professor of Chemistry. He received a B.Sc. in chemistry at Hacettepe University, Ankara. He completed his master degree in organic/computational chemistry and obtained his Ph.D. in the field of organic, computational and medicinal chemistry in the same institution. He worked as Research Assistant between the dates 2002-2011 at Hacettepe University. He currently works at Computer-Aided Drug Design Center, Biruni University.

Dr. Ece serves as associate editor of BMC Chemistry - Part of Springer Nature. He received two successive awards from Trinity College Dublin in 2017 and 2018.

Dr. Ece gave several talks as invited speaker at international/national scientific organizations including NATO-ASI Summer School, Training Courses etc. He organizes symposiums and hands-On Training Courses on Computer-Aided Drug Design.

His research group (ECE Research) is mainly focused on the computer-aided drug design & discovery. In that aspect, he uses both quantum chemical and molecular mechanics calculations. Supported by the leading software companies in the field, Ece Research uses effective and specialized computational tools to address a particular problem or to enlighten an experimental finding in medicinal, organic or pharmaceutical chemistry.

He believes that there is no boundaries in different fields of sciences. Scientists should set aside the differences and collaborate with each other. It is the reason that the motto of ECE Research is "Combining Multidisciplinary Research".

Abstract

Gettıng A Computatıonal Study Publıshed: Assessıng The Relıabılıty Of Computatıonal Modelıng From Edıtor's Perspectıve

The cost of drug design and discovery needed to bring a new drug to market estimates \$2.8 billion.[1] Thus, new approaches were found necessary to go beyond the limitations of those time-consuming and expensive traditional processes. With the advancement of computer technology, computer-aided drug design (CADD) tools have been a state-of-the-art technology. Not surprisingly, it has been used by many scientific disciplines such as organic chemistry, biochemistry, biophysics, pharmacology, physical chemistry, genetics, toxicology, etc.[2] Besides software that require users to be familiar with some coding or at least basic or some advanced commands, there have been advanced software at the market that are more user friendly. However, one should keep in mind that CADD is not done with just a few clicks. The misuse of software that results from the lack of proper training and the required knowledge in the area might and will drastically yield failures. Considering a large number of journals but by contrast a few numbers of experts as reviewers and editors in the field, there exists many published papers which have sometimes serious scientific flaws.

Many methods used in CADD are based on quantum mechanics[3] and molecular mechanics[4]. Each requires selection of correct method depended on the specific model under study. In addition, depending on the availability of experimental data, validation should be done carefully before applying a model on an unknown system. Internal validation, cross validation, fisher validation,

student t-test, robust initial enhancement (RIE), receiver operating characteristic (ROC), Boltzman enhanced discrimination of the ROC curve, enrichment factor (EF) etc. are amongst some statistical metrics that should be considered to avoid unsound results.

In this updated study, the critical points will be discussed in getting a computational study published. The reliability of different computational studies will be assessed by giving some successfully published papers and rejected manuscripts.

REFERENCES
1. 1. Wouters, O. J., McKee, M., & Luyten, J. (2020). Estimated research and development investment needed to bring a new medicine to market, 2009-2018. Jama, 323(9), 844-853.
2. 2. Stromgaard, K., Krogsgaard-Larsen, P., & Madsen, U. (2009). Textbook of drug design and discovery. CRC press.
3. 3. Ece, A., & Pejin, B. (2015). A computational insight into acetylcholinesterase inhibitory activity of a new lichen depsidone. Journal of enzyme inhibition and medicinal chemistry, 30(4), 528-532.
4. 4. Ece, A. (2020). Towards more effective acetylcholinesterase inhibitors: a comprehensive modelling study based on human acetylcholinesterase protein–drug complex. Journal of Biomolecular Structure and Dynamics, 38(2), 565-572.

Assoc. Prof. Dr. Zoe COURNIA

Short Biography
Dr. Cournia is a Researcher – Associate Professor level at the Biomedical Research Foundation, Academy of Athens, where she works on anticancer drug and materials design using High Performance Computing (http://www.drugdesign.gr). She graduated from the Chemistry Department, University of Athens in 2001 and received her PhD at the University of Heidelberg in Germany in 2006. She then worked as a postdoctoral researcher at the Chemistry Department, Yale University, USA, on computer-aided drug design and in 2009 she became a Lecturer at Yale College. She has been awarded with the American Association for Cancer Research Angiogenesis Fellowship (2008), the "Woman of Innovation 2009" Award from the Connecticut Technology Council, USA, the Marie Curie Fellowship from the European Union (2010), the "Outstanding Junior Faculty Award" from the American Chemical Society (2014) and the first "Ada Lovelace Award" from the "Partnership for Advanced Computing in Europe" (2016). She was a member of the Infrastructure Advisory Group (INFRAG) of the European High Performance Computing Joint Undertaking in 2018-2021 and in 2022 she was appointed as the Greek representative in the Innovative Health Initiative Joint Undertaking. She is an Executive Editor with the Journal of Chemical information and Modeling, American Chemical Society and the national representative of Greece in the Division of Computational and Theoretical Chemistry in the European Chemical Society. She is currently teaching at the Master's program "Data Science and Information Technologies" at the Department of Informatics and Telecommunications, National University of Athens. She is the Founder of the SME Ingredio, a mobile phone app that informs consumers on the potential hazards of chemical ingredients in food and cosmetics products using open, peer-reviewed data (http://www.ingred.io/android).

Abstract
Predicting protein-membrane interfaces using ensemble machine learning and molecular simulations

Abnormal protein-membrane attachment is involved in deregulated cellular pathways and in disease. Therefore, the possibility to modulate protein-membrane interactions represents a new promising therapeutic strategy for peripheral membrane proteins that have been considered so far undruggable. A major obstacle in this drug design strategy is that the membrane binding domains of membrane proteins may not be known.

We show several examples of atomistic and coarse-grained Molecular Dynamics simulations of membrane-associated proteins, where we study protein-membrane interactions and identify their membrane binding regions.[1,2,3] However, although they produce highly accurate results, MD simulations bear a great computational cost making such predictions laborious.

The development of fast and efficient algorithms predicting the protein-membrane interface would shed light into the accessibility of membrane-protein interfaces by drug-like molecules. Herein, we describe an ensemble machine learning methodology and algorithm for predicting membrane-penetrating amino acids. We utilize available experimental data in the literature for training 21 machine learning classifiers and a voting classifier. Evaluation of the ensemble classifier accuracy produced a macro-averaged F_1 score $= 0.92$ and an MCC $= 0.84$ for predicting correctly membrane-penetrating amino acids on unknown proteins of a validation set. Predictions were further verified in independent test sets.[4]

Protein-membrane interacting regions can be further utilized in targeting protein-membrane interactions with drug-like molecules that could represent a new promising therapeutic strategy.

Here, we also present a drug design pipeline for drugging protein-membrane interfaces using the DREAMM (Drugging pRotein mEmbrAne Machine learning Method) web-server. DREAMM works in the back-end with a fast and robust ensemble machine learning algorithm for identifying protein-membrane interfaces of peripheral membrane proteins. Additionally, DREAMM also identifies binding pockets in the vicinity of the predicted membrane-penetrating residues in protein conformational ensembles provided by the user or generated by DREAMM. DREAMM has been made onboarded to the European Open science Cloud and is accessible at https://dreamm.ni4os.eu.[5]

References

1) Gkeka P, Evangelidis T, Pavlaki M, Lazani V, Christoforidis S, Agianian B, Cournia Z*. Investigating the Structure and Dynamics of the PIK3CA Wild-Type and H1047R Oncogenic Mutant. *PLoS Comput Biol.* 2014, 10 (10):e1003895.

2) Andreadelis I, Kiriakidi S, Lamprakis C, Theodoropoulou A, Doerr S, Chatzigoulas A, Manchester J, Velez-Vega C, Duca J. S., Cournia Z*. Membrane Composition and Raf[CRD]-Membrane Attachment Are Driving Forces for K-Ras4B Dimer Stability. *J Phys Chem B*, 2022, 26(7): 1504-1519

3) Lamprakis C, Andreadelis I, Manchester J, Velez-Vega C, Duca JS, Cournia Z.* Evaluating the Efficiency of the Martini Force Field to Study Protein Dimerization in Aqueous and Membrane Environments. *J Chem Theory Comput.* 2021, 11;17(5):3088-3102

4) Chatzigoulas A, Cournia Z (2022) Predicting protein-membrane interfaces of peripheral membrane proteins using ensemble machine learning. Brief Bioinform 2022, bbab518. doi: 10.1093/bib/bbab518

5) Chatzigoulas A, Cournia Z (2022) DREAMM: A web-based server for drugging protein-membrane interfaces as a novel workflow for targeted drug design, Bioinformatics, *in press*

Prof. Dr. Ramazan ALTUNDAŞ

Short Biography

Department of Chemistry
School of Science
Gebze Technical University
Phone: +90 262 605 3092
E-mail: raltundas@gtu.edu.tr

Prof. Dr.	Ataturk University, Department of Chemistry	2011
Assoc. Prof.	Ataturk University, Department of Chemistry	2006
Assit. Prof.	Ataturk University, Department of Chemistry	1997-2000
PhD.	Organic Chemistry- Ataturk University	1995
Ms.	Organic Chemistry- Ataturk University	1987
Visiting Scientist	University of North Carolina, Chapel Hill, NC, USA	2012
Postdoc.	Florida A&M University, Tallahassee, Florida, USA	1999
Postdoc.	Duquesne University, Pitsburgh, PA, USA	1998
Scientist	Organix Inc. Woburn, Boston ,USA	2000

Duties

|		
Director	Director of Eastern Anatolia High Technology Application and Research Center (DAYTAM)	2016-2017
Current Position	Dean, School of Science, Gebze Technical University	2020-

Reserach interest:
Synthesis of active pharmaceutical ingredient (API)
Drug Discovery
Determination of Impurities:Syntheses of impurities of drugs
Agrochemicals
Enantioslective alkylation of cyclicoxonitriles.
Syntheses of heterocyclic compounds bearing multistereo and prochiral centers
New methodologies for b-aminoacids

Abstract

The synthesis of ibrutinib and its intermediates

Ibrutinib, Imbruvica®, has been used for the treatment of Waldenstrom`s macroglobulinemia (WM), Mantle cell lymphoma (MCL) and Chronic lymphocytic leukemia (CLL). Ibrutinib has been synthesized in good yield by conventional synthetic strategies along with the Suzuki coupling reaction which include a homogeneous catalytic system. In this conference, alternative methods for the synthesis of ibrutinib and its intermediates will be discussed.
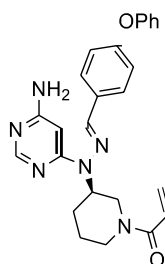
Ibrutinib

IS-16

Assist. Prof. Dr. Özge ŞENSOY

Short Biography
Ozge Sensoy has her research studies focused on understanding molecular mechanisms of biologically important systems and also providing mechanistic insight at the molecular level. She has been working with GPCRs and their interacting partners as well as RAS proteins. She has been awarded various prestigious grants and fellowships including COST and EMBO. She has been the author of more than 20 papers, and the inventor of 1 international and 1 national patents.

Abstract
Hidden and underestimated modulators of protein function: Posttranslational Modifications

Proteins are complex biological molecules that maintain physiological processes in the cells. Some of them serve as structural scaffolds while the others as catalysts. As such, the body needs various types of these molecules to maintain homeostasis in the cell, which, in part, is provided by alternative splicing, where different exons are combined to produce proteins with unique functions. Moreover, the variety can also be further increased by means of posttranslational modifications which extend the chemical repertoire of standard amino acids by modifying an existing functional group or introducing a new one. In this talk, I will give two examples to one of these posttranslational modifications, namely, phosphorylation. In the first example, I will talk about the impact of phosphorylation on RAS proteins and demonstrate how it provides an avenue for targeting the undruggable protein (1). In the second example, I will talk about the impact of phosphorylation on the enzymatic steps catalyzed by farnesyl transferase (Ftase) (2). The results showed that phosphorylation, which was occurred in hyperinsulinemia, revealed potential allosteric pockets, which can be targeted by small therapeutics molecules.

References:
(1) Ilter, et,al, 2022, Inhibition of mutant RAS-RAF interaction by mimicking structural and dynamic properties of phosphorylated RAS, E.life, Accepted
(2) Pekel et.al, 2022, Mechanistic insight into impact of phosphorylation on the enzymatic steps of farnesyltransferase, Protein Science, 31, 10, e4414.

**Asst. Prof. Dr. Necla BİRGÜL IYISON**

Short Biography

Dr. Necla Birgül received her MSc and PhD from the University of Hamburg in January 2001. Did her postdoc with Prof. Dr. Gerd Gaede, University of Cape Town, South Africa, 2001-2001., Instructor at Boğaziçi University, Istanbul, Turkey 2001-2004. Since 2004 Assistant Professor at Boğazici University, Istanbul, Turkey.

Abstract

<div align="center">

GPCRs as next-generation pesticides

</div>

Introduction: G-protein coupled receptors (GPCRs) are membrane receptors which have diverse roles in various signaling pathways. GPCRs are popular drug targets and suitable candidates for next-generation pesticides. Allatostatin receptor type-c (AstR-C) is a class A GPCR responsible for the regulation of Juvenile Hormone (JH) secretion in insects. JH is vital for growth, development, metamorphosis, and reproduction. Only AST-C peptide has been identified for the receptor as a natural ligand. Therefore, AstR-C represents a potential pesticide target against the Pine processionary moth, the main factor limiting the growth and survival of the Mediterranean pine forests. The study aims to provide novel potent agonists of AstR-C for next-generation pesticide design.

Strategy for next generation pesticides
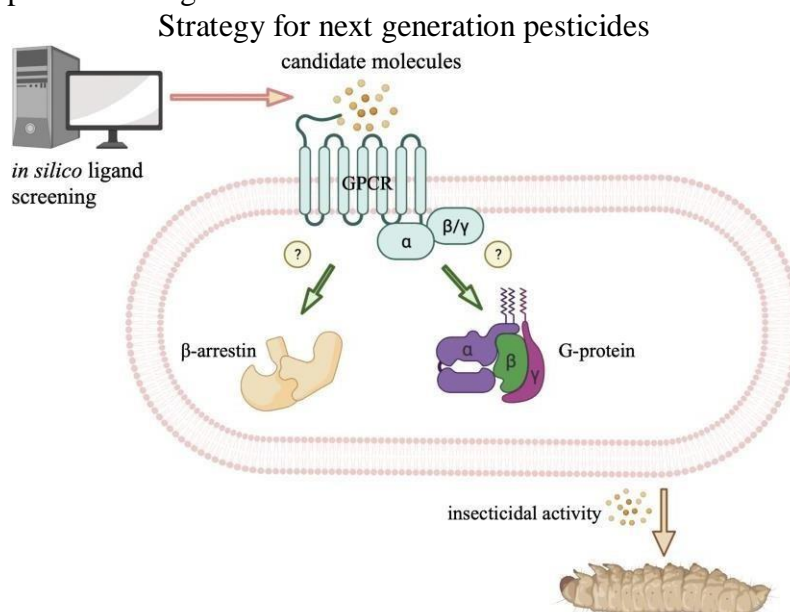
Methods: Virtual screening was performed on previously described orthosteric pocket against ChemDiv libraries to discover potential AstR-C agonists. Molecular dynamics (MD) simulations and MM-GBSA calculations were applied to hit molecules. Biological evaluation of the agonist candidates was performed through TGF-shedding assay and in vivo lethality tests on larvae.

Results and Discussion: Docking and MD simulations revealed the orthosteric pocket interactions, especially between the ECL-2 residues and compounds. The in silico investigations presented ten agonist candidates, and 4 of them were purchased for biological tests. Lethality tests on larvae with promising candidates showed activity with LC50 values ranging from 406.121 to 1000 mg/L.

Conclusions: A combination of in silico, in vitro and in vivo techniques were used to identify new agonists of AstR-C, and four novel agonists of AstR-C have been discovered. Their activity against the receptor has been verified; these molecules represent next-generation pesticides against Thaumetopoea pityocampa.

Prof. Dr. Andreas BENDER

Short Biography

Dr Andreas Bender is a Professor for Molecular Informatics at Cambridge University, working on data analysis methods related to compound safety and efficacy, and Chief Technology & Informatics Officer (CITO) at PangeAI, part of Pangea Botanica. Previously he was a Director for Digital Life Sciences at Nuvisan in Berlin, as well as as an Associate Director for Data Science and AI in the Clinical Pharmacology & Safety Sciences group at AstraZeneca. On the entrepreneurial side, Andreas was involved in setting up Healx Ltd. (for data-driven drug repurposing) and PharmEnable Ltd. (for designing novel chemistry for targets that are difficult to drug conventially), both based in Cambridge/UK. He received his PhD from the University of Cambridge and worked in the Lead Discovery Informatics group at Novartis in Cambridge/MA as well as at Leiden University in the Netherlands before his current post.

Abstract

Artificial Intelligence in Drug Discovery 2022 – Aspects of Data, Validation, and Translation

While Artificial Intelligence (AI) had a profound impact on areas such as image and speech recognition, comparable advances in drug discovery are rare. In this contribution, we will firstly discuss in which ways chemical and biological data differs fundamentally from data available in other domains, both in its quantity and its underlying characteristics. Subsequently, we will discuss model validation, and while this is very difficult to really achieve in chemical space in a meaningful way. Finally, we will conclude by outlining what is needed to translate advances in model performance to increased probability of success in the context of drug discovery.

PD Dr. Zohreh Hosseinzadeh

Short Biography

PD Dr. Zohreh Hosseinzadeh is a group leader at Leipzig University. She received her "Habilitation" in physiology (2019) and PhD in Biology at Eberhard-Karls University, Tübingen (in 2015).

She has been awarded several grants and prizes including: ERC starting grant, Marie Curie, DFG grant, a Australia-Germany DAAD international grant, Cambridge bursary from eye trust bursary, excellent PhD student award, and Pro-Retina fellowship in cooperation with University of Harvard.

Her research interest lies in exploring the functionality (healthy) or dysfunctionality (degeneration) of retina towards finding therapies.

Abstract

''can we restore vision in blind eye''

Retinal diseases such as retinitis pigmentosa (RP), macular degeneration, and diabetic retinopathy, as well as traumatic injury, result in loss of retinal neurons and blindness. The expression of ion channels by Müller glial cells (MGCs) may change in response to various retinal pathophysiological conditions. We explore that an inhibition of store-operated Ca2+ entry (SOCE) and its major component, Orai1 channel, in MGCs protects photoreceptors from degeneration. Outcomes revealed increased Orai1 expression in MGCs of retinal degeneration 10 (rd10) mice. Enhanced expression of oxidative stress markers has been a crucial pathological mechanism in rd10 degenerated retina. Molecular simulations assist us to better understand the structural and dynamical features of the inhibitor to the target structure Orai1. Our results provide new insights in the physiology of MGCs in retinal degeneration and spots the light on SOCE and Orai1 as new therapeutic targets.

Assist. Prof. Dr. Timuçin AVŞAR

Short Biography

Dr. Timuçin AVŞAR graduated from Istanbul Technical University, Molecular Biology and Genetics Program in 2007 and completed the Molecular Biology, Genetics and Biotechnology Master program in 2009 Then, he continued his Ph.D. at the same department and completed his graduation in 2015. During his Ph.D. studies he focused on two main areas; multiple sclerosis and brain tumors. Dr. Timuçin Avşar was the coordinator of the molecular neurosurgery laboratory of Dr. Türker Kılıç at the Institute of Neurological Sciences, Marmara University. He studied different brain tumors and vascular anomalies at this laboratory. During his Ph.D., he visited many laboratories in both Germany and United States for collaborations.

Dr. Avşar also worked as a research and development coordinator in private research laboratories and led many national and international projects. Since 2015 October he is an assistant professor at Bahçeşehir University Medical Faculty, Medical biology department, and the Neurooncology Laboratory director. Avşar Lab currently focused on personalized brain tumor therapy studies, especially on glioma types.

Abstract

Prof. Dr. Thomas MAVROMOUSTAKOS

Short Biography

I have completed my Bachelor studies in the Chemistry Department of National Kapodistrian University of Athens, in 1985. I then moved to University of Connecticut, USA where I pursed graduates studies in the Medicinal Chemistry Section of Pharmacy Department. After continuing with one more year Postgraduate studies with Professor A. Makriyannis I returned back to Athens in 1991. I served as a research director in the Laboratory of Molecular Analysis of Institute of Organic and Pharmaceutical Chemistry in the National Hellenic Research Foundation for seventeen (17) years. In 2007 I was elected as an Associate Professor in the Laboratory of Organic Chemistry and in 2012 I was promoted to Full Professor. I served also for several years as a President to a Research Center in Cyprus oriented to develop new natural products.

I was awarded by Academy of Greek science for the best research in 1998 and 2022 related to hypertension. I have received fellowships from Royal Society, Fulbright and Institute of Federal Fellowships in Greece to exert research activities in England, USA and Germany. I have been funded by several European and National Programs to exert my research activities. I have also been funded to use the European Facilities (i.e Trieste Elettra, BMRZ in Frankfurt, x-ray diffractometers in Graz Austria, NMR center in Ljubljana Slovenia).

My research interests include: (a) Rational Drug Design; (b) Understand the molecular features responsible for drug activity through Molecular Docking, Molecular Dynamicsand Quantitative Structure Activity Relationships; (c) Drug delivery aspects; (d) Drug;membraneinteractions.

I have been teaching for several years Organic Chemistry courses and the optional course of the Rational Design providing to students the principles that govern the production of a new drug. I have collaborated with Synergix company writing a part of Molecular Conceptor that is now a commercial product. I have educated more than 80 graduate students and 60 undergraduate ones. I published more than 300 articles and chapters with h-index=38. I have also published more than 180 articles in national Greek scientific and public journals. I had received European and National funding's as Principal Investigator and Participant. I gave many invited speeches in International and National Conferences as well as Theology Speeches as I have also gained a Ph.D. degree in Theology. I served in many European and National committees for proposal evaluations. I served also as an evaluator in high esteem journals (J.Med. Chem., European J. Med. Chem., Mini Reviews of Medicinal Chemistry, Current Medicinal Chemistry, Biophysica Biochimica Acta etc). I served in more than 80 committees for obtaining Ph.D. and Msc diplomas.

Abstract

The polydynamic capacity of AT1 antagonists as drugs

AT1 antagonists are well tolerated drugs that act on the Renin Angiotensin System to prevent the vasoconstriction caused by the peptide hormone Angiotensin II. These peptide mimetic Trohan horses exert also other beneficial activities. One among them is their ability to act against COVID-19 virus. In collaboration with Prof. J. Matsoukas group and an extensive international network we examine their inhibitory effects on this virus. To achieve our aims we use computational and biological tools. The results are promising and clearly show that AT1 antagonists are polydynamic drugs with great capacity to serve as beneficial entities for the humanity to other diseases and not only to hypertension.

Prof. Dr. Devrim GÖZÜAÇIK

Short Biography

Professor Devrim Gozuacik obtained his MD degree from Hacettepe School of Medicine. He received his MS degree of Biochemistry from Ecole Polytechnique and Paris-Sud University and his PhD degree of cancer cell biology from Pasteur Institute and Necker Children's Hospital Research Center in Paris. Then, he moved to the Weizmann Institute of Science for his postdoctoral studies on cancer-cell death connections.

After a 14 years academic career in Sabanci University, in 2020, he was appointed as a Research Professor in Koç University School of Medicine and in Koç University Research Center for Translational Medicine (KUTTAM).

Prof. Gozuacik also serves as Board Member of the International Cell Death Society and as an Affiliate Member and an Advisory Board Member of the NIH-supported AIM Center of Biomedical Research Excellence in the University of New Mexico, USA. He serves as the Associate Editor of the Autophagy journal and an Editorial Board Member of Cell Communication and Signaling journal and Turkish Journal of Biology.

In the past, Prof. Gozuacik served as a Founding Board Member of EFSUN Nanodiagnostics Center of Excellence, a Founding Board Member of Turkish Molecular Biology Association (MBD) and Cell Death Research Association (HÖAD). He was also an Advisory Board Member of TÜSEB Biotechnology Institute. He served as a project and academic referee forinternational agencies, such as Cancer Research-UK, Wellcome Trust and several European national granting agencies.

Prof. Gozuacik is a recipient of several scientific awards, including Hoffmann-La Roche Future Leader of Biotechnology, EMBO-SDIG Award, TGC Sedat Simavi Award, TÜBA-GEBİP Award, IKU Onder Oztunali Award and Elginkan Technology Award.

Prof. Gozuacik gave invited talks in >100 conferences, including Gordon Research Conferences, EMBO Meetings and Keystone Symposia, and co-organized 9 international conferences in Turkey.

He is the author of >100 publications that received 20.000 citations. He filed 12 medical patents. Dr Gozuacik's research focuses on the study of basic autophagy signaling in mammalian cells and autophagy abnormalities in human diseases, especially in cancer.

Abstract

Discovery of new regulators of autophagy in cancer and their evaluation as drug targets in cancer development, metastasis and relapse

Autophagy is key biological event that occurs at low basal levels in all cell types from yeast to mammals under non-deprived conditions, performing homeostatic functions such as protein degradation and organelle (e.g., mitochondria) turnover. It is rapidly upregulated during cellular stress, providing cells with recycled intracellular building blocks and substrates for energy generation and survival.

Autophagy dysregulation or abnormalities play a critical role in the pathogenesis and progress of several human health problems, including neurodegenerative disorders, infectious diseases, and cancer.

In our laboratory, we focus on the discovery of novel autophagy regulators and study implications of our findings in disease pathogenesis. Moreover, we investigate means to modulate autophagy and related pathways for treatment purposes. In this speech, implications of our research on autophagy and cancer for target discovery and drug development will bediscussed.

Selected References:

1) Akkoc Y, Dalci K, Karakas HE, Erbil-Bilir S, Yalav O, Sakman G, Celik F, Arikan S, Zeybek U, Ergin M, Akkiz H, Dilege E, Dengjel J, Dogan-Ekici AI, **Gozuacik D[x]**. Tumor-derived CTF1 (cardiotrophin 1) is a critical mediator of stroma-assisted and autophagy-dependent breast cancer cell migration, invasion and metastasis **Autophagy, 2022** Jun 28:1-18. doi: 10.1080/15548627.2022.2090693.

2) Kocaturk NM, Peker N, Eberhart K, Akkoc Y, Deveci G, Dengjel J, **Gozuacik D[x]**. Novel protein complexes containing autophagy and UPS components regulate proteasome-dependent PARK2 recruitment onto mitochondria and PARK2-PARK6 activity during mitophagy. **Cell Death and Disease, 2022** Nov 10;13(11):947. doi: 10.1038/s41419-022-05339-x.

3) Unal O, Akkoc Y, Kocak M, Nalbat E, Dogan-Ekici AI, Yagci Acar H, **Gozuacik D[x]**. Treatment of breast cancer with autophagy inhibitory microRNAs carried by AGO2-conjugated nanoparticles. **Journal of Nanobiotechnology**, **2020** Apr 28;18(1): 65. doi: 10.1186/s12951-020-00615-4.

4) Ozturk DG, Kocak M , Akcay A, Kinoglu K, Kara E, Buyuk Y, Kazan H and **Gozuacik D[x]**. MITF/*MIR211* axis is a novel autophagy amplifier system during cellular stress. **Autophagy**, **2019**, 15(3): 375-390.

5) Erbil S, Oral O*, Mitou G*, Cenk Kig, Durmaz-Timucin E, Guven-Maiorov E, Gulacti F, Gokce G, Dengjel J, Sezerman OU, **Gozuacik D[x]**. RACK1 is an Interaction Partner of ATG5 and a Novel Regulator of Autophagy. **The Journal of Biological Chemistry**, **2016**, 291(32):16753-65.

Prof. Dr. Tuğba BAĞCI ÖNDER

Short Biography

Prof. Tuğba Bağcı Önder graduated from the Department of Molecular Biology and Genetics, Bilkent University in 2002. She then earned her Ph.D. degree in Neuroscience at Sackler School of Graduate Biomedical Sciences at Tufts University in 2008. She pursued her postdoctoral work at Harvard Medical School, Massachusetts General Hospital on the development of tumor-specific pro-apoptotic therapies in animal models of brain cancer. In 2012, she joined Koç University School of Medicine and established the Brain Cancer Research and Therapy Laboratory. Her research group is currently working on the understanding of epigenetic regulation of cell death, therapy resistance and progression of cancers. Her work is supported by FP7 Programme-Marie Curie Career Integration Grant, TÜBİTAK, TUSEB, Royal Society-UK and Koç University Research Center for Translational Medicine (KUTTAM). Prof. Bağcı Önder is also a recipient of Barbara Talamo Trainee (2008), UNESCO-L'oreal Women in Science (2013), BAGEP (2014), Sedat Simavi Heath Sciences (2021) and International Cell Death Society Rising Women in Science (2022) awards.

Abstract

Exploiting epigenetic vulnerabilities of cancer cells to overcome therapy resistance.
A mechanism of therapy resistance is transcriptional dysregulation of cell death and survival-related genes. Changes in the epigenome are thought to play a critical role in acquired therapy resistance. Epigenetic modifications occur on chromatin and consist mainly of DNA methylation, histone acetylation and methylation, governed by the activity of several chromatin-modifying proteins. To decipher the relationship between therapy response and epigenetics, we undertake loss-of-function approach and interrogate the roles of chromatin modifying proteins with functional screens. These screens are based on genetic or chemical ablation of protein functions. In the first one, we use shRNA or CRISPR/Cas9-based libraries, in the second one we use chemical probes to discover novel molecular mechanisms to overcome therapy resistance. We utilize next generation sequencing to profile and map the differences between drug-sensitive and drug-resistant populations of cancer cells, that we generate in our laboratory. This talk will give an overview of our current approaches and highlight the roles of our recently identified molecular mechanisms.

Assoc. Prof. Dr. Johannes KIRCHMAIR

Short Biography
Johannes Kirchmair is an associate professor in cheminformatics at the Department of Pharmaceutical Sciences, Division of Pharmaceutical Chemistry of the University of Vienna and head of the Computational Drug Discovery and Design Group (COMP3D). After earning his PhD from the University of Innsbruck (2007), Johannes started his career as an application scientist at Inte:Ligand GmbH (Vienna). In 2010 he joined BASF SE (Ludwigshafen) as a postdoctoral research fellow. Thereafter he worked as a research associate at the University of Cambridge (2010-2013) and ETH Zurich (2013-2014). Johannes held a junior professorship in applied bioinformatics at the University of Hamburg (2014 to 2018) and an associate professorship in bioinformatics at the University of Bergen (2018 to 2019). He has been a visiting professor or lecturer at the National Institute of Warangal (2016), the University of Cagliari (2017) and the University of Vienna (2018).

Abstract
In silico methods for flagging compounds that are likely to interfere with biological assays

Small molecules interfering with biological assays continue to pose significant challenges in compound screening. In recent years a number of computational approaches have been introduced for flagging potentially "badly behaving compounds", "bad actors", "nuisance compounds" or "frequent hitters". These include rule-based approaches, statistical methods and machine learning approaches. This contribution will start with a succinct overview of the scope and limitations of the existing in silico approaches. Then, we will introduce the latest version of Hit Dexter, an array of machine learning models for frequent hitter prediction. These models are complemented by a number of rule-based and similarity-based approaches for the assessment of the risk of colloidal aggregation   and   other   undesirable   properties. On holdout data, the Hit Dexter machine learning models achieved high accuracy and good early enrichment. The models were also able to correctly characterize compounds with specific biological and physicochemical properties, such as compounds linked to dark chemical matter or colloidal aggregation. The Hit Dexter platform is accessible via https://nerdd.univie.ac.at.

Assoc. Prof. Dr. Avia ROSENHOUSE-DANTSKER

Short Biography

Avia Rosenhouse-Dantsker, D.Sc., is a Clinical Associate Professor at the University of Illinois Chicago. Her research background ranges from quantum theory and computational biology to biophysical chemistry, molecular biology, and electrophysiology. Her work has resulted in multiple publications including in Nature Chemical Biology, PNAS, J Neuroscience, J Lipid Research, JBC, and others. Her current research employs experimental and computational approaches to elucidate structural and functional mechanisms of protein modulation with a special emphasis on the co-modulation of ion channels by lipids (e.g., cholesterol, phosphoinositides, and others).

Abstract

The story of an anomaly: the effect of cholesterol on atrial and hippocampal Kir3 channels

During the past two decades, cholesterol has emerged as a central regulator of ion channels, such as the inwardly rectifying potassium (Kir) channels. Most ion channels, including Kir channels, are inhibited by cholesterol. In contrast, Kir3.2 (GIRK2) and Kir3.4 (GIRK4) are amongst the very few channels activated by this essential lipid. Similarly, in vitro cholesterol enrichment and high cholesterol dietary intake activate Kir3 channels in freshly isolated atrial myocytes and CA1 hippocampal pyramidal neurons (rat). Kir3 channels play central roles in slowing the heart rate, generating late inhibitory postsynaptic potentials, and mediating the effect of a wide range of hormones and neurotransmitters. Hence, elucidating the mechanisms responsible for the cholesterol-driven activation of these channels is of interest from both a fundamental and clinical point of view. Our studies interrogating how cholesterol activates these channels uncovered the biophysical mechanism underlying these unexpected observations and revealed synergism in the modulation of Kir3.2 and Kir3.4 between cholesterol and $PI(4,5)P_2$, a phosphoinositide necessary for activating all Kir channels. Further research identified putative cholesterol binding sites in the transmembrane domain of Kir3.2 and Kir3.4 and unveiled a molecular switch that could convert a cholesterol-activated Kir3 channel into a cholesterol-inhibited one. Finally, despite the blood-brain barrier, atorvastatin countered the effect of a high-cholesterol diet on hippocampal Kir3 currents (rat). Collectively, these results provide a detailed molecular mechanism of the tunable cholesterol regulation of potassium channels.

Assist. Prof. Dr. Murat Alper CEVHER

Short Biography
Dr. Murat Alper Cevher has completed his undergraduate and graduate studies at NYC, City University of New York, Hunter College working on co-transcriptional gene regulation. He received various awards during his studies. Later, he continued his post PhD studies at The Rockefeller University working on the 30-subunit Mediator coactivator complex. He received the competitive American Cancer Society postdoctoral fellowship to support his work. In 2015, Dr. Cevher joined Bilkent University as an assistant professor and established his own research group. Since then, his laboratory was funded by TUBITAK 1001 and EMBO Installation Grant. In 2020, Dr. Cevher was funded and continued his research at The Rockefeller University as a visiting assistant professor. Recently, Dr. Cevher's R01 grant application as Co-Investigator was recommended for funding by the NIH council.

Abstract
The 30-subunit Mediator coactivator complex and its connection to cancer
Mediator coactivator complex (Mediator) is involved in the regulation of most, if not all, protein coding genes. Mediator serves as a bridge by connecting the enhancer bound activators with the promoter bound general transcriptional machinary. However, among the activators, except for a handful of them, we still do not know the ones that bind the Mediator to regulate their target genes. Here, through cell based followed by proteomics approaches, we identify cell type specific, novel and clinically significant activators that coprecipiate with the Mediator. We further verify direct interactions via biochemical assays. We believe that identifying the Mediator interacting activators and understanding their binding surfaces may allow us to design inhibitors to block a specific pathway in diseased states.

Assist. Prof. Dr. Antoine MARION

Short Biography

Dr Antoine Marion received his PhD from the Université de Lorraine, Nancy, France, in 2015. His thesis work focused on developing a new theoretical chemistry approach that simulates the dynamics of large biomolecular systems with a quantum mechanical description of all the molecules at play. He then moved to the Technical University of Munich, Munich, Germany, to pursue his research on quantum mechanical (QM) methods adapted to biomolecular phenomena, and extended his expertise to molecular mechanics (MM), molecular docking, and hybrid QM/MM. Dr Marion joined the Department of Chemistry at the Middle East Technical University, Ankara, Turkey, in 2018 as an assistant professor. There, he built his laboratory to study chemical and biochemical phenomena at different scales by combining and developing the most relevant molecular modelling approaches; from elaborate electronic structures of small molecules to the complex dynamics of large macromolecules of biological interest.

Dr Marion received the best PhD thesis award 2015, and the BAGEP award 2021 in chemistry. He was granted two TUBITAK 1001, in 2019 and 2022.

He is the CTO and co-founder of Meddenovo İlaç Tasarım ve Danışmanlık A.Ş. supported by TUBITAK BIGG.

Abstract

The role of multiscale molecular modelling in rational drug design

Molecular modelling is as old as chemistry itself. It is our way to imagine molecules, the small objects that we manipulate daily without being capable of seeing them. In biochemistry, approaches based on empirical, classical, and/or quantum mechanical models have become more and more popular over the past decades, and have now demonstrated their great value when used either independently or in parallel with experiments. Each approach bears its own degree of complexity and range of applicability. The choice of the method often relies on a critical balance between accuracy and computational resources. This choice is dictated by or determines the physical/chemical questions to be addressed. Combining the strengths of different theoretical methods and designing specific models allows one to reach a comprehensive understanding of events that involve many complex phenomena and to predict the properties of novel biochemical systems: e.g., drug design, protein/substrate interactions, large macromolecular motions, allosteric effects, enzymatic reactivity, biomimetics. We will illustrate how different methods in molecular modelling can help to address different questions in rational drug design.

Woody SHERMAN

Prof. Dr. Kemal YELEKÇİ

Short Biography
Kemal Yelekçi graduated from Middle East Technical University, Chemistry Department. He was granted the Fulbright scholarship to pursue his doctoral degree in the US. He received his Ph. D. degree from Ohio University in synthetic organic chemistry. He worked at Northwestern University (Chicago, USA) as a Post Doc in medicinal chemistry, drug design, and synthesis. After returning to Turkey, he has promoted to Associate professor (1989) and Full Professor (1996) at Marmara University. He joined Kadir University in 2001 to present. His main interests are research and development involving studies of drug design and drug action, receptor-ligand interaction and transporter protein mechanisms, *in silico* screening, calculation of free energy profile, and elucidation of the flexibility and dynamical behavior of the protein-substrate complex. To these aims, our research group exploits computational techniques such as classical molecular dynamics (MD) simulations, molecular modeling quantum mechanics (QM), lead optimization to the ADMET analysis homology modeling and docking methods to investigate the structure, kinetics, and thermodynamics of biological molecules, especially enzyme- ligand complexes. Applications of drug design tools to case studies such as cancer and Parkinson's disease.

Abstract

Designing Of Isoform-Selective Novel Inhibitors Against Class Iia Histone Deacetylases Utilizing Molecular Modeling and In Silico Screening
The fundamental cause of human cancer is strongly influenced by down- or upregulations of epigenetic regulations. Upregulated histone deacetylases (HDAC) are effectively neutralized by the action of HDACs inhibitors (HDACi). However, cytotoxicity has been reported in normal cells because of the non-specificity of several available HDACis in clinical use or at different phases of clinical trials. Constant Search for specific HDAC isoform inhibitors is increasingly developing to avoid this side effect. Because of the high amino acid sequence and structural similarity among HDAC enzymes, it is believed to be challenging to obtain isoform selectivity. In our study, we examined the similarity of class IIa HDACs (4, 5, 7, and 9) by aligning their structures and amino acid sequences, active site extraction, and recognition of the critical amino acid residues within the catalytic channel. X-ray crystal structure of the human HDAC4 was used as a template for the homology modeling of human HDACs 5 and 9. Consequently, isoform-selective inhibitors against class IIa HDACs were identified via structure- and ligand-based drug design. Based on the highest binding affinity and isoform-selectivity, the top-ranked inhibitors were in silico tested for their absorption, distribution, metabolism, elimination, and toxicity (ADMET) properties, which were classified as drug-like compounds. Later, molecular dynamics simulation (MD) was carried out for all compound-protein complexes to evaluate the structural stability and the binding mode of the inhibitors, which showed high stability throughout the 100 ns simulation.

Prof. Dr. Mine YURTSEVER

Short Biography
She received her B.S, M.S and Ph.D degrees from the Chemistry Department of Middle East Technical University. She conducted her Ph.D studies at Darmstadt Technical University under the supervision of Prof. Jürgen Brickmann. Then, she joined Istanbul Technical University, Chemistry Department as a faculty member in 1996 and since then she works at the same department.
Her research interests scan a wide range of topics mainly in the field of computational chemistry, like understanding of structure-activity-property relationships of chemical and biological systems, DFT calculations and MD simulations of nano-sized materials, virtual screening and design of new anti-cancer drugs.

Abstract
DNA Binding Simulations of Antineoplastic Drugs

Introduction: Elucidation of DNA binding mechanisms of anticancer (antineoplastic) drugs plays an important role on the discovery of new drugs targeting human DNA. Fludarabine, Pemetrexed, Cladribine, Clofarabine, and Azacitidine, are very well-known marketed anticancer drugs falling under the antimetabolite purine-analog drug class. Although these drugs were used in the past with FDA approval for treating various types of cancer , their main indications for DNA binding, nucleotide regioselectivity, and mode of binding on DNA have not been yet discovered in detail in the scientific literature. Therefore, this study attemps to decipher mechanistic insights of DNA- drug interactions causing either silencing of specific nucleotides within the genes and/or breaking the double helix of cancerous cell DNA (apoptosis) via performing molecular docking and molecular dynamics simulations. Our in-silico strategies were validated by the simultaneously performed experimental studies of Prof. Gölcü's group. The computational studies were repeated for the non-drug molecules, obtained by altering the functional groups of the studied drugs.

Drug-DNA Complex
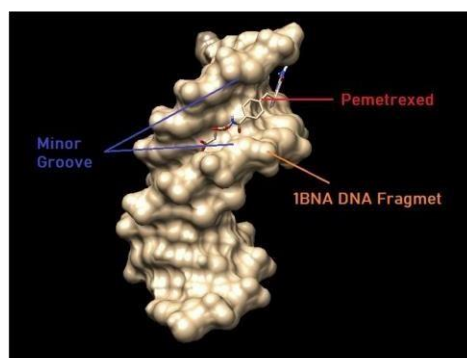
Pemetrexed is bound in the minor groove of the DNA chain.

Methods: Molecular docking simulations were performed to gain information abot the binding modes and non-covalent interactions of the drugs at their binding region. MD simulations were performed to follow time-dependent stability of the drugs.

Results and Discussion: The drug-DNA interactions determine how the DNA of cancerous cells can be disabled. The major interaction playing role in DNA binding is H-bonding. Upon replacing the functional groups, the regioselectivity of the drug molecules, the strength of the H-bonding between drug and DNA nucleotides can be altered.

Conclusions: The impact of structural modifications of drugs on their DNA-binding modes were explored.

Keywords: DNA binding, antineoplastic drugs, MD

Prof. Dr. Serdar DURDAĞI

Short Biography

Research Group of Prof. Durdağı applies computational chemistry methods to biological systems. Inter-disciplinary research of group focuses on protein modeling and dynamics, ligand- and structure-based drug design, investigation of molecular mechanisms of protein/drug, protein/protein, protein/DNA interactions and optimizations protocols for rational drug design. For this aim, together with applications of biophyscial approaches and molecular modeling applications research Lab of Prof. Durdağı also develops programing codes for several biological problems.

Prof. Durdağı published two books and seven book chapters on computer-aided drug design. He has around 180 research articles in top peer-reviewed medicinal chemistry and computational biophysics journals with h-index of 39. He has also more than 20 international patents and patent applications. The total citations of Prof. Durdağı's research articles are more than 4000.

Prof. Durdağı received his PhD degree in Freie Univ. Berlin in 2009 and his PhD studies is supported by EU FP6 Marie Curie Research Fellowship and his PhD thesis was graded with *summa cum laude* (with highest honor) degree. He also received many prestigious research grants (i.e., Max Planck Inst., Canadian Institute of Health Research-CIHR, Alberta Innovates Health Solutions-AIHS). Prof. Durdağı worked as postdoctoral fellow (2009-2013) and senior researcher (2012-2013) in University of Calgary (Canada) and Max-Planck Institute (Germany), respectively.

The group of Dr Durdağı works on several projects for better understanding the drug-receptor and protein-protein, protein-DNA interactions of different systems using several computational modeling approaches and designing novel therapeutic compounds. Prof Durdağı's research group carried out many national and international projects so far (TUBITAK, H2020, FP6 and FP7). Prof. Durdağı received many prestigious national and international awards including The Scientific and Technological Research Council of Turkey-TUBITAK's Incentive Award in Health Sciences (2016); Contribution to Science Awards (2016, 2021); Health Institutes of Turkey - TUSEB's Aziz Sancar Incentive Award (2017); Science Academy's Young Scientist Award (2014).

Prof. Dr. Durdağı is also the Founder and CEO of Istanbul MedChem.

Prof. Dr. Bert de GROOT

Short Biography
https://www3.mpibpc.mpg.de/groups/de_groot/degroot_cv.pdf

Abstract

Relative and absolute alchemical protein-ligand binding free energies

Alchemical free energy calculations have come of age. Based on rigorous first principles of statistical mechanics, these calculations explore physical paths not experimentally accessible and provide unprecendented accuracy in the prediction of processes as diverse as protein thermostability and ligand binding free energies. Based on the pmx framework coupled to the GROMACS molecular dynamics engine, results of high-throughput relative as well as absolute ligand binding free energies are presented.

Assoc. Prof. Dr. Nurcan TUNÇBAĞ

Short Biography
Dr. Tuncbag is an associate professor at Koç University jointly in the Department of Chemical and Biological Engineering and School of Medicine. She received her undergraduate degree in Chemical Engineering from Istanbul Technical University (İTÜ), and her master and doctorate degrees from Koç University Computational Sciences and Engineering department. She did her post-doctoral research in Massachusetts Institute of Technology (MIT) Biological Engineering Department between 2010-2014. She carried out her academic studies at Middle East Technical University (ODTÜ) between 2014-2021. Her works in computational systems biology and bioinformatics have been recognized with young scientist awards by TÜBİTAK, TÜBA, TÜSEB and BA. In 2019, she was selected for the International Rising Talent award by UNESCO-L'Oreal Foundation. She has been a member of the Global Young Academy since 2020. Her research interests are computational systems biology, bioinformatics, network-based medicine, network modeling, multi-omic data integration, single cell and bulk omic data analysis, and discovery of latent cancer driver mutations.

Abstract

Network Medicine: Leveraging Integrated Connections of Multi-Omic Data

We are in an age of "big data" in biological and health sciences. These big data include several layers including electronic health records, phenotype data, imaging data, and at the molecular level the multi-omics data and beyond. The shifts in data size and type have created opportunities for computational scientists to step in and make an impact in biology and medicine. In today's world, patient-specific data storage and transforming these data into clinical decisions are fundamental to personalized medicine. Beyond the list of molecules, there is a necessity for computations to consider multiple data jointly and reconstruct the relations between these molecules. In this era of "big data", we conduct interdisciplinary projects to deliver a "precision medicine" approach by leveraging sophisticated computational methods for data integration and network reconstruction. In this talk, I will present the ongoing projects in our research group ranging from multi-omic data analysis and integration techniques to their application todifferent diseases and conditions.

Prof. Dr. Gizem Dinler Doğanay

Abstract
Druggable peptide design and synthesis to inhibit anti-apoptotic pathways targeting critical protein-protein interactions in cancer

Breast cancer-dependent mortality that is the leading cause of female death, continues to rise despite the progression in diagnosis and therapeutic strategies in cancer. Main cause in cancer drug resistance is due to application of higher doses of therapeutic agents, requiring more effective tailored therapies and seeking new therapeutic targets against cancer. A growing interest in probing the potential of protein-protein interactions (PPIs) is driven by the urgent need to find novel therapeutic targets against such diseases. With this motivation, we aimed to find the interaction surface between Bag-1 (Bcl-2-associated athanogene 1) and C-Raf to target RAS/Raf/MEK/ERK pathway. We probe the interaction surface using various mass spectrometric methods and found the sites that are critical for drug targetting. In my talk, I will discuss the details of these findings and further suggest peptides for inhibitory purposes.

Prof. Dr. Erden Banoğlu

Short Biography
Prof. Banoglu received his PhD in Medicinal and Natural Products Chemistry from the University of Iowa (USA) in 1997, and later joined to Gazi University at the Department of Pharmaceutical Chemistry where he still works as the Department Head. He also worked in Aberdeen University (Scotland) as a British Council Scholar, in Kumamoto University (Japan) as a JICA scholar and did postdoctoral study in the Department of Biomedical Sciences at the University of Rhode Island (USA). Currently, his research group is involved in the discovery and development of new molecules for pathologies associated with cancer development and inflammation. An important aspect of his research activities includes the combined use of chemical, computational and pharmacological tools in order to eventually provide new chemotypes for novel therapies of inflammation-related disorders and cancer. He is also the co-founder of the OncoCube Therapeutics (USA) where the preclinical to clinical studies are being continued for the small molecule cancer therapeutics. He is also the Principal Member of the Turkish Academy of Sciences (TÜBA).

Abstract
A journey from selective FLAP inhibitor to selective mPGES-1 inhibitor: A new therapeutic modality for reducing inflammation and pain.

Classical non-steroidal anti-inflammatory drugs (NSAIDs) show their efficacy by preventing inflammatory prostaglandin (PG)E_2 synthesis through non-selective inhibition of cyclooxygenase enzymes (COX-1 and COX-2). While COX-1 maintains the production of PGs important for normal physiology and homeostasis, the inducible COX-2 isoform primarily regulates inflammatory PGE_2 synthesis upon an inflammatory stimulus. However, chronic NSAIDs usage has been associated with serious gastrointestinal (GI) side effects since nonselective COX inhibition interferes with both the inflammatory PGE_2 and homeostatic PGs production, thereby disrupting the normal GI physiology. Subsequent discovery of selective COX-2 inhibitors without GI toxicity was also disappointing, as their chronic use has resulted in increased cardiovascular risks in predisposed patients, and they are withdrawn from clinical use. More recently, inducible microsomal prostaglandin E_2 synthase-1 (mPGES-1), which catalyzes the terminal step downstream of COX-2 for excessive inflammatory PGE_2 production, has attracted researchers as a new target for anti-inflammatory drug discovery as a safer alternative to COX inhibiting NSAIDs. Based on this background, we will share our scientific journey leading to the discovery of novel drug-like mPGES-1 inhibitors originating from a 5-lipoxygenase activating protein (FLAP) inhibitor chemotype with potencies at sub nM range and with *in vivo* efficacy, which warrant further exploration as safer substitutes to classical NSAIDs.

OP-1

Do blade motions directly induce Piezo1 mechanotransduction? Evidence from fluorescence microscopy

Alper Devrim ÖZKAN

OP-2

Atomic Details of Angiotensin II Type 1 and Type 2 Heterodimers

Ismail Erol[1], Bunyemin Cosut[1], Serdar Durdagi[3]

[1]Department of Chemistry, Gebze Technical University, Kocaeli, Turkiye
[2]Computational Biology and Molecular Simulations Lab, Department of Biophysics, School of Medicine, Bahcesehir University, Istanbul, Turkiye
[3]Molecular Therapy Lab, Department of Pharmaceutical Chemistry, School of Pharmacy, Istanbul, Turkiye

Ismail Erol / Department of Chemistry, Gebze Technical University, Kocaeli, Turkiye

Introduction: Angiotensin II type 1 (AT1R) and type 2 (AT2R) receptors have key roles in renin-angiotensin system (RAS) and belong to the class A GPCR family [1]. AT2R has inhibitory effect on AT1R when these two receptor interacts with each other. AT1R-AT2R heterodimers identified with several methods (coimmunoprecipitation, fluorescence resonance energy transfer, bioluminescence resonance energy transfer) in different cell types [1]. However, to date, there is no study that shows the atomic details of this heterodimerization.

Methods: In this study, we used molecular dynamics simulation to reveal AT1R-AT2R heterodimerization at the atomic level.

Results and Discussion: In some of the dimerization interfaces inactivation of the AT1R was observed.

Conclusions: Preliminary results show, AT1R-AT2R heterodimers can consist of different interfaces.

Keywords: AT1R, Renin-Angiotensin System, Molecular Dynamics Simulation, Heterodimer

OP-3

Ahmet Emin TOPAL

Investigation of ring-shaped supramolecular oligomer structures of rhodopsin proteins

Rhodopsin proteins are G-protein coupled receptors (GPCRs) that can form rows of dimers. Oligomerization of rhodopsin might have important roles for vision and the response of rod photoreceptor cells to light. Previous works of theoretical crystal packing and coarse-grained molecular dynamics simulations of rhodopsin indicate the presence of arc-shaped structures, however, their presence in solution remains elusive. Here, atomic force microscope (AFM) images of nanoring assemblies measured in native disk membranes isolated from rod outer segments of wild-type mice retina are presented. The nanoring structures observed are present inside and outside the protein nanodomains. These nanorings may contain rhodopsin molecules because they are abundant within the native membranes measured via AFM.

DISCOVERY OF PROMISING SMALL MOLECULES INHIBITING THE PD1/PDL1 MECHANISM IN CANCER: THREE DIFFERENT APPROACHES, ONE COMMON GOAL

Pinar Siyah[1], Serdar Durdagi[1], Busecan Aksoydan[1]
[1]Bahcesehir University

Pinar Siyah / Bahcesehir University

Introduction: As a result of the interplay between programmed death 1 (PD-1) and programmed death ligand-1 (PD-L1); T lymphocyte proliferation, survival, and effector functions (cytotoxicity and cytokine-releasing capabilities) are suppressessed. One possible treatment for cancer is the bloking the PD-1/PD-L1 interaction, thay can results in reviving the cytotoxic T lymphocytes to fight cancer cells. Nonetheless, no small molecule inhibitors targeting this mechanism have been authorized so far. This drug screening study's primary objective is to identify promising inhibitors by conducting computer aided drug discovery studies.

Methods: A pharmacological library of approximately 10,000 compounds containing both FDA-approved drugs and the compounds in clinical phase investigations were targeted into PD1, PD1-PDL1 complex, and PDL1-PDL1 homodimer complexes. For these three targets, we carried out an initial study, and the outcomes indicated that the PDL1-dimer structure was a best target for small-molecule inhibitors among these structures. Three computational approaches were taken into account in virtual screening study : (i) structure-based, (ii) structure-based pharmacophore (hybrid), and (iii) machine learning-based QSAR.

Results and Discussion: Anidulafungin, deferoxamine, bemotrizinol, neratinib, ubiquinol, dequalinium and vilanterol have all been found as promising PDL1 inhibitors based on the results obtained from the three computational methods.

Conclusions: Promising small molecules inhibiting the PD1/PDL1 mechanism was identified.

Keywords: inhibitors, immune checkpoints, FDA-approved drugs, repurposing, PD1-PDL1

Rapidly Advancing CRISPR Systems Hold a Great Potential in Research on Drug Targets

Göknur Giner[1], Kate Zhang[3]

[1]The University of Melbourne
[2]The Walter and Eliza Hall Institute of Medical Research
[3]University of Cambridge

Göknur Giner / The University of Melbourne

Introduction: In only a few years, as a breakthrough technology, clustered regularly interspaced short palindromic repeats/CRISPR-associated protein (CRISPR/Cas9) gene editing systems have ushered in the era of genome engineering with the plethora of applications, particularly in medicine, biology, pharmacology, and biotechnology.

Methods: This talk focuses on some of the most promising CRISPR gene editing tools, such as transcriptional knock-out and activation screens and base editors. Here we discuss how we utilized those technologies in modeling venetoclax resistance in two different types of cancers and how we handled the computational aspects of analyzing two different types of CRISPR screens from high throughput next-generation sequencing platforms. One of those screens is the CRISPR activation mouse model that is established in our laboratory for inducing gene expression in vivo and in vitro for lymphomas, and the second one is the whole genome knock-out screen to investigate the impact of combination therapies in breast cancer.

Results and Discussion: Besides recapitulating the tremendous potential held by recent CRISPR technologies in drug development pipelines using the aforementioned applications, we also demonstrate our most recent web application that offers a few modules for biologists to explore their own CRISPR data sets to identify and understand the role of potential drug targets for a given disease of interest.

Conclusions: Utilizing CRISPR screens such as transcriptional knock-out and activation screens and base editors to edit the DNA enable researchers to uncover and validate new drug targets, gain insights into resistance mechanisms for targeted therapies and develop new effective therapies.

Keywords: CRISPR, Targeted Therapies, Computational Biology, Base Editors, Gene Editing

OP-6

Drug Utilization in Turkish Children: A Systematic Review of Observational Studies

Ahmet Akici[1], N Ipek Kirmizi Sonmez[2], Dieudonne Havyarimana[1], Narin Akici[3], Ertan Direnc[4], Volkan Aydin[5]

[1]Department of Medical Pharmacology, School of Medicine, Marmara University, Istanbul
[2]Department of Pharmacology, School of Pharmacy, Bahcesehir University, Istanbul
[3]Department of Pediatrics, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey
[4]School of Medicine, Marmara University, Istanbul
[5]Department of Medical Pharmacology, International School of Medicine, Istanbul Medipol University, Istanbul, Turkey

N Ipek Kirmizi Sonmez / Department of Pharmacology, School of Pharmacy, Bahcesehir University, Istanbul

Introduction: Observational drug utilization studies (ODUS) can provide detailed information on drug use in countries and target populations. The difficulties of conducting clinical drug trials in children put forth the necessity of disseminating ODUS and meta-analyses in this age group. We aimed to perform a systematic review of ODUS on children in Turkey.

Methods: We searched those ODUS whose full-texts were accessible via the internet network and published as "original research" which used prescriptions and medical record data among children between 2008-2021 in Turkey. We only included the articles with full-text/abstract published in English. We described various scientific properties of the publications, design of the study and the groups of the examined drugs.

Results and Discussion: We identified 20 ODUS; 25.0% of which were published in SCI/SCIE journals. Articles indexed in the WoS (85.0%) received a mean of 7.6±16.7 citations. The focus on neonates was 10.0%. We determined that a quarter of these studies were carried out nationwide. The majority of the studies (85.0%) used data from hospitals. The average study period was 2.0±1.4 years and 70.0% of the studies were published within two years of data collection. We detected that 55.0% of all studies focused on antibiotics, 10.0% on asthma medications, and 10.0% on general drug use.

Conclusions: Considering the size of the national medical resources/records, it is remarkable that a limited number of studies were conducted on children after the introduction of new law concerning ODUS in Turkey. Moreover, existing studies were mainly conducted with a retrospective design and focused mostly on antibiotics.

Keywords: drug utilization, observational studies, clinical trials, pediatric population, retrospective design.

OP-7
ANALYZING OF EFAVIRENZ RESISTANCE OF SOME REVERSE TRANSCRIPTASE MUTATIONS BY IN-SILICO METHOD

OFCAN OFLAZ[1], Hasan Tahsin Şen[2], Gökhan Demiroğlu[3]

[1]LOKMAN HEKİM University, Faculty of Medicine, Medical Biology
[2]LOKMAN HEKİM University, Faculty of Pharmacy, Pharmaceutical Chemistry
[3]LOKMAN HEKİM University, Faculty of Medicine, Phase III

OFCAN OFLAZ / LOKMAN HEKİM University, Faculty of Medicine, Medical Biology

Introduction: The human immunodeficiency virus (HIV) is an important virus that attacks the body's immune system and causing the AIDS acquired with the progression of the infection. According to current data, there are more than 29 thousand HIV-positive individuals in our country. Antiretroviral therapy (ART) is the only successful approach to the treatment of HIV infection. Antiretroviral resistance leads to disruption of treatment, increase in viral load, and as a result, positive individuals encounter AIDS. Efavirenz is one of the reverse transcriptase inhibitors used in the treatment of HIV. RT is an enzyme with a stable asymmetric heterodimer structure that involved in polymerization. Mutations in the HIV genome can lead to ART resistance. Estimating the changes in the three-dimensional structure of the protein due to mutations plays a key role in understanding the mutation mechanism and producing a new active substance.

Methods: In our study focused on the K103N, K103N + L100I, K103N + V108I and K103N + P225H mutations that were proven to cause efavirenz resistance. Homology models are based on the 1fk9 theme. Models created via Swiss-Model. Change of active site, electrostatic change and hydrophobic change were performed. Docking scores were obtained with homology models and Efavirenz docking study. MDocking studies were performed using the Maestro module of Schrödinger software 2022-1 version and these scores interpreted for drug resistance statutes.

Results and Discussion: The homology models were analyzed using the UCSF Chimera program.

Conclusions: Our study will contribute to the literature and will pave the way for the development of new active substances.

Keywords: Drug Resistance, Homology Modelling, HIV-1, Docking

Anticancer investigation of platinum and copper-based complexes containing quinoxaline ligands

Hager Sadek El–Beshti Sadek El–Beshti[1], Yasemin Yildizhan[2], Hakan Kayi[3], Yuksel Cetin[2], Zelal Adigüzel[4], Gamze Gungor-Topcu[4], Zuhal Gercek[5], Şeniz Özalp-Yaman[1]

[1]Atilim University
[2]TUBITAK, Marmara Research Center
[3]Ankara University
[4]Koç University
[5]Bulent Ecevit University

Şeniz Özalp-Yaman / Atilim University

Introduction: Across the globe, today, cancer accounts for many fatalities, thus calling for better and updated antineoplastic agents within biomedicine and health sciences. In this regard, inorganic chemistry for pharmaceutic purposes is essential in creating drugs based in metal to fight cancer as such medicine has been shown to be potentially effective to fight cancer in humans. In light of this background, this research focuses on synthesis and anticancer activity of 2,3-di-pyridin-2-yl-quinoxaline (dpq), 2,3-di-thenyl-2-yl-quinoxaline (dtq), 2,3,2',3'-tetra-pyridin-2-yl-[6,6']biquinoxaline) (tpbq) and 2,3,2',3'-tetra-thenyl-2-yl-[6,6']biquinoxaline (ttbq) containing copper(II) and platinum(II) compounds as prodrug candidates.

Optimized structures of (a) Cu(dpq)2Cl2, (b) Cu(dtq)2Cl2, (c) Pt(dpq)2Cl2, (d) Pt(dtq)2Cl2 (e) Cu(tpbq)Cl2, (f) Pt(tpbq)Cl2, (g) Cu(ttbq)Cl2, and (h) Pt(ttbq)Cl2 neutral complexes.
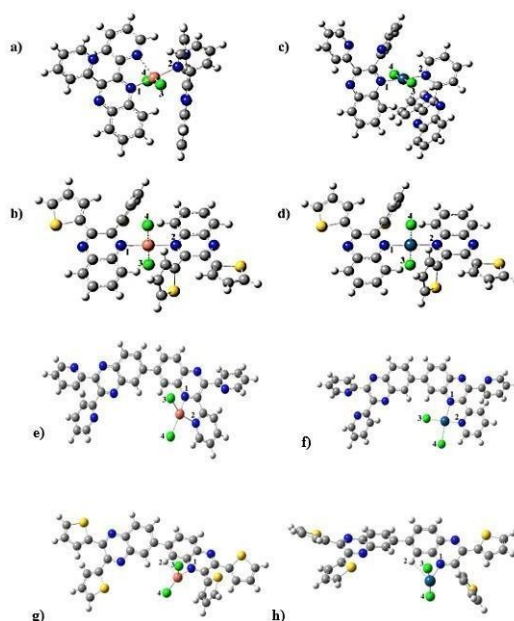
Methods: The binding interaction of these compounds with CT -DNA and HSA were assessed with different spectroscopic and viscometric, measurements. The nuclease activity, cytotoxicity examinations and IC50 values, cell death mechanism, and invasion/migration inhibition behavior were also carried out for each compound.

Results and Discussion: The nature of the binding of the complexes on DNA were revealed as electrostatic interaction between the cationic metal complex ions and the negative phosphate groups of CT-DNA, except Pt(tpbq)Cl2, Pt(ttbq)Cl2, and Cu(tpbq)Cl2; van der Waals and hydrogen bonds interaction were proposed for these complexes. The U87 and HeLa cells were investigated as the cancer cells most sensitive to our complexes. The exerted cytotoxic effect of complexes was attributed to the formation of the reactive oxygen species in vitro.

Conclusions: It is clearly demonstrated that Cu(dtq)2Cl2, Cu(ttbq)Cl2, Pt(ttbq)Cl2 and Pt(tpbq)Cl2 have the highest DNA degradation potential and anticancer effect among the tested complexes by leading apoptosis. Wound healing and invasion analysis results also supported the anticancer activity of those complexes.

Keywords: Quinoxaline, DNA binding, MTT cell viability, ROS generation, Apoptosis

Screening of small molecule libraries using combined text mining, ligand- and target-driven based approaches for identification of novel granzyme H inhibitors

Saima Ikram[1], Jamshaid Ahmad[2], Fawad Ahmad[2], Serdar Durdagi[1]

[1]Bahçeşehir University, School of Pharmacy
[2]Peshawar University Pakistan
[3]Bahçeşehir University

Saima Ikram / Bahçeşehir University, School of Pharmacy

Introduction: Granzymes are serine proteases synthesized by CTL and NK cells. Five granzyme genes (GzmA, -B, -H, -K, -M) are present in humans, which are located at three different chromosomal loci. Serine protease binding pocket constitutes a catalytic triad (i.e., His59, Asp103 and Ser197). Granzymes are released into target cells by a specialized process known as granule exocytosis pathway. After internalization, these proteases initiate apoptosis. Their intracellular activity is regulated by specialized inhibitors knows as SERPINs. However, if these proteases are secreted in excess into the extracellular environment, their regulation becomes important as otherwise they start self-damage to the tissues thereby worsening the disease conditions.

Methods: In the current study, we investigated small molecule databases for the identification of potential molecules having the ability to inhibit GzmH by combined molecular simulations, which can ultimately be used as a potential therapeutic agent.

Results and Discussion: Analysis of the interaction fraction of all the studied ligands at the binding pocket of the protein shows that main interactions are constructed via hydrogen bonding and hydrophobic interactions. Compound $C_{19}H_{17}N_7O_4S$ showed the highest average MM/GBSA score (-70.18 kcal/mol). It mainly forms nonbonding chemical interactions with Arg43 (100% throughout the simulations time) and hydrophobic interactions with His59. In addition, a π-cation interaction was observed with Lys42.

Conclusions: There is no any small molecule or synthetic molecule inhibitor reported so far for extracellular GzmH. We have identified 12 potential hit inhibitors of this enzyme from two individual small molecule databases that can be used for drug target.

Keywords: Human granzyme H, SERPINs, Natural killer cells, Molecular docking

TW68, stabilizes the Cryptochromes, controls hunger blood glucose level in ob/ob and fat induced mice

Saliha Surme[1], Cagla Ergun[2], Seref Gul[3], Yasemin Kubra Akyel[4], Ozgecan Savlug Ipek[5], Onur Ozcan[1], Cihan Aydın[6], Ahmet Ceyhan Goren[7], Mustafa Guzel[5], Alper Okyar[8], İbrahim Halil Kavakli[1]

[1]Koç University, Department of Molecular Biology and Genetics
[2]Koc University, Department of Chemical and Biological Engineering
[3]Istanbul University, Department of Biology, Biotechnology Division
[4]Istanbul Medipol University, School of Medicine, Department of Medical Pharmacology
[5]Istanbul Medipol University, Regenerative and Restorative Medicine Research Center (REMER)
[6]Istanbul Medeniyet University, Department of Molecular Biology and Genetics
[7]Bezmialem University, Faculty of Pharmacy
[8]Istanbul University, Department of Pharmacology, Faculty of Pharmacy

Saliha Surme / Koç University, Department of Molecular Biology and Genetics

Introduction: Cryptochromes are transcriptional repressors of the circadian clock in mammals. Previously revealed that CRYs inhibit glucagon-mediated G-protein coupled receptors and gluconeogenesis. We aimed to find small molecules that increase the stability of the CRYs. Such molecules may potentially be used as anti-diabetic drugs, which control glucose levels.

Methods: We used a structure-based drug design against the primary packet of CRY, which is responsible for their degradation. We screened 2 million molecules and found that 100 molecules have binding energies lower than -12 kcal/mol. We experimentally test these molecules' effect on the circadian clock and the stability of CRYs. We identified a novel molecule, TW68, that stabilizes CRYs. Further cellular and biochemical studies indicated that TW68 causes the lengthening of the period of circadian rhythm and increases the stability of the CRYs. We used biotinylated-TW68 and showed its physical interaction with CRY1-2 through their primary pocket. We treated HepG2 cells with TW68 and discovered it inhibits glucagon-mediated glucogenesis by inhibiting the transcription of Pck1 and G6pc, key genes for gluconeogenesis.

Results and Discussion: These results signify the therapeutic potential of TW68 for treating type 2 diabetes mellitus. We determined a nontoxic dose of TW68 and its pharmacokinetic profile in mice. Results yielded a non-toxic effect with an excellent pharmacokinetic profile at 20 mg/kg on ob/ob diabetic mice. Blood analysis revealed that TW68-treated animals had normal glucose levels compared to the controls.

Conclusions: Collectively, all in-vitro and in-vivo data suggest TW68 can be used as a therapeutic agent to control hunger blood glucose levels in diabetic patients.

Keywords: Diabetes, Biological Clock, Cryptochrome, Computational Drug Screening, Pre-Clinical Studies

Bioactive Drug Candidate New Molecule Synthesis

Oznur Eyilcim[1], Fulya Gunay[2], Yuk Yin Ng[2], Ozlem Ulucan[2], Zuhal Turgut[1], Omer Tahir Gunkara[1]

[1]Yildiz Technical University
[2]İstanbul Bilgi University

Oznur Eyilcim / Yildiz Technical University

Introduction: Heterocyclic compounds such as maleimide, which play a key role in modern drug design, are present in the skeleton of many important drugs. Its derivatives attract more and more attention over time by researchers in the fields of organic synthesis, medicinal chemistry and drug development. Many of these derivatives, which are known to exhibit various biological activities, have been synthesized and characterized for antibacterial, antifungal, antitumor, antituberculosis, analgesic, antiprotozoal, cytotoxicity studies.

Methods: An indole substituted maleimide derivative was synthesized. This compound was reacted with 4 and 6 chain alkyl structures and formed into substituted cycloalkyl amines are attached to the chain ends. Their structures were determined by 1H-NMR spectroscopy, 13C NMR spectroscopy and HRMS. MTT and Docking studies were performed to determine biological activities.

Synthesis Scheme
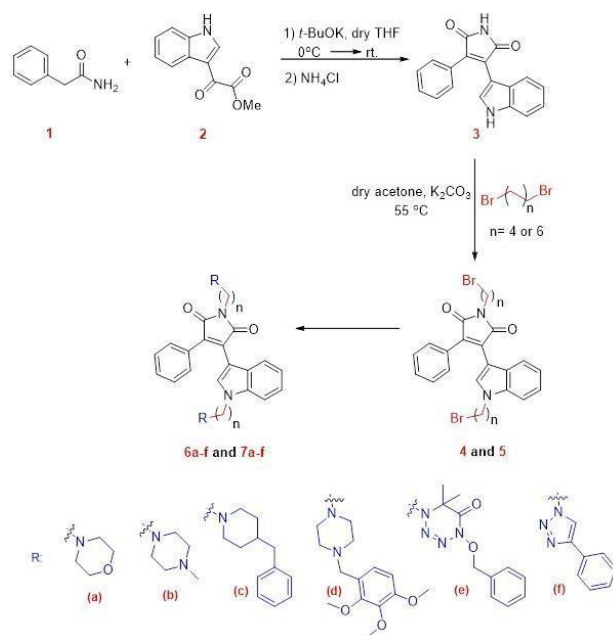
Results and Discussion: In vitro anti-cancer activities of the compounds were evaluated against two types of breast cancer cell line (MDA-MB-231 and MCF-7) by MTT assay. Among these 12 new compounds, 8 compounds exhibited the best activity against both types of breast cancer cell. IC50 values for were found as 1.65 μM, 3.06 μM, 4.37 μM, 6.57 μM, 7.58 μM , 18.71 μM, 12.95 μM, and 14.35 μM for MDA-MB-231 cell line; 3.21 μM, 4.00 μM, 5.33 μM, 6.22 μM, 7.42 μM, 16.80 μM, 16.94 μM and 29.28 μM, for MCF-7 cell line.

Conclusions: Finally, the synthesis of new indole substituted maleimide derivatives that may show GSK-3β inhibitory properties or be studied as anti-cancer agents has been carried out. Biological activity studies (MTT and Docking) of these new molecules were made.

Keywords: maleimide derivatives, GSK-3β inhibitors, MCF-7, MDA-MB-231, breast cancer

OP-12

Investigation of the antiviral and immunomodulatory effects of Zingiber officinale upon SARS-CoV-2 infection using in vitro airway cells culture model

Yuksel Cetin[1], Ahsen Morva[1], Seyma Aydinlik[2], Aysen Gungor[1], Gulsah Akbas[1], Merve Tosun[1], Jenya Dursun[1]

[1]TUBITAK MAM, Life Sciences, Medical Biotechnology Unit
[2]TUBITAK MAM, Life Sciences, Industrial Biotechnology Unit

Yuksel Cetin / TUBITAK MAM, Life Sciences, Medical Biotechnology Unit

Introduction: Despite this emergency call aiming to limit the social, economical and health-related burden by generation of effective vaccine against COVID-19 outbreak , scientists still continue to screen alternatives cure options like herb medicine. However, many countries have been used phytotherapy as an complementary treatment against increased plasma concentrations of pro-inflammatory cytokines throughout COVID-19 pandemic. Based on the fact that the potential healing mechanisms of herbs are not well known, the aim of this study is to investigate antiviral and immunomodulatory effects of Zingiber officinale upon SARS-CoV-2 infection using an in vitro co-culture model of colon/airway cells with macrophages.

Methods: Zingiber officinale obtained from the Mediterranean region was extracted with ethanol and the composition was evaluated with GC-MS. The cytotoxic effects of the extracts were evaluated by using colorimetric MTT assay on the Cercopithecus aethiops kidney (Vero E6), human kidney (HEK293T), human lung adenocarcinoma (Calu-3), human colon adenocarcinoma (Caco-2) and human peripheral blood monocyte (THP-1) cell lines. The antioxidant activity of the extracts was determined using DCFDA assay. The antiviral potential of the extracts was investigated by performing Pseudovirus Neutralization assay. Finally, the mmunomodulatory effects of the extracts on lipopolysaccharide (LPS)/ pseudovirus induced cytokines TNF-α, IL1-β, IL-6, and IL-8 production were determined by flow cytometry in co-culture of THP-1 macrophage with Calu-3 cell lines.

Results and Discussion: The results of this study was demonstrated antioxidant and antiviral activity of Zingiber officinale

Conclusions: This study may initiate the development of novel nutraceutical herbal formulations as an alternative therapy for the prevention and treatment of COVID-19.

Keywords: Zingiber officinale, Mediterranean Herbs and Spices, Antiviral Activity, SARS-CoV-2, Immunomodulatory Effects

OP-13

Delivery of Autophagy Inhibitor siRNA with "smart" Nanoparticles against Triple Negative Breast Cancer

Nada Walweel[1], Venhar Cinar[1], Erhan Demirel[2], Cansu Ümran Tunç[1], Zuhal Hamurcu[1], Halil Ulutabanca[1], Yasemin Yüksel Durmaz[2], <u>Omer Aydin</u>[1]

[1]Erciyes University, Kayseri 38039, Turkey
[2]Istanbul Medipol University, Istanbul, 34810, Turkey

Omer Aydin / Erciyes University, Kayseri 38039, Turkey

Introduction: Although apoptosis is the most utilized cell death pathway in cancer therapy, recent research suggests that alternative mechanisms, particularly autophagy, may offer a novel approach to cancer treatment. Further, autophagy is proposed as a potential cause for the evolution and progression of resistance toward several anticancer drugs, including doxorubicin(DOX). We hypothesized that a combination therapy of autophagy protein inhibitor siRNA/(siLC3) complexation with "smart" nanoparticles that we engineered, and DOX would elevate DOX sensitivity in metastatic breast cancer.

Methods: First, we synthesized and characterized a polymeric "smart" gene carrier system with ATRP and "click" reactions. and tested its therapeutic potential with cellular viability/colony formation assays, WB, and fluorescence imaging.

Results and Discussion: We showed that our approach could efficiently suppress the autophagy-related gene LC3, inhibit cellular autophagy and exhibit enhanced anticancer activity. Furthermore, MDA-MB-231, co-administration of siLC3/DOX was more effective than either treatment. The inhibition of cell proliferation, colony formation, and migration in the cells demonstrated this. Nevertheless, our combination increased apoptosis rate 4.8-fold. Combined treatment also inhibited PARP, cyclin D1, and Src signaling in tumor cells. Finally, the results of acridine orange staining, which is used to detect autophagy-related vesicles; autophagosomes, confirm that autophagy suppression is evident.

Conclusions: Our findings showed that combining autophagy suppression with chemotherapy delivered by "smart" nanoparticles for breast cancer therapy has a synergistic effect. We are currently running in vivo experiments of our approach in the TNBC model. This study was supported by ERU-BAP(FYL-2022-11565), TUBITAK 118Z952(COST Action CA17103), and TÜSEB Drug R&D Program (Grant No: 3802)

Keywords: "smart" nanocarrier, Triple-negative breast cancer, Autophagy, LC3 siRNA, Doxorubicin

OP-14

Discovery of Potent Cholinesterase Inhibition-Based Multi-Target-Directed Lead Compounds for Synaptoprotection in Alzheimer's Disease

Bengisu Turgutalp[1], Bengisu Turgutalp[2], Prabesh Bhattarai[2], Prabesh Bhattarai[3], Tugba Ercetin[4], Rengin Reis[5], Rengin Reis[6], Chiara Luise[7], Enise Ece Gurdal[1], Enise Ece Gurdal[8], Andreas Isaak[9], Derya Biriken[2], Derya Biriken[10], Elisabeth Dinter[2], Elisabeth Dinter[11], Hande Sipahi[5], Dirk Schepmann[12], Anna Junker[9], Bernhard Wunsch[12], Wolfgang Sippl[7], Hayrettin Ozan Gulcan[4], Caghan Kizil[2], Caghan Kizil[3], Mine Yarim[1]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Yeditepe University, 34755 Istanbul, Turkey
[2]German Centre for Neurodegenerative Diseases (DZNE), Helmholtz Association, 01307 Dresden, Germany
[3]Department of Neurology, Columbia University Irving Medical Center, 10032 New York, USA
[4]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Eastern Mediterranean University, Famagusta, TRNC, via Mersin 10, Turkey
[5]Department of Toxicology, Faculty of Pharmacy, Yeditepe University, 34755 Istanbul, Turkey
[6]Department of Toxicology, Faculty of Pharmacy, Acibadem Mehmet Ali Aydinlar University, 34758 Istanbul, Turkey
[7]Department of Medicinal Chemistry, Institute of Pharmacy, Martin-Luther-Universität Halle-Wittenberg, 6099 Halle (Saale), Germany
[8]Institute of Chemistry, Martin-Luther-Universität Halle-Wittenberg, 06120 Halle, Germany
[9]European Institute for Molecular Imaging (EIMI), der Westfälischen Wilhelms-Universität D-48149 Münster, Germany
[10]Department of Medical Microbiology, Ankara University Faculty of Medicine, 06620 Ankara, Turkey
[11]Department of Neurology, University Clinic, TU Dresden, 01307 Dresden, Germany
[12]Institute of Pharmaceutical and Medicinal Chemistry, University of Münster, D-48149 Münster, Germany

Bengisu Turgutalp / Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Yeditepe University, 34755 Istanbul, Turkey

Introduction: Multiple biological mechanisms act in concert during the etiological manifestation of Alzheimer's disease (AD). Drug development efforts mainly focused on single targets failed to provide an effective treatment. Therefore, we designed cholinesterase inhibition (ChEI)-based multi-target-directed ligands (MTDLs).

Methods: We built a library of seventy 4-methylbenzothiazole-piperazine propanamide derivatives, sequentially screened for in vitro ChEI; determined σ1R, σ2R, NMDAR-GluN2B binding affinities, and P2X7R antagonistic activity; performed molecular docking studies for potent ligands/inhibitors on their corresponding targets. We performed cytotoxicity studies on human neuroblastoma, liver hepatoma, embryonic kidney cells. We assessed cytoprotective activities in human neuroblastoma and primary human fetal cortical astrocytes with stress inducers H_2O_2 and Amyloid-β42 respectively. We screened the in vivo activity of hit compounds in zebrafish model of acute amyloidosis-induced synaptic degeneration. We

screened CYP450 enzyme inhibition profile for 3A4, 2D6, and 2C9 subtypes and determined the penetration by blood-brain barrier (BBB) and gastrointestinal tract (GIT).

Results and Discussion: Out of seventy compounds, twenty-two displayed potent ChI. Following radioligand binding affinity assays, we designated nine potent ChI-based hit MTDLs, which fulfill in silico drug-likeness criteria and do not cause cytotoxicity in three cell lines. Seven compounds displayed cytoprotective activity in two stress-induced cellular models. Compared to the benchmark drug donepezil, six compounds showed equal/better synaptic-protective activity in vivo. Two P2X7R antagonists alleviated the activation state of microglia in vivo. Five compounds were BBB and GIT permeable, and four did not inhibit CYP450 subtypes.

Conclusions: Our four ChEI-based lead MTDLs are promising drug candidates for synaptic integrity protection and can serve as disease-modifying AD treatment.

Discovery pipeline of ChI-based lead MTDLs
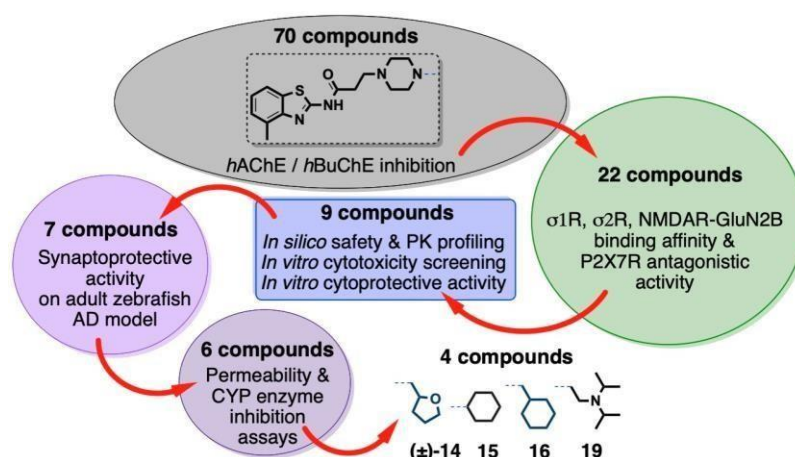
Keywords: Alzheimer's disease, Cholinesterase inhibitors, Multi-target-directed ligands

Naproxen derivatives: model compound in prostate cancer

Kaan Birgül[1], Kaan Birgül[2], Yeliz Yıldırım[3], Hatice Yeşim Karasulu[3], Ercüment Karasulu[3], Yeliz Yıldırım[4], Hatice Yeşim Karasulu[5], Ercüment Karasulu[6], Abdullahi Ibrahim Uba[7], Kemal Yelekçi[7], Hatice Bekçi[8], Ahmet Cumaoğlu[8], Levent Kabasakal[9], Özgür Yılmaz[10], Ş. Güniz Küçükgüzel[11]

[1]Bahçeşehir University, School of Pharmacy, Department of Pharmaceutical Chemistry, İstanbul, Turkey
[2]Marmara University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, İstanbul, Turkey
[3]Ege University, Center For Drug R&D And Pharmacokinetic Applications (ARGEFAR), İzmir, Turkey
[4]Ege University, Department of Chemistry, Faculty of Science, İzmir, Turkey
[5]Ege University, Faculty of Pharmacy, Department of Pharmaceutical Technology, İzmir, Turkey
[6]Ege University, Faculty of Pharmacy, Department of Biopharmaceutics and Pharmacokinetics, İzmir, Turkey
[7]Kadir Has University, Faculty of Engineering and Natural Sciences, Department of Biopharmaceutics and Genetics, İstanbul, Turkey
[8]Erciyes University, Faculty of Pharmacy, Department of Biochemistry, Kayseri, Turkey
[9]Marmara University, Faculty of Pharmacy, Department of Pharmacology, İstanbul, Turkey
[10]TUBİTAK Marmara Research Center, Materials Institute, Kocaeli, Turkey
[11]Fenerbahçe University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, İstanbul, Turkey

Kaan Birgül / Bahçeşehir University, School of Pharmacy, Department of Pharmaceutical Chemistry, İstanbul, Turkey

Introduction: Methionine aminopeptidase2 (MetAP2) is a bifunctional protein that plays a critical role in the growth of different types of tumours. Naproxen ((S)-2-(6-methoxy-2-naphthyl)propanoic acid) is a non-steroidal anti-inflammatory drug, also known to have anticancer activities. In light of the literature, thiosemicarbazides, 1,2,4-triazole-3-thiones and thioether derivatives have been reported to have anticancer activity on different cancer cell lines.

Methods: According to all information, novel MetAP2 inhibitors were designed and synthesized according to the molecular modeling studies. Synthesized compounds in-vitro anticancer activity were performed against PC-3, DU-145 (androgen independent), and LNCaP (androgen dependent) cell lines. The efficacy of potent compounds on MAPK and AKT pathway were investigated. Based on the results, (S)-3-((2,4,6-trimethylphenyl)thio)-4-(4-fluorophenyl)-5-(1-(6-methoxynaphtalen-2-yl)ethyl)-4H-1,2,4-triazole (Compound 5n) were selected for further investigations.

Results and Discussion: Apoptosis studies of compound 5n and activity against MetAP2 enzyme were investigated. In-vivo studies of compound 5n were performed. Compund 5n's efficacy on nude mices that developed prostate cancer with LNCaP cells has been proven. Additionally healthy mice, treated mice with compound 5n and untreated mices blood results were investigated.

Conclusions: The purpose of this study is to develop an inhibitor against the enzyme MetAP2, which causes the development of prostate cancer. The development of the new inhibitor, molecular modeling studies were done and one of the selected compunds was proven to be a MetAP2 inhibitor. Beside of the western blot, apoptosis and MetAP2 enzyme assay; the compound's anticancer activity were proven with in-vivo studies.Acknowledgement: This study was supported by a grant of TUBITAK (Project number: 215S009)

Asymmmertric synthesis methods

Bahadır BÜLBÜL[1]

[1]Duzce University Faculty of Pharmacy

Bahadır BÜLBÜL / Duzce University Faculty of Pharmacy

Introduction: The journey of chirality started at the beginning of the 19th century. It is a helpfull concept in explaining the natural interactions. Pasteur's meticulous observation of sodium ammonium tartrate crystals' structure, scientists have discovered many features of chiral molecules. The number of newly approved single enantiomeric drugs increases every year and takes place in the market. Especially after the thalidomide disaster in the late 1950s, marketing drugs as pure enantiomers have gained more importance than ever. In order to prevent these kinds of tragedies,

Development of knowledge and terminology about chirality.
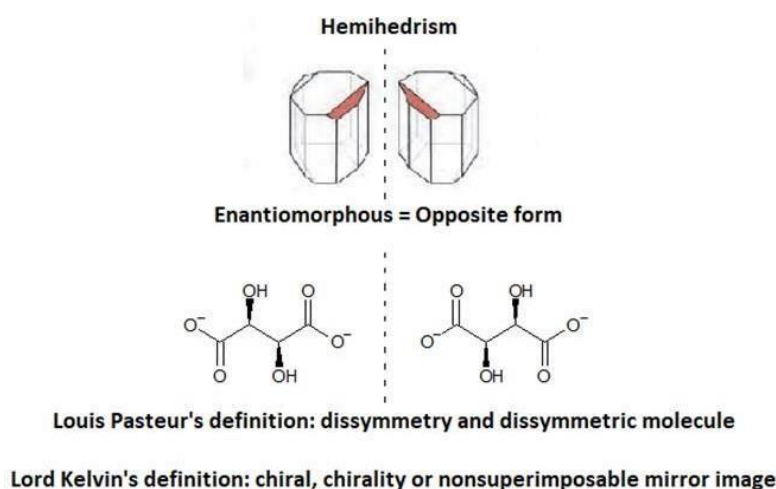
Development of knowledge and terminology about chirality.

Methods: An extensive literature review has been carried out and the salient points have been brought together.

Results and Discussion: Asymmetric synthesis are beneficial in new drug synthesis. However, enzymes and organocatalysts can be preferred more for industrial production for environmental sustainability. Also, the recycling processes for chiral auxiliaries can be done more efficiently to reuse the reactive instead of post-reaction destruction. In addition, pharmacognosy studies that will add new molecules to the chiral pool are critical. Interdisciplinary studies that hybridize pharmacognosy and plant biotechnology can program living organisms to produce a new molecule.

Conclusions: The world of chirality, which attracted attention with Pasteur's careful observation, is still one of the critical research topics today. Especially their different behavior in biological environments makes enantiomers particularly worthy of investigation. In addition,

the ethical and moral dimensions of the thalidomide disaster make these studies a responsibility for scientists.

Virtual Screening for Novel Small Molecule Inhibitors Against IL-17A Downstream Signaling for the Treatment of Multiple Sclerosis

Müge Didem Orhan[1], Lalehan Oktay[1], Serdar Durdağı[1], Timuçin Avşar[1]

[1]Bahçeşehir University

Lalehan Oktay / Bahçeşehir University

Introduction: Multiple Sclerosis (MS) is an inflammatory, demyelinating, and neurodegenerative disease of the central nervous system. Interleukin-17 (IL-17A) is a proinflammatory cytokine involved in the pathogenesis of autoimmune diseases. Although monoclonal antibodies that block IL-17A signaling have shown exceptional effectiveness, an FDA-approved oral IL17-A protein inhibitor is currently unavailable. Upon binding of small molecules to the dimer interface, unpacking of the N-terminal domain was previously reported and this conformational change inhibits coupling of IL-17A and its receptor. Furthermore, also reported was the elucidated C-terminal and N-terminal binding pockets, which would cause a steric block for receptor binding and also induce conformational change.

Methods: Here, the receptor binding of IL-17A have been tackled using a crystallized 3-D structure of the IL-17A homodimer coupled with its receptor. Binding domains of the receptor and IL17-A ligand previously reported were screened against ~2300 FDA approved drug. Residue-based MM/GBSAs of existing crystal structures with small molecules bound to the dimerization interface have confirmed the crucial residues involved in the dimerization of IL-17A and binding of small molecules. The dimerization interface was further screened using the apo form IL-17A structure against and the OTAVA Drug-like Green chemical database of about ~170.000 compounds by employing various docking algorithms and all-atom MD simulations.

Results and Discussion: Promising inhibitor candidates will be used in vitro and further considered for in vivo experiments.

Conclusions: The IL17-A dimerization interface will be elucidated and promising drug candidates will be further screened.

Keywords: Multiple Sclerosis, Drug Repurposing, IL17-A, interleukin

INVESTIGATION OF THE EFFECT OF TGF-ß SIGNALING REGULATION ON CYTOTOXIC ACTIVITY OF IRINOTECAN IN COLORECTAL CANCER

Ebru Nur AY[1], Melda Sarıman[1], Remzi Okan Akar[1], Engin Ulukaya[1]

[1]Istinye University

Ebru Nur AY / Istinye University

Introduction: Inhibition of Transforming Growth Factor Beta Receptors (TGFß-R) signaling in cancer cells is reported to be a potential therapeutically strategy, as well as how to impair TGFß-R gene signaling in colorectal cancer (CRC) cells is largely unexplored. In this context, in order to increase the effectiveness of treatment, TGFß-RI/II inhibitors and/or their combination with different anti-cancer agents have been tried for cancer therapies. In our study, we scope out the effects of changes TGFß-R gene on the cytotoxic activity of irinotecan, which is a chemotherapeutic drug, in human colon cancer cell line (HCT 116).

Graphical Abstract
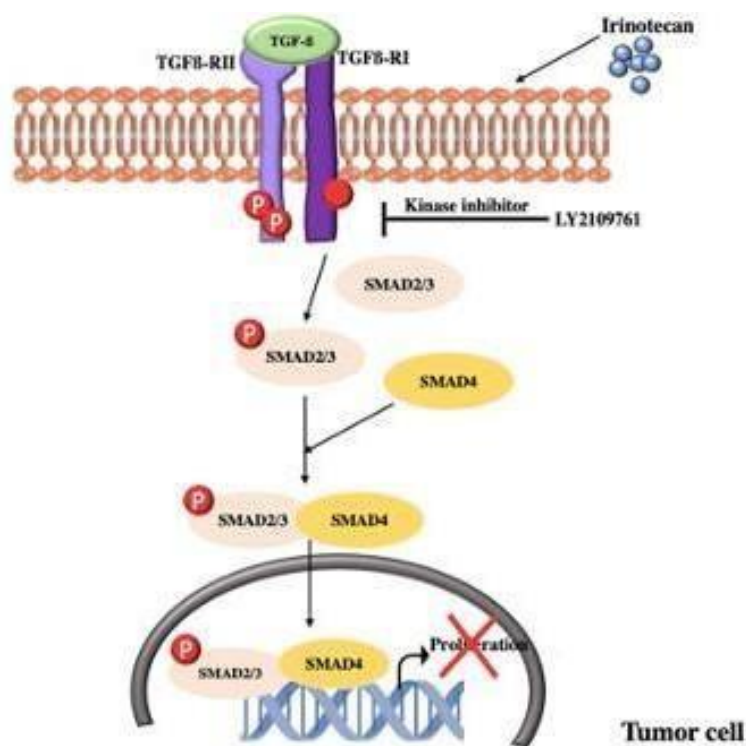
Methods: The TGFß-R gene was suppressed by TGFß-RI/II inhibitor (LY2109761) on HCT 116 through pharmacological inhibition. Then, the determined appropriate dose of irinotecan and LY2109761 was applied to HCT 116 as combination therapy. The effects of the drug/inhibitor alone and combination therapy on cell viability is demonstrated by sulforhodamine B assay (SRB). After treatment, differences of TGFß-RII, phospo-SMAD2/3, TGF-ß, Caspase 3 and p21 genes at the level of protein were determined by western blot method. Apoptotic effects were evaluated by flow cytometry analysis.

Results and Discussion: TGFß-RI/II inhibitor LY2109761 (10 uM) and irinotecan (50 TDC) combination therapy showed anti-proliferative activity on HCT 116 cells in a dose and time-dependent manner.

Conclusions: These results suggest that the combination therapy caused a dramatic decrease in cell viability in HCT 116 cells. Therefore, it was concluded that it might be used as an effective treatment strategy for colorectal cancer.

Keywords: HCT 116, Cytotoxicity, Irinotecan, TGFß-RI/II inhibitor LY2109761

Mechanistic View of Proglumetacin Binding to Dihydrofolate Reductase: A Drug Repurposing Study

Ebru Cetin[1], Hanife Pekel[2], Özge Sensoy[2], Ali Rana Atilgan[1], Canan Atilgan[1]

[1]Sabanci University
[2]Istanbul Medipol University

Ebru Cetin / Sabanci University

Introduction: Dihydrofolate reductase (DHFR) is essential for nucleotide synthesis. Recently, we have designed a derivative of trimethoprim (TMP), which was known as the primary inhibitor of DHFR. This derivative was successful on strains harboring L28R mutation as opposed to TMP. However, mutations at positions 30 and 153, which are considered relatively mild compared to L28R, still emerged under evolutionary pressure of the inhibitor, thus necessitating discovery of allosteric regions that can be targeted by therapeutic molecules.

Methods: In line with this finding, we proposed that our recently discovered cryptic site, which was invoked by D27E, I94L, F153S mutants,2 can be utilized for eliciting an allosteric inhibitory response. To achieve this, we have first conducted a drug repurposing study using site-tethering studies and pharmacophore design. Then, we have carried out molecular dynamics simulations on the highest-score candidates to ensure stability of the drug; amongst our pool of candidates, proglumetacin emerged as the best choice.

Results and Discussion: Our initial analyses revealed that proglumetacin binding increases the flexibility of the active site, hence distorting the binding cavity. Subsequently, to understand the dynamic relation between dihydrofolate (DHF) and proglumetacin (GLM) we conducted simulations on the DHFR-DHF-GLM ternary complex and observed that GLM indeed distorted the binding cavity and enforced an inactive conformation of the substrate.

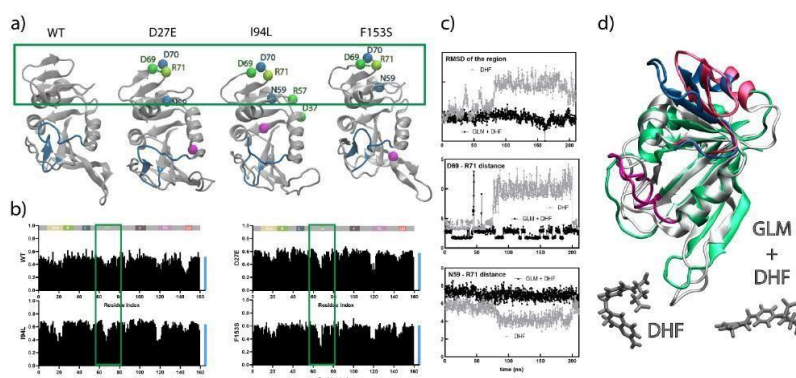## Depiction of the Cryptic Site

Figure 1. a) The hydrogen motif was found similar in three mutants. b) Order parameter of these mutants. Rather than the hydrogen bond they share, they also represent a disruptive decrease in the order parameters in the depicted region. c) RMSD of the residues 53-60 and 69-85 region which is used as the target for docking studies. The distances of gained and lost

hydrogen bonds. d) green: GLM+DHF blue: open conformation of the site, silver: DHF, red: closed conformation of the site. magenta: M20 loop

Conclusions: In accord with our relaxation analysis, we conjecture that GLM lowers order parameters of the enzyme side chains while maintaining synchronization, pushing DHF towards a loose state where critical binding geometry cannot be attained.

Keywords: drug repurposing, cryptic site, binding mechanism and dynamics, site-tethering, pharmacophore design

Development and Characterization of Selective HDAC6 Inhibitors for the Treatment of Castration Resistant Prostate Cancer and Reversal of Taxane Resistance

Büşra Yıldırım[1], İpek Bulut[1], Batuhan Mert Kalkan[1], Buse Cevatemre[2], S. Can Özcan[2], Ceyda Açılan Ayhan[2], Ceyda Açılan Ayhan[4], Adam Lee[3], Arasu Ganesan[3]

[1]Koc University, Graduate School of Health Sciences, Istanbul, Turkey
[2]Koc University, Research Center for Translational Medicine, Istanbul, Turkey
[3]University of East Anglia, UK
[4]Koc University, School of Medicine Istanbul, Turkey

Büşra Yıldırım / Koc University, Graduate School of Health Sciences, Istanbul, Turkey

Introduction: Epigenetic changes in tumors cause development of resistant phenotypes and they are the potential drivers of drug resistance. There are important preclinical data showing that histone deacetylase inhibitors (HDACi's) may be useful in the treatment of castration resistant prostate cancer (CR-PCa). HDAC6 is the only HDAC, whose knockout is not lethal in mice, and its absence leads to reduction of tumor size. The aim of this project is to find and characterize new HDAC6 inhibitors (HDAC6i's) that potentially synergizes with taxanes or reverses the taxane resistance in CR-PCa cells.

Methods: A viability screen in the presence of 38 HDAC6i's that we synthesized, either alone or in combination with taxanes via SRB and CTG assays performed. 9 of the inhibitors were picked and their efficacy was tested in vitro using HDAC6 enzyme activity assays, their specificity was determined via their inhibition of HDAC1 and HDAC8 activity. The target engagement of HDAC6i in cells was determined via CETSA.

Results and Discussion: Three of the HDAC6 inhibitors, AF-4, AF-11 and AD-165, were more selective towards HDAC6, synergized with taxanes and partially reverted resistance in cells. Further analysis suggested that while AF-4 and AF-11 did not affect the cell cycle, AD-165 effectively arrested cells in G2/M phase.

Conclusions: AD-165 was the most potent HDAC6i, based on its IC50, specificity, selectivity, and exhibition of the expected phenotypes, therefore was selected for additional studies. Currently, we are investigating the mechanism of action of AD-165 in KD-PCa through RNA-seq analysis and testing its efficacy in reduction of tumor size in mice.

Keywords: Anticarcinogenic Agents, Castration-Resistant, Epigenetic Repression, Chemoradiotherapy, Drug Resistance

Short Talk-1

A Comprehensive Drug Repositioning Approach Against Melanoma

Feyza Maden[1], Edanur Akarsu[1], Ezgi Keske[3], Beste Turanlı[2], Nagehan Ersoy Tunalı[3], <u>Saliha Ece Acuner Zorluuysal</u>[1]

[1]Department of Bioengineering and Science and Advanced Technologies Research Center (BILTAM), Istanbul Medeniyet University, Istanbul
[2]Department of Bioengineering, Marmara University, Istanbul
[3]Department of Molecular Biology and Genetics and Science and Advanced Technologies Research Center (BILTAM), Istanbul Medeniyet University, Istanbul

Saliha Ece Acuner Zorluuysal / Department of Bioengineering and Science and Advanced Technologies Research Center (BILTAM), Istanbul Medeniyet University, Istanbul

Introduction: Melanoma is a dangerous type of skin cancer with a high mortality rate and an increasing incidence in the world. Due to the difficulties in treatment and rapid metastasis of the disease, the development of effective drug discovery methods has gained importance. With the drug repositioning method, new areas of use for existing drugs can be determined.

Methods: In the drug repositioning step, a gene expression-guided search tool was used to predict significantly relevant drug-gene pairs in melanoma. The drugs in the resulting significant pairs were categorized into groups based on their relevance to cancer: 1. antineoplastic, 2. complementary drug in cancer treatment, 3. novel, i.e. not related to cancer treatment yet. Representative drug-protein pairs were selected for each group and molecular docking studies were performed. The top 5 docking results for the novel drug gene pairs were structurally analyzed further and lastly, their effects were tested by in vitro studies using two cancer cell lines (A375 and SK-MEL-28) and a healthy cell line (HFF-1).

Results and Discussion: 5 potential drugs; namely, Venlafaxine, Tenofovir, Olanzapine, Haloperidol and Doxepin, are proposed against melanoma based on the integrative drug repositioning and molecular docking approach. When these candidate drugs were further tested in vitro; it was observed that Doxepin (antidepressant) and Tenofovir (anti-HIV) are the most promising drug candidates for the treatment of melanoma.

Conclusions: Combination of computational and experimental approaches provides a successful means to develop new therapeutics or to repurpose the existing ones in many important diseases such as melanoma.

Keywords: melanoma, drug repositioning, molecular docking, cell culture

Short Talk-2

A Hierarchical Virtual Screening of the NCI Compound Library Reveals Novel and Potent Allosteric Inhibitors of the Oncogenic Phosphatase SHP-2 with Potential Anticancer Activity

Mine Isaoglu[1], Medine Gulluce[2], Serdar Durdagi[3], Mehmet Karadayi[2], Ahmet Hacimuftuoglu[4]

[1]Atatürk University, Institute of Natural and Applied Sciences, Erzurum 25240, Turkey
[2]Atatürk University, Faculty of Science, Department of Biology, Erzurum 25240, Turkey
[3]Bahçeşehir University, School of Medicine, Department of Biophysics, Computational Biology and Molecular Simulations Laboratory, Istanbul 34734, Turkey
[4]Atatürk University, Faculty of Medicine, Department of Medical Pharmacology, Erzurum 25240, Turkey

Mine Isaoglu / Atatürk University, Institute of Natural and Applied Sciences, Erzurum 25240, Turkey

Introduction: SHP-2 is the first identified oncogenic tyrosine phosphatase and is involved in many signaling pathways that regulate cell proliferation, differentiation and apoptosis. SHP-2 overexpression has been linked to several malignancies, including breast, gastric and lung cancer. Therefore, SHP-2 represents a promising target for therapeutic intervention.

Methods: A total of 265.242 compounds from the NCI database were docked into the allosteric site of SHP-2WT (PDB ID: 5EHR) using Glide/HTVS, SP, XP and IFD algorithms, respectively. Next, selected hits based on docking scores and molecular interactions obtained with the IFD protocol were submitted to the MetaDrugTM platform to predict their therapeutic activity and toxicity. The filtered hits were further investigated by molecular dynamics technique in a simulation time of 50 ns, followed by free energy calculations using the MM/PBSA approach. The in vitro inhibitory activities of selected final hits against SHP-2WT were then confirmed using a phosphatase assay kit.

Results and Discussion: Our study identified three novel lead candidates as potent allosteric SHP-2 inhibitors. The docking and dynamics simulations showed that these compounds interact with the critical amino acid residues and thus remain stable in the allosteric pocket. Binary QSAR models predicted that they may have anticancer activity and low toxicity. Moreover, all significantly inhibited the in vitro activity of the SHP-2WT in the micromolar range.

Conclusions: The potent allosteric SHP-2 inhibitors first reported in this study are potential natural therapeutic peptides for the treatment of SHP2-overexpressing cancers. Therefore, they should be studied more intensively to investigate their biological and medicinal properties in vitro and in vivo.

An overview of molecular docking and three-dimensional interaction analysis.
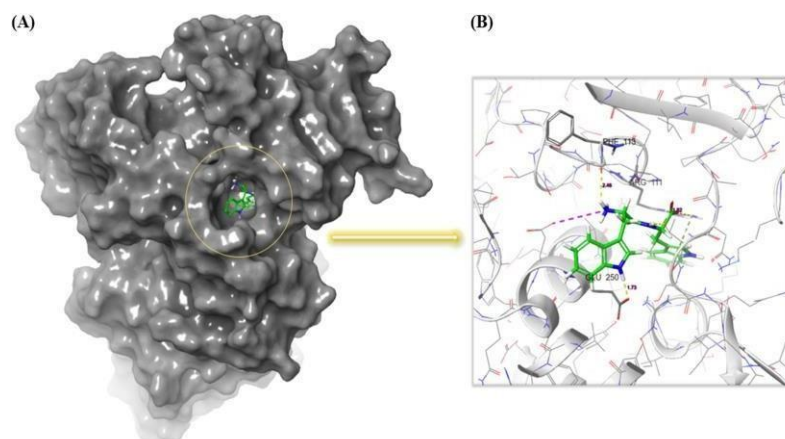
(A) Docking of a hit ligand to the tunnel-like allosteric site of SHP-2WT (PDB ID: 5EHR) using the IFD protocol. (B) Visual inspection of intermolecular interactions between the hit ligand and amino acid residues in the allosteric binding site.

Short Talk-3

Investigation of Potential Candidates as FOXM1 Inhibitors for the Treatment of Triple Negative Breast Cancer by In silico and In vitro Studies: A Drug Repurposing Study

Khaled A. N Abusharkh[1], Ferah Comert Onder[2], Zuhal Hamurcu[3], Bulent Ozpolat[4], Mehmet Ay[5]

[1]Çanakkale Onsekiz Mart University, School of Graduate Studies, Department of Chemistry, Çanakkale, Türkiye, Al-Quds University, Faculty of Science and Technology, Department of Chemistry and Chemical Technology, East Jerusalem, Palestine.
[2]Çanakkale Onsekiz Mart University, Faculty of Medicine, Department of Medical Biology, Çanakkale, Türkiye.
[3]Erciyes University, Faculty of Medicine, Department of Medical Biology, Kayseri, Türkiye.
[4]Houston Methodist Research Institute, Department of Nanomedicine. Neil Cancer Center-Houston Methodist, Director of Innovative Cancer Therapeutics, USA
[5]Çanakkale Onsekiz Mart University, Faculty of Science, Department of Chemistry, Natural Products and Drug Research Laboratory, Çanakkale, Türkiye.

Khaled A. N Abusharkh / Çanakkale Onsekiz Mart University, School of Graduate Studies, Department of Chemistry, Çanakkale, Türkiye, Al-Quds University, Faculty of Science and Technology, Department of Chemistry and Chemical Technology, East Jerusalem, Palestine.

Introduction: Triple-negative breast cancer (TNBC) is the most aggressive type of breast cancer which presents a high rate of relapse, metastasis, and mortality. This type is associated with poor prognosis compared to other breast cancer subtypes in patients. Nowadays, the absence of approved specific targeted therapies to eradicate. The Forkhead box M1 (FOXM1) protein is a member of the forkhead/winged helix (FOX) family, which is involved in mitotic progression and cell division. We have previously shown that FOXM1 is frequently overexpressed in TNBC cells, and its increased transcriptional activity leads to tumorigenesis and poor patient prognosis in TNBC patients. Currently, there is no FDA-approved FOXM1 inhibitor, which is the main motivation for us to develop FOXM1 inhibitors.

Methods: In this study, we performed in silico drug repurposing study to discover potential analogs of reference and effective molecules targeting the FOXM1 DNA-binding domain (DBD). Pharmacophore mapping and Screen library modules of Discovery Studio (DS) have been used to screen the approval drugs. Docking studies were performed by using CDOCKER module of DS and Autodock vina. The selected drugs were tested in MDA-MB-231 cell lines in in vitro.

Results and Discussion: As a result, the binding and CDOCKER interaction energies were determined between protein-ligand complexes compared to control. The resulting compounds displayed molecular interactions with expected amino acid residues including His287, Arg297, Leu291 etc.

Conclusions: These drugs can be potential, and their scaffolds may lead to discovery of novel candidates. This study was supported by Çanakkale Onsekiz Mart University. The Scientific Research Coordination Unit, Project number FDK-2022-4145.

Keywords: Forkhead box M1 (FOXM1), TNBC, drug repurposing, molecular docking

Short Talk-4

Structural examination of an otopetrin-like proton channel in crayfish ganglia

Mustafa Erdem SAĞSÖZ[2], Kaan ARSLAN[1], Turgut BAŞTUĞ[1], Nuhan PURALI[1]

[1]Hacettepe University, Faculty of Medicine, Biophysics Dept.
[2]Atatürk University, Faculty of Medicine, Biophysics Dept.

Mustafa Erdem SAĞSÖZ / Atatürk University, Faculty of Medicine, Biophysics Dept.

Introduction: Autopetrins(Otop1–Otop3) encompass one of two known eukaryotic families of proton-selective channels. Otop1 is required for Otoconia formation and as a possible mammalian sour taste receptor (Saotome 2019). Otopetrin-Like A (OtopLA) has been shown to have a role in sensing low proton concentration in Drosophila melanogaster (Ganguly 2021).

Methods: Crayfish is kept, fed and decapitated according to local ethical guidelines. Ganglia tissue extracted, RNA isolated and reverse transcriptised from these materials. cDNA synthesis were done with RACE kits. With the help of properly designed primers PCRs were done. NextGen was used for sequencing of samples. ORF is determined and 682 amino acid (AA) sequence is found. Then, the AA sequence was modeled using the Alphafold2 tool without using any templates (Mirdita 2021). Transmembrane protein structure prediction (Feng 2020) was obtained using some web based applications and VMD.

Results and Discussion: Possible function and subunits of the amino acid sequence derived from mRNA which was isolated from Astacus leptodactylus ganglia and has 95% similarity to Penaeus vannamei proton channel OtopLc-like (NCBI Sequence ID: XM_027357161.1) mRNA, were tried to be interpreted by structural analysis using AlphaFold (Jumper 2021) and VMD (Humphrey 1996).

Otopetrin family proton channel
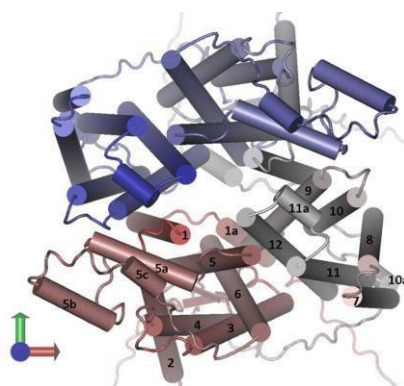
Astacus leptodactylus putative proton channel.

Conclusions: Our sequence is found to be structurally very similar to previously determined Otopetrin like proton channels (Saotome 2019). Possible proton transport paths and fuctioning of proton channel will be studied by molecular dynamics tools.

Keywords: Otopetrin, proton channel, Astacus leptodactylus, ganglia, crayfish

Short Talk-5

A STUDY IN SILICO ON ALDOLASE C AS A NEW TREATMENT TARGET IN COLORECTAL CANCER

Aliye Demet DEMİRAG[1], Mustafa YILDIRIM[2], Necla BENLİER[3], Gürkan BAL[4]

[1]Yeditepe University, Vocational School, Internet and Network Technologies Department, 34755, Istanbul,Turkey
[2]Sanko University, Faculty of Medicine, Division of Medical Oncology, Gaziantep, Turkey
[3]Sanko University, Faculty of Medicine, Division of Pharmacology, Gaziantep, Turkey
[4]Institute for Allergology, Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, 10117 Berlin, Germany,

Mustafa YILDIRIM / Sanko University, Faculty of Medicine, Division of Medical Oncology, Gaziantep, Turkey

Introduction: The leading cause of cancer-related death worldwide is colorectal cancer. Aldolases have varying levels of expression in human tissues, and aberrant expression has been seen in a number of human diseases and cancerous tumors. However, in recent years, protein-protein interactions or epigenetic changes have been reported to have non-enzymatic functions. These actions of enzymes and proteins are referred to as "moonlight effects". Apart from its normal physiological roles, ALDO C has been shown to have a role in cancer development. In an immunohistochemical study, it was shown to be expressed in 49% of patients with colon cancer. ALDOC-positive cases were associated with higher T and M grades and a worse prognosis as determined by Kaplan-Meier analysis. Univariate and multivariate analyses demonstrated that ALDO C expression is an independent prognostic factor for CRC patients. This role of Aldo C in colorectal cancer makes it a therapeutic target.

Methods: The Discovery Studio program was used to calculate their binding affinities and determine how much of an interaction they contributed to. The PyMOL program was used to perform ligand analysis corresponding to their binding affinity. Knowing the target receptor's active site, types of interactions, and bond lengths allowed us to interpret the stability of insertion.

Results and Discussion: In this study, we discovered that Kaempferitrin, 9-[4,5-dihydroxy-6-(hyroxymethyl)oxan-2yl]-1H-purin-6-one, and Thalassiolin-B effectively inhibited Aldo C (Figure 1).

Figure 1

Kaempferitrin (ΔG:-10.6 kcal\mol)   9-[4,5-dihydroxy-6-(hyroxymethyl)oxan-2yl]-1H-   Thalassiolin-B (ΔG:-9.2 kcal\mol)
purin-6-one (ΔG:-10.5 kcal\mol)
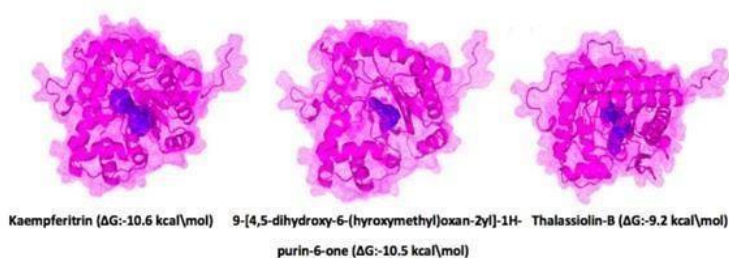
Molecular interaction and binding energies of the Aldonase C molecule and 3 molecules that play an active role in colon cancer.

Conclusions: Colorectal cancer has a high mortality and morbidity rate despite new diagnostic and therapeutic approaches. Therefore, research to create new colorectal cancer prevention agents is still in demand.

Keywords: Aldolase C, Molecular docking, Colon cancer

Short Talk-6

Selective Downregulation of Gene Expression in Hypoxic Cancer Cells by an Activatable G-Quadruplex Stabilizers

Nezahat Gokce Ozsamur[1], Busra Uyar[1], Fatma Secer Celik[1], Sundus Erbas Cakmak[1]

[1]Konya Food and Agriculture University

Nezahat Gokce Ozsamur / Konya Food and Agriculture University

Introduction: G-quadruplex is a nucleic acid secondary structure formed in guanine-rich regions of DNA and RNA sequences. Four guanine molecules form a square planar arrangement in which each guanine is hydrogen-bonded to the two adjacent guanines to make tetramers. These structures are located at minisatellites, telomeres, mitotic and meioticdouble- strand break sites, and transcriptional start sites and are involved in several cellular processes, including gene transcription, translation, DNA replication, and genomic stability.

Methods: Novel cationic BODIPY-based G4 stabilizers designed for selective stabilization and oxidation of DNA. Ligands were synthesized and characterized. To determine the G-quadruplex binding affinity of ligands, FRET DNA melting analysis was done with the use of labeled G-quadruplex forming oligomers, including telomere, oncogene promoter fragments, and double-stranded DNA that does not form G-quadruplex. The ligand cytotoxicity was determined using MTT assay in MCF7 cell line. The effect of ligand on the expression of oncogenes was analysed. Oxidative potential of one of the ligands was investigated by monitoring the absorbance of 1,3-diphenylisobenzofirane singlet oxygen trap molecule.

Results and Discussion: MCF7 cells incubated under hypoxic environment are shown to display downregulation of oncogenes c-myc, bcl-2, and hif-1a in presence of ligands compared to the cells in normal oxygen atmosphere. The melting temperature of DNA oligomers is enhanced significantly as a result of stabilization. Efficient singlet oxygen generation with the oxidizing ligand was observed.

Conclusions: With this study, the first hypoxia-targeted G-quadruplex stabilizations.is reported with the potential of selective cancer therapy at the transcription level. Authors acknowledge the support by TÜBİTAK 2247 Program, Grant No: 120C125

Keywords: G-quadruplex, cancer, drug

Short Talk-7

THE EFFECT OF HYDROXYCHLOROQUINE IN eNOS SYSTEM

Muhammet Zahit Çelik[1], Cenk A. Andaç[2], Fatma Uysal[1], Seyfullah Oktay Arslan[1]

[1]Department of Medical Pharmacology, School of Medicine, Ankara Yıldırım Beyazıt University, Ankara
[2]Department of Medical Pharmacology, School of Medicine, Yeditepe University, Istanbul

Muhammet Zahit Çelik / Department of Medical Pharmacology, School of Medicine, Ankara Yıldırım Beyazıt University, Ankara

Introduction: Hydroxychloroquine (HCQ) is an antimalarial that is widely used in the management of rheumatoid arthritis and other autoimmune diseases. Although some cardiac adverse effects, mainly QT interval prolongation and cardiomyopathy, have been reported upon clinical application of HCQ, beneficial cardiovascular effects of HCQ in rheumatoid arthritis patients as well as its antihypertensive effects have also been reported [1]. We have previously reported that low concentrations of HCQ (10-6-10-5 M) induces endothelium-dependent vasodilation in rat aorta [2]. A series of inhibitors of K+ channels, Ca++ channels, COX enzymes and nitric oxide synthase were also used in presence of HCQ to shed light onto the mechanism of action of HCQ. We concluded that inhibition of Ca++ and K+ channels as well as the COX enzymes did not significantly alter the vasodilating effect of HQC, while the inhibition of eNOS increased the vasoconstriction of rat aorta. Therefore, we conducted a series of in-silico studies to address eNOS activation by HQC.

Methods: Autodock_vina (64 bit version) was used for docking computations. AMBER v20 suite of packages were used to carry out MD and MM-PBSA computations.

Results and Discussion: Caveolin-1 (Cav-1) is a modulatory protein that binds to eNOS to prevent eNOS activation by Calmodulin (CaM). Our docking and MD computations suggest that HCQ inhibits Cav-1+eNOS interaction to activate eNOS.

Conclusions: We conclude that HCQ exerts it effect by increasing membrane-bound concentration of activated eNOS.

Keywords: eNOS, HCQ, Cav-1, Dock, Molecular Dynamics

Short Talk-8

Development of Gold Nanoparticle Conjugated Drug Delivery Systems for Ovarian Cancer Treatment

Gizem Kursunluoglu[1], Cansu Umran Tunc[2], Muhammed Ihsan Han[3], Munevver Akdeniz[4], Aybuke Kutlu[4], Mukerrem Betul Yerer[5], Omer Aydin[6]

[1]NanoThera Lab, Drug Application and Research Center (ERFARMA), Erciyes University, 38039, Kayseri, Turkey,
[2]NanoThera Lab, Drug Application and Research Center (ERFARMA), Erciyes University, 38039, Kayseri, Turkey; Department of Biomedical Engineering, Erciyes University, 38039, Kayseri, Turkey
[3]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Erciyes University, Kayseri, Turkey
[4]NanoThera Lab, Drug Application and Research Center (ERFARMA), Erciyes University, 38039, Kayseri, Turkey; Department of Biomedical Engineering, Erciyes University, 38039, Kayseri, Turkey
[5]Drug Application and Research Center (ERFARMA), Erciyes University, 38039, Kayseri, Turkey; Department of Pharmacology, Erciyes University, Pharmacy Faculty, Kayseri, Turkey
[6]NanoThera Lab, Drug Application and Research Center (ERFARMA), Erciyes University, 38039, Kayseri, Turkey; Clinical Engineering Research and Implementation Center (ERKAM), Erciyes University, 38030, Kayseri, Turkey

Gizem Kursunluoglu / NanoThera Lab, Drug Application and Research Center (ERFARMA), Erciyes University, 38039, Kayseri, Turkey,

Introduction: Drug delivery systems help overcome these limitations and problems. In particular, nanotherapeutics are capable of improving the efficacy of chemotherapy drugs with their high carrier capacity and ability to load hydrophobic compounds. In this study, two different naproxen derivative potent chemotherapy drugs were synthesized and their anti-cancer activity was investigated in ovarian cancer cells. The low solubility of these drug candidates in aqueous media limits the determination of their effects and studies at high concentrations. In this study, to overcome the limitations caused by the insolubility of drug molecules, drug molecules were loaded onto the surface of gold nanoparticles (AuNPs).

Methods: The water distribution and bioavailability of drugs were investigated by binding to the surface of 13nm size AuNPs. Drug-AuNP conjugations were characterized by DLS and UV/Vis spectroscopy, NTA and their activity was studied in ovarian cancer cells.

Results and Discussion: With drug AuNP conjugation, the distribution of drugs in the aqueous medium was increased. Drug-AuNP conjugates increased anti-cancer activity compared to free drugs in ovarian cancer cells with excellent stability for up to 12 weeks. The increased solubility of the drug by AuNP conjugation showed that it enhanced the cytotoxic effect of drug molecules on cancer cells. With this developed nanoformulation, it was observed that apoptotic cells increased significantly and apoptosis increased in ovarian cancer.

Conclusions: The study demonstrated the increased efficacy of naproxen-derived hydrophobic drugs. Loading SH-containing drugs onto the surface of AuNPs may be a general strategy for increased solubility and utilization of hydrophobic therapeutics.

Keywords: Drug delivery, AuNPs, naproxen derivative drugs, ovarian cancer

Short Talk-9

Virtual Screening of Small Molecule Libraries Against ERCC1-XPF for the Identification of Potent Inhibitors

Salma Ghazy[1], Serdar Durdagi[1]

[1]Bahcesehir University

Salma Ghazy / Bahcesehir University

Introduction: A fundamental characteristic of cancer is its acquired ability to evade chemotherapeutic drugs. Nuclear excision repair is a pathway of choice in repairing DNA lesions brought about by drugs like Cisplatin. ERCC1-XPF complex plays the main role in this pathway, monitoring the healing of intrastrand Pt-DNA adducts in addition to interstrand crosslinks, and double-strand breaks. Unrepaired DNA lesions interrupt mechanisms such as DNA replication and transcription, inducing apoptosis to lead to cancer cell death and tumor diminishing. ERCC1-XPF also shares in preserving genome consistency. The inhibition of ERCC1-XPF – via substituting the side chain of the Phe293 residue on the ERCC1 protein in dimerization form with XPF – enhances chemotherapy and bypasses the resistance mechanism of cancer cells. This study aims to screen small molecule drug libraries to obtain compounds with ERCC1-XPF inhibiting properties through the molecules' binding affinities to the XPF protein's HhH2 domain with interaction sites I, II, and III.

Methods: The predicted binding affinities of compounds were computed by variousmolecular docking scoring functions, including Glide, AutoDock Vina, and GOLD. Next, a neural network model was constructed on Canvas and then evaluated, followed by the calculation of the R2 value for further optimization. Lastly, a molecular dynamics simulation was conducted to observe how a biomolecular system functions and interacts with its environment.

Results and Discussion: The highest docking scores were shown with interaction site II using Glide XP. RMSD values of MD simulations show a maximum value of 4Å.

Conclusions: Results seem promising and further drug libraries will be investigated in detail.

Keywords: MD simulation, Virtual screening, Cancer, Neural Network, ERCC1-XPF

Short Talk-10

Selagibenzophenone Derivatives as novel dual Topoisomerase I/II inhibitors: In vitro biological evaluation and in silico approaches

Serhat Donmez[1], Hazal Nazlıcan Atalay[1], Zeynep Ozlem Cinar[1], Ringaile Lapinskaite[2], Stefan Malatinec[2], Anil Odabasi[3], Gizem Nur Duran[4], Lukas Rycek[2], Mehmet Ozbil[4], Tugba Boyunegmez Tumer[5]

[1]Graduate Program of Molecular Biology and Genetics, School of Graduate Studies, Canakkale Onsekiz Mart University, Turkey
[2]Department of Organic Chemistry, Faculty of Science, Charles University, Czech Republic
[3]Robert College,Arnavutkoy, Besiktas, Istanbul, Turkey
[4]Biotechnology Institute, Gebze Technical University, Turkey
[5]Department of Molecular Biology and Genetics, Faculty of Science, Canakkale Onsekiz Mart University, Turkey

Serhat Donmez / Graduate Program of Molecular Biology and Genetics, School of Graduate Studies, Canakkale Onsekiz Mart University, Turkey

Introduction: The development of novel dual Topoisomerase I/II inhibitors is a novel approach in the treatment of cancer. In this study, novel Selagibenzophenone A-B derivatives (SDs) were synthesized and tested for their anticancer activities and dual topoisomerase I/II inhibition capacities by using in vitro and in silico techniques.

Methods: The cytotoxic effect of SD's on healthy, prostate, colon and breast cancer cells was determined by SRB assay. Then, long and short-term anticancer effects of lead compounds (IC50 $\leq$ 10 μM) on cancer cells were analyzed by wound healing and colony formation assays. The topoisomerase I/II dual inhibition potential of these compounds were elucidated by enzyme inhibition assays and molecular docking analyses. Binding free energy of protein-ligand complexes determined by molecular dynamic simulations.

Results and Discussion: The lead SD's were selectively inhibited the cell survival, migration and colony formation capabilities of the prostate and colon cancer cell lines with minimal effect on healthy cells. Moreover, the most effective SD's inhibited both Topoisomerases I and II enzyme activity. As in the same line with enzyme inhibition assays, in silico molecular docking and dynamics studies showed that these molecules yielded high binding affinity to topoisomerase's catalytic side. The lead compounds were also found to be druggable according to Lipinski and Veber filter.

Conclusions: In summary, SD's have the potential as dual topoisomerase inhibitors and canbe further developed as candidate anticancer agents. Further, in vitro/in vivo and in silico analyzes are being carried out by our research team to confirm their potency and to understand their mechanism of action.

Acknowledgement:

Keywords: Cancer, Topoisomerase, Dual inhibition, in silico molecular docking, in vitro

Short Talk-11

NisPec stabilized gold nanospheres as a detoxifier for toxic compounds and antimicrobial for pathogens

Zeynep Demirsoy[1], Melisa Aysan[2], Saliha Öçüt[2], Eda Eserözbek[2], Fatmanur Elif Sara[2], Mahmut Deniz Yılmaz[3], Gülcihan Gülseren[2]

[1]Department of Biotechnology, Konya Food and Agriculture University
[2]Department of Molecular Biology and Genetics, Konya Food and Agriculture University
[3]Department of Bioengineering, Konya Food and Agriculture University

Zeynep Demirsoy / Department of Biotechnology, Konya Food and Agriculture University

Introduction: Some chemical compounds cannot be metabolized and excreted by organisms, so they cause severe toxicity issues. To ensure systemic detoxification of those toxic compounds, enzymes can be used as ideal therapeutics owing to their high substrate specificity and catalytic efficiency, but their low stability and high immunogenicity limit their applications.

Methods: The NisPec stabilized gold nanospheres' oxidative catalytic ability was analyzed following the decrease of the morin absorption peak. The cytocompatibility of gold nanospheres was assessed by Alamar blue viability testing, and antimicrobial activity was analyzed with MIC assay by using gram-positive and negative strains.

Results and Discussion: To prevent the drawbacks of detoxifying enzymes, we synthesized gold nanospheres stabilized by the pectin-nisin conjugate, which are highly stable and cytocompatible. These nanospheres could effectively oxidize our model compound morin in the presence and absence of hydrogen peroxide via forming radical oxygen species (ROS). In addition to their detoxifier properties, our gold nanospheres showed antimicrobial properties for both gram-positive and negative bacteria, taking advantage of the high surface-to-volume ratio of gold nanospheres and antimicrobial properties of nisin antimicrobial peptide and pectin carbohydrate.

Conclusions: NisPec stabilized gold nanospheres hold great potential to be used as a detoxifier for toxic compounds that cannot be oxidized and cleaved from the organisms with their high oxidizing capability even in the absence of hydrogen peroxide, high stability, and cytocompatibility. Moreover, they can be used as an effective antimicrobial agent since they are not cytotoxic for human cells but show effective antimicrobial properties for gram-positive and negative bacteria.

Keywords: Gold Nanosphere, Nisin, Pectin, Detoxification, Antimicrobial

Short Talk-12

Exploring Drug Loading and Release Capacities of Hexagonal Boron Nitrides (hBNs) in Cancer Treatment

Misra Yamansavascilar Naganlu[1], Banu Kocaaga[1], Zehra Cobandede[2], Hulya Yilmaz[2], F. Seniha Guner[1]

[1]Istanbul Technical University, Department of Chemical Engineering, Maslak 34469 Istanbul
[2]Sabancı University, Nanotechnology Research and Application Center, Tuzla 34956 Istanbul

Misra Yamansavascilar Naganlu / Istanbul Technical University, Department of Chemical Engineering, Maslak 34469 Istanbul

Introduction: Cancer is one of the most serious diseases worldwide. The aim of this study is to carry out in vitro studies to investigate anticancer drug-loading and release efficiency of hBNs. The use of hBN in cancer treatment is very promising because of its small size, and unique physicochemical property including biocompatibility.

Methods: We used FT-IR, TEM, SEM, DLS, and AFM analysis to identify the conformational, morphological, and structural properties of hBNs after their synthesis process with a CVD method. In addition, we used UV/Vis, FT-IR, SEM, size distribution, and zeta potential to determine the drug-loading capacity.

Results and Discussion: We determined that hBNs have excellent uniformity, and platelet-like structures. Then, we observed the non-covalent interaction of drug-hBN in different pH mediums and with various drug concentrations in each pH medium to determine the optimum drug-loading condition. The results demonstrate that our maximum drug-loading value (%32.75, 0.657 mg/mg) has a high efficiency compared to other studies. Then, we observed the drug release studies in two different pH mediums which reflect pH of the cancer cell (pH 4.5), and the healthy cell, and bloodstream (pH 7.4).

Conclusions: It is expected from drug delivery systems that cancer drug should be as stable as possible in the nanocarrier-system; however, it should not be released into the bloodstream except for a minimum drug leakage (<10%). In this way, our drug release study had a <10% amount in pH 7.4 PBS medium. This implies that our study is extremely promising, and our drug-hBN nanosystem will be significantly successful in cancer treatment.

Graphical Abstract
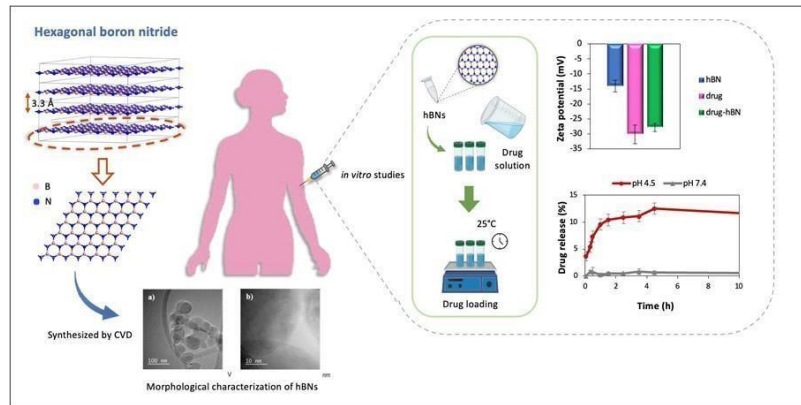
In vitro drug release studies of hexagonal boron nitrides which synthesized by chemical vapor deposition method

Keywords: cancer treatment, drug delivery, targeted delivery, hexagonal boron nitrides

Rational Design Strategy for a Genetically Encoded Iron Biosensor

Melike Berksöz[1], Canan Atılgan[1]

[1]Sabancı University

Melike Berksöz / Sabancı University

Introduction: Genetically encoded fluorescent biosensors (GEFB) are molecular tools that couple ligand-induced conformational changes to a fluorescence output. Structural determinants of successful biosensors are difficult to predict which makes the development of new biosensors a long trial-and-error process. In this work, we propose a design strategy that combines Alphafold2 (AF2) with all-atom molecular dynamics (MD) simulations for predicting GEFB structure and dynamics. H. influenza ferric binding protein (FBP) is selected as a model sensor protein.

Methods: We constructed the primary sequence of the biosensor by inserting a circularly permuted green fluorescent protein into a loop in FBP which allosterically controls iron binding dynamics. Consequently, we utilized Colabfold to predict the apo and holo forms of the sensor. Highest scoring models were chosen as the initial structures for 1 μs-long MD simulations. For control purposes, we also simulated bright and dark forms of wild type (WT) green fluorescent protein (GFP).

Results and Discussion: AF2-predicted biosensors are predicted to fold properly without the need for any interdomain linkers. Occupancies of hydrogen bonds involving chromophore atoms differ between the bright and dark forms of WT-GFP, as well as between the apo and holo forms of the designed biosensor. Strikingly, hydrogen bond occupancies calculated from the equilibrated trajectories of the apo form and the bright state of the GFP have matching profiles.

Conclusions: Our results suggest that hydrogen bond dynamics around the chromophore can be a good predictor of biosensor efficiency. We believe this approach can help accelerate development of a broader range of fluorescent biosensors.

Keywords: Genetically Encoded Fluorescent Biosensor, Alphafold 2, Molecular Dynamics Simulations, Chromophore Charge State, Hydrogen Bond Dynamics

Synthesis, Structure Elucidation and Molecular Docking Studies of Novel Thiosemicarbazide Derivatives

Nazar Dokumacı[1], Murat Oluş Özbek[2], Göknil Pelin Coşkun[1]

[1]Acıbadem Mehmet Ali Aydınlar University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry
[2]Gebze Technical University, Faculty of Engineering, Department of Chemical Engineering

Nazar Dokumacı / Acıbadem Mehmet Ali Aydınlar University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry

Introduction: Gastric infections are one of the leading cause of mortality among the other infections. Prolongation of the ulcer treatment in the gastrointestinal system could be a result of Helicobacter pylori infection. The focus on urease enzyme in H. pylori related infections is the answer for prolonged gastric ulcerations. Therefore, here in this study, new molecules which may posses urease inhibition activity were synthesized.

Methods: To synthesize the novel compounds, 4-amino salicylic acid (4-ASA) was chosen as the starting compound. 4-ASA is heated under reflux in the presence of methanol and sulphuric acid to give compound 1. Compound 1 is then heated with hydrazine hydrate to give compound 2. The substituted isothiocyanates were added to compound 2 in the presence of ethanol and refluxed for 20-72 h. All the synthesized compounds were monitored using TLC. The purity of the compounds were proven by LCMS (Agilent 1220) and MS (Advion Expression CMS) analysis. The structures of the compounds were elucidated using 1H-NMR and 13C-NMR (BRUKER 400 MHz ,Billerica, MA). The docking studies were performed in AutoDock program. The crystal structures of the H.pylori HypB and Urease were downloaded from protein data bank (PDB) (accession code: 4LPS and 1E9Z, respectively) (http://www.rcsb.org/pdb/).

Results and Discussion: The structural analysis of the thiosemicarbazides were correlated with the literature data. The synthesized compounds showed remarkable urease inhibitory activity compared to the standart urea.

Conclusions: The synthesized thiosemicarbazides have a great potential to be the new urease inhibitors for H. pylori treatment.

Keywords: 4-ASA, thiosemicarbazide, urease, docking, LCMS

Short Talk-15

A novel 4-thiazolidinone derivative induces cell death in hepatocellular carcinoma cells: in vitro assay, molecular docking, and ADME studies

Faika Başoğlu Ünal[1], Eda Becer[2], Hilal Kabadayı Ensarioğlu[4], Nuray Ulusoy Güzzeldemirci[5], Ebru Didem Coşar[5], H. Seda Vatansever[4]

[1]European University of Lefke, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Lefke, Northern Cyprus, TR-10 Mersin, Turkey.
[2]Eastern Mediterranean University, Faculty of Pharmacy, Famagusta, North Cyprus.
[3]DESAM Institute, Near East University, Nicosia, Northern Cyprus, TR-10 Mersin, Turkey.
[4]Manisa Celal Bayar University, Faculty of Medicine, Department of Histology and Embryology, Manisa, TURKEY
[5]İstanbul University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, İstanbul, TURKEY.

Faika Başoğlu Ünal / European University of Lefke, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Lefke, Northern Cyprus, TR-10 Mersin, Turkey.

Introduction: Thiosemicarbazones are drug candidate heterocyclic compounds due to their biological activities such as anti-tumor, anti-inflammatory, antimicrobial and antidiabetic. The main purpose of this study that investigates the effect of a novel 4-thiazolidinone derivative bearing imidazo[2,1-b]thiazole application in hepatocellular carcinoma cells.

Methods: The designed and synthesized compound was characterized using various spectroscopic methods. The effective dose of 4-thiazolidinone derivative was determined by MTT analysis. After thiazolidinone untreated (control) and treated cells were fixed with 4% paraformaldehyde, the distributions of Bax, Caspase3, Ki67, RIP3, and RIPK1 were analyzed by indirect immunoperoxidase method. Furthermore, the binding interaction of the designed compound to Bax, and Caspase-3 were elucidated using an in silico molecular docking software.

Results and Discussion: After thiazolidinone application, an increase was observed in Bax, Caspase3 immunoreactivities compared to the control group. In addition, Ki67 immunoreactivities were decreased, while RIP3 and RIPK1 immunoreactivities were similar to the control group. Our results showed that the 4-thiazolidinone derivative induced apoptotic cell death rather than necroptosis. Furthermore, a molecular docking study was carried out to elucidate the affinity and interactions in the active site of BAX and Caspase-3. As the results of the molecular docking studies, it was observed that the compound exhibits H-bond interaction with various significant amino acid residues in the active site of both BAX and Caspase-3.

Conclusions: In conclusion, this study exhibited that a novel 4-thiazolidinone derivative illustrated great anticancer activity on HepG2 cells via inducing apoptotic cell death. Furthermore, some critical interactions between the synthesized compound and the active site of the BAX and Caspase-3.

Keywords: Thiazolidinone, Hepatocellular carcinoma, Apoptosis, Molecular docking

Short Talk-16

Drug-Gene Interaction-based Pre-Existing Biological Knowledge

Ümmü Gülsüm Söylemez[1], Fei Zou[2], Burcu Bakır-Güngör[3], Malik Yousef[4]

[1]Muş Alparslan University
[2]University of North Carolina
[3]Abdullah Gul University
[4]Zefat Academic College

Malik Yousef / Zefat Academic College

Introduction: A Drug-Gene interaction is a relationship between a drug and a genetic variation that may have an impact on a patient's response to drug therapy. Numerous machine learning models were presented to examine this interaction on the biological knowledge. Breast cancer is the second most common type of cancer worldwide and is the leading cause of cancer-related death among women. Diagnosis of breast cancer and diagnosis by interpreting test results require expert human knowledge, but successful studies are carried out in the diagnosis of breast cancer with the development of machine learning techniques.

Methods: The current work is aimed to develop a novel prediction approach based on the Grouping-Scoring-Modeling(G-S-M) approach. Grouping that can correctly make predictions about having breast cancer or not based on drug-gene interaction. Our approach has three main parts. The first one is a grouping that includes pre-existing biological knowledge about the interaction between drugs and genes. Each drug has its own, interacting partner genes. Along this line, we had drug groups. We then scored each group according to the criterion of success in distinguishing capability. This step is the second main part. According to the scoring, we ranked each group. Next, we send it to the modeling part for classification. We used a random forest model for the modeling part, and this is the last main part.

Results and Discussion: The results demonstrated that our novel method has a considerable success for all performance measures.

Conclusions: Our method will play an important role in disease prediction based on drug gene interaction.

Keywords: Drug Response, Drug-Gene Interaction, Breast Cancer

Paclitaxel-loaded Graphene Nanocarriers with Antidot Nanoholes

Sahila Jabrayilova[1], Mehdi Meran[1]

[1]Bioengineering Department, Faculty of Engineering and Natural Sciences, Üsküdar University

Sahila Jabrayilova / Bioengineering Department, Faculty of Engineering and Natural Sciences, Üsküdar University

Introduction: The development of novel and effective drug delivery systems with the ability to exhibit the desired therapeutic profile and efficacy is one of the fundamental problems confronted by modern nanomedicine. Various investigations have been carried out to develop new approaches for effective drug delivery systems using numerous nanocarriers, such as dendrimers, polymeric particles, liposomes, and micelles. Two-dimensional (2D) nanomaterials such as graphene and its derivatives have been under investigation due to their outstanding structural characteristics at the nanoscale level which make them suitable for biological settings.

Methods: Herein all-atom molecular dynamics simulations were employed to study graphene loaded with paclitaxel drug molecules. The graphene nanocarriers were first decorated with rhombus nanoholes. The objective was to investigate the arrangement and binding of drug molecules into graphene with antidote nanoholes. All the simulations are performed using the LAMMPS software package. Nose-Hoover thermostat was used to control the constant temperature at 300 K. All MD simulations were carried out with the velocity Verlet numerical integrator. After the relaxation period, the system is undergone MD simulation for a total duration of 10.0 ns using a 1.0 fs time step.

Results and Discussion: The drug molecules' free binding energies, RDF, MSD, and density distribution analysis were studied.

Simulation Scheme
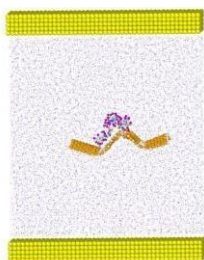
Conclusions: The results showed that the arrangement of nanoholes and their diameter have different effects on the binding energy of the PTX molecules. It is observed that there is a threshold in the diameter at which drug molecules lose their van der Waals interactions with graphene nanocarriers.

Keywords: Nanohole, Nanocarrier, Graphene, Paclitaxel, Cancer

Short Talk-18

Interaction Surface of Bcl-2 and Beclin 1 was Revealed by Mass Spectrometry

Miray Turk[1], Yagiz Akbas[1], Ozge Tatli[2], Baran Dingiloglu[1], Gizem Dinler Doganay[1]

[1]Istanbul Technical University
[2]Istanbul Medeniyet University

Miray Turk / Istanbul Technical University

Introduction: Bcl-2 is responsible for intrinsic apoptosis initiation. Its interaction partner Beclin 1 forms pre-autophagosomal complex in macro-autophagy. Interaction of Bcl-2 with Beclin 1 prevents Beclin 1 from forming pre-autophagosomal complex and inhibits autophagy initiation. Hence, Bcl-2/Beclin 1 complex generates a decision point between apoptosis and autophagy. Although certain interaction points were determined in the literature, comprehensive studies are still needed to fully reveal their interaction surface. We aimed to probe binding interface of native Bcl-2 and Beclin 1. Determination of this surface may provide druggable sites which can be targeted by anti-cancer drugs.

Methods: Full-length Bcl-2 and Beclin 1 proteins were produced in mammalian cells and affinity purified. Activity of proteins was verified in vitro via interaction assays. Interaction region of Beclin 1 with Bcl-2 in Bcl-2/Beclin 1 complex was revealed by limited tryptic digestion coupled with LC/MS/MS.

Results and Discussion: Bcl-2 and Beclin 1 proteins were successfully purified with >80% purity. Their interaction capability was verified by in vitro interaction methods. Peptides acquired from tryptic digestion, indicating interaction region of Beclin 1 with Bcl-2 in Bcl-2/Beclin 1 complex, were identified with LC-MS/MS. ECD and BH3 domains of Beclin 1 were found to be the key interaction points between Bcl-2 and Beclin 1.

Conclusions: BH3 domain of Beclin 1 was accepted as the main interaction point between Bcl-2 and Beclin 1 up to date. According to our data, ECD domain of Beclin 1, in addition to the BH3 domain, is found critical for their interaction and offers this domain as potential druggable site.

Keywords: Bcl-2, Beclin 1, Apoptosis, Autophagy

Development of Peptide Nanofiber Antiviral Treatment

Gülcihan Gülseren[1]

[1]Konya Food and Agriculture University

Gülcihan Gülseren / Konya Food and Agriculture University

Introduction: The development of treatment methods for antiviral treatments has become a major and shared challenge for all scientific disciplines. Multifunctional nanoparticles emerged as a potential solution with their target-specific designs. Especially peptide nanofibers hold a significant place among these nanomaterials due to their multi-epitope presenting surfacearea, biocompatibility, and easily modifiable features. These structures offer a wide range of applicability, including both protein mimicry and native protein inhibition.The ultimate goal of our study is to develop a successful treatment system against lung pathogens.

Methods: Inhibitor binding experiments, cell culture, peptide characterization, molecular modeling

Results and Discussion: In this proposed study, two different inhibitor peptide sequences presenting peptide amphiphiles were utilized to inhibit the receptor-binding domain of the spike protein. The first epitope is inspired by heparin which is commonly used for SARS-CoV-2 treatment and the second epitope is the RBD inhibitor peptide sequence. The inhibitor was administered as nanofiber and protein binding was successfully exhibited. The binding energy of the heparin-binding sequence was calculated as -51.2 kcal/mol by our group, which is considered a promising result. In addition, low MW heparin was considered quite effective for the treatment of lung diseases.

Conclusions: As it is known, antiviral treatment studies require long processes. This study consisting of easily attainable components will be able to offer effective solutions in a faster fashion. The system to be prepared can be manipulated with different epitopes, and cystic fibrosis, lung cancer, etc.

Keywords: Peptide amphiphies, nanofibers, bioactive domains, inhibitor, antimicrobial

Synthesis of Beta-Carboline derivatives

Serkan Öncüoğlu[1], Alper Köse[1], Emre Gitgör[1]

[1]Dokuz Eylul University Faculty of Science Department of Chemistry

Serkan Öncüoğlu / Dokuz Eylul University Faculty of Science Department of Chemistry

Introduction: Phosphodiesterase type 5 (PDE5) is a key enzyme involved in theregulation of cGMP-specific signaling pathways by catalyzing thehydrolysis of the cyclic nucleotide cGMP into guanosine monophosphates.It's an essential regulator in normal physiologicalprocesses such as smooth muscle contraction and relaxation and it isthe major PDE isozyme in penile corpus cavernosum tissue that playsa key role in the control of penile erection. Tadalafil is anorally active tetrahydro-b-carboline (THBC) derivative with PDE5inhibitory properties that is marketed for the treatment of maleerectile dysfunction. Its local vasodilatation action is mediatedthrough high levels of cGMP in male corpus cavernosum. Azatoxin and derivatives there of formula B-D are illustrative of a new class of antitumor drugs that are topoisomerase II (top 2) inhibitors. The pharmacophore inhibits the catalytic activity of the purified enzyme but does not unwind relaxed or supercoiled DNA.

Methods: Beta-carboline derivative was formed as a result of sequential reactions by leaving L-tryptophan. Then, new tadalafil and azatoxin-like compounds were synthesized by forming the fourth ring on this compound

Synthesis Plan
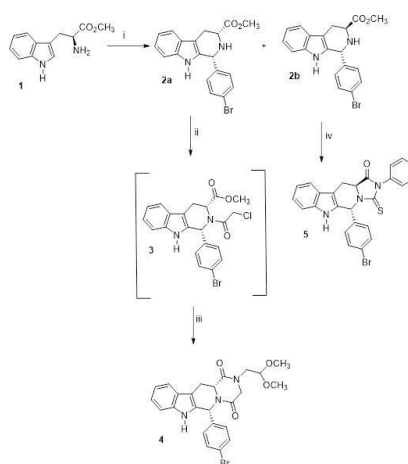
Results and Discussion: Some derivatives have been synthesized. Studies are ongoing to test the biological affinities of these compounds. It is aimed to derivatize compounds according to the recommendations of in silico studies

Conclusions: Beta carboline derivatives, which can be topoisomerase 2 inhibitors and phosphodiesterase 5 inhibitors, have been synthesized

Keywords: PDE5 inhibitors, topoisomerase inhibitors, tadalafil, azatoxin

Short Talk-21

Design of Tomentosin Moiety Sulfamide Derivatives and Investigation on Their Interaction with Anticancer-related Enzyme Topimerase II via In silico Approaches

Ahmet Çağan[1], Akın Akıncıoğlu[1], Tuba Aydın[1]

[1]Agri İbrahim Çeçen University

Ahmet Çağan / Agri İbrahim Çeçen University

Introduction: Molecular docking studies in medicinal chemistry before synthesis means saving money and time in today's conditions. In this way, it is possible to distinguish the most suitable ones for the desired result among many possible derivatives to be synthesized.

Tomentosin and Sulfamide Derivatives
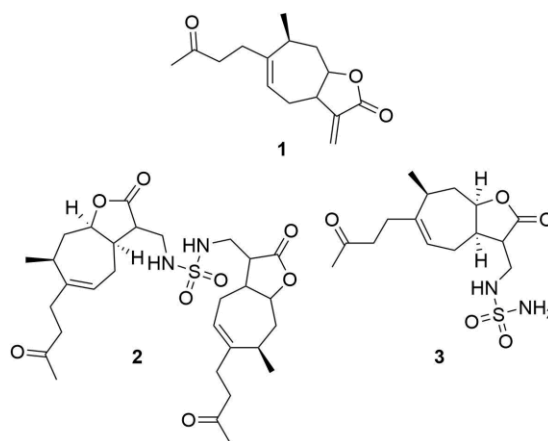
Methods: Tomentosin (1) is a natural sesquiterpene lactone-derived substance found in the flowers of Inula japonica (Piao et al. 2016), Inula viscosa, as well as many Inula subspecies, Carpesium faberi, Pulicaria undulata and many more. It is known to have antifungal, anti-inflammatory, and anti-cancer effects (Abdallah et al. 2019). In addition, it is also known that sulfamide derivatives show anticancer activities (Supuran et al. 2003).

Results and Discussion: In this study, interactions of sulfamide derivatives 2 and 3 with Topoisomerase II (PDB ID: 4FM9) enzyme were investigated using molecular docking method by Chimera 1.16.

Conclusions: 1.Piao, D., Kim, T., Zhang, H. Y., Choi, H. G., Lee, C. S., Choi, H. J., ... & Son, J. K. (2016). DNA topoisomerase inhibitory activity of constituents from the flowers of Inula japonica. Chemical and Pharmaceutical Bulletin, 64(3), 276-281. 2.Abdallah, H. M., Mohamed, G. A., Ibrahim, S. R. M., Asfour, H. Z., & Khayat, M. T. (2019). Undulaterpene A: A new triterpene fatty acid ester from Pulicaria undulata. Pharmacognosy Magazine, 15(65), 671.3.Supuran, C. T., Casini, A., & Scozzafava, A. (2003). Protease inhibitors of the sulfonamide type: anticancer, antiinflammatory, and antiviral agents. Medicinal Research Reviews, 23(5), 535-558.

Keywords: docking, tomentosin

PP-1

Development Of Novel Fluorescent Tyrosınase Enzyme Sensor and Tyrosınase Actıvable Photodynamıc Therapy Agent

<u>Imran Verirsen</u>[1], Busra Uyar[1], Naime Demirok[1], Nezahat Gokce Ozsamur[1], Sundus Erbas Cakmak[1]

[1]Konya Gıda ve Tarım Üniversitesi

Imran Verirsen / Konya Gıda ve Tarım Üniversitesi

Introduction: Tyrosinase is involved in melanin production and is an important biomarker for some diseases including melanoma. In the project, a novel near-IR emitting fluorescent tyrosinase probe and an enzyme-activatable photodynamic therapy (PDT) agent were synthesized. Tyrosinase-dependent oxidation leads to convertion of pyridinium BODIPYs to pyridine derivatives and either increases fluorescence or PDT activities. Selective activities of the probe and PDT agent were demonstrated in B16-F10 mouse melanoma cells.

Methods: Compounds were synthesised and characterised by Nuclear Magnetic Resonance (1H, 13C) and HRMS spectrometry. Photophysical properties of molecules were determined by UV-Vis and fluorescence spectroscopic analysis. Cytotoxicities were determined by MTT assay. In vitro tyrosinase imaging and tyrosinase dependent therapeutic effects were tested on tyrosinase producing B16 cells and compared with MCF7 and HEP3B cells in the presence or absence of enzyme inhibitor.

Results and Discussion: Strong emission and PDT dependent phototoxicity were observed by the probe and PDT agent respectively, in tyrosinase expressing cells compared to other. Probe is not toxic at the application dose while PDT agent display significant toxicity upon irradiation. Kojic acid, tyrosinase inhibitor, is shown to decrease both fluorescence and PDT action further demonstrating the tyrosinase dependency of the agents.

Conclusions: Project would contribute to the field of biosensors and personalized photodynamic therapy, will inspire the development of new generation smart probes and therapeutic agents.Project is supported by TÜBİTAK 1001, grant no: 221Z058.

Keywords: tyrosinase enzyme, fluorescent sensor, activatable photosensitizer, melanoma cancer

PP-2

CREATION OF HOMOLOGY MODELS OF SOME HIV-1 INTEGRASE MUTATIONS AND INVESTIGATION OF THEIR RELATIONSHIP WITH CABOTEGRAVIR BY IN SILICO METHODS

Hasan Tahsin Şen[1], Ofcan Oflaz[1], İsmail Çelik[2]

[1]Lokman Hekim Üniversitesi
[2]Erciyes Universty

Hasan Tahsin Şen / Lokman Hekim Üniversitesi

Introduction: The human immunodeficiency virus (HIV) is the virus that causes worldwide HIV infection and causes acquired immunodeficiency syndrome (AIDS) when the most advanced stage. HIV is spread through contact with the in biological fluids. Integration of viral DNA into cellular DNA is an essential step in the replication cycle of HIV and other retroviruses. The first antiviral drugs used to target integrase. After an HIV-positive person begins ART, drug resistance may develop due to mutation. Analyzing changes in protein structures caused by mutations is important in the management of therapy and the development of new active substances.

Methods: Integrase mutations causing raltegravir and elvitegravir resistance and interaction with cabotegravir that the current integrase inhibitor, were analyzed in-silico. E138A, G163R and S230R mutations with low-level resistance to raltegravir and elvitegravir were analyzed. Homology models created via Swiss-Model. The homology models were analyzed using the UCSF Chimera 1.16 program. Docking scores were obtained with homology models and raltegravir and elvitegravir against cabotegravir docking study. Molecular docking studies were performed using the Glide module of Schrödinger software 2022-1 version and these scores were interpreted for drug resistance statutes. Molecular dynamics simulations were performed with Gromacs for the investigation of protein-ligand complex stability obtained from molecular docking studies.

Results and Discussion: Our study it is suggested that cabotegravir will be more effective on mutations or be compatible with other drugs.

Conclusions: Our study will contribute to the literature and will pave the way for the development of new active substances.

Keywords: HIV, Drug Resistance, In Silico, Docking, Dynamics Simulations

The Degradation Reaction Mechanism of Ampicilin with Hydroxyl Radical

Şeyda Aydoğdu[1], Arzu Hatipoğlu[1]

[1]Yildiz Technical University, Department of Chemistry, 34220, Istanbul, Turkey

Şeyda Aydoğdu / Yildiz Technical University, Department of Chemistry, 34220, Istanbul, Turkey

Introduction: Antibiotics are used to prevent and treat diseases for humans and animals [1]. Due to the widespread use of antibiotics, their residues are increasingly detected in aquatic environments and even in drinking water [2, 3]. Although in low concentrations, they are harmful to both humanity and the ecosystem due to their antibiotic resistance. The beta-lactam antibiotics constitute one of the oldest and most widely used anti-bacterial agents [4]. Ampicillin (AMP) is an important beta lactam antibiotic. Because of the toxic effects and antibiotic resistance of AMP residuals, effective techniques need to be designed to remove them from aquatic environments. However, the detailed explanation of mechanisms and determination of intermediates can not be fully explained by experimentally.

Methods: In this work, the degradation mechanism of ampicillin with OH radical was investigated by Density Functional Theory (DFT). The molecular structures of all reactants, prereactive complexes, transition states, and products were optimized at the B3LYP/6-31G (d,p) level. The solvation effects were computed using the Conductor Like Polarizable Continuum Model (CPCM).

Results and Discussion: The rate constants of all the possible reaction paths were calculated by means of the Transition State Theory. The branching ratios, product distributions, and thermodynamic properties were also calculated.

Conclusions: The primary reactions of AMP+OH reaction are divided into two patterns, hydrogen abstraction and hydroxyl radical addition.

Keywords: Antibiotics, Ampicillin, DFT, kinetic, water

Molecular Docking Study of Some Nitro-Substituted Benzamide Compounds as Cyclin-Dependent Kinase Inhibitors and The Anticancer Activity in TNBC cells

Gulce Davutlar[1], Nebahat Sahin[1], Ozlem Maraba[1], Mehmet Ay[2], Ferah Comert Onder[3]

[1]Çanakkale Onsekiz Mart University, School of Graduate Students, Department of Medical System Biology, Çanakkale, Türkiye
[2]Çanakkale Onsekiz Mart University, Faculty of Science, Department of Chemistry, Natural Products and Drug Research Laboratory, Çanakkale, Türkiye
[3]Çanakkale Onsekiz Mart University, Faculty of Medicine, Department of Medical Biology, Çanakkale, Türkiye. 2Çanakkale Onsekiz Mart University, Faculty of Science, Department of Chemistry, Natural Products and Drug Research Laboratory, Çanakkale, Türkiye

Gulce Davutlar / Çanakkale Onsekiz Mart University, School of Graduate Students, Department of Medical System Biology, Çanakkale, Türkiye

Introduction: Triple negative breast cancer (TNBC) is a highly aggressive and the most common subtype of breast cancers. The treatments in patients cannot be achieved with known inhibitors. Therefore, there is an increasing interest to find new and potential therapeutics against effective drug targets. CDKs that are crucial regulatory enzymes in the cell cycle progression, are called cyclin-dependent protein kinases. The development of effective CDK4/6 inhibitors has become a promising cancer therapy. Nitro-containing amide compounds have been widely used and are known for their anticancer activities.

Methods: The aim of this study is to examine the synthesized eight compounds against CDK4/6. In silico molecular docking study was carried out by the Glide/SP method of Maestro Schrödinger. The anticancer activity potentials of the compounds were screened in TNBC cell lines in in vitro analysis such as colony formation and cell proliferation as dose- and time-dependent manner studies. Molecular network analysis for protein was visualized and protein-protein interaction analysis was carried out.

Results and Discussion: According to our in vitro results, all compounds were tested in various TNBC cell lines. Several compounds were displayed with high inhibition potential and cytotoxicity in MDA-MB-231 and BT549 cell lines at very low concentrations. The colonies of TNBC cell lines were inhibited between 1 and 5 μM concentrations. The hydrogen binding was observed between the compounds and related amino acid residues in the binding pocket of the target.

Conclusions: Therefore, these nitro-containing aromatic amide compounds may be used for further in in vitro and in vivo studies as potential candidates of CDK4/6.

Keywords: CDK4/6, nitro-compounds, TNBC, molecular docking

In Silico Determination of Potential Candidates as AXL Kinase Inhibitors

Nebahat Sahin[1], Bulent Ozpolat[2], Ferah Comert Onder[3]

[1]Çanakkale Onsekiz Mart University, School of Graduate Students, Department of Medical System Biology, Çanakkale, Türkiye
[2]Houston Methodist Research Institute, Department of Nanomedicine. Neil Cancer Center-Houston Methodist, Director of Innovative Cancer Therapeutics, USA
[3]Çanakkale Onsekiz Mart University, Faculty of Medicine, Department of Medical Biology.
1Çanakkale Onsekiz Mart University, School of Graduate Students, Department of Medical System Biology, Çanakkale, Türkiye

Nebahat Sahin / Çanakkale Onsekiz Mart University, School of Graduate Students, Department of Medical System Biology, Çanakkale, Türkiye

Introduction: Triple negative breast cancer (TNBC) is very aggressive and is a subtype of breast cancer. AXL receptor tyrosine kinase is a transmembrane protein that is overexpressed in various cancers, including TNBC and plays a role in the development of resistance to chemotherapy and immunotherapy. Blocking the overexpression and activity of AXL is a strategy for the treatment of TNBC. Its overexpression is associated with adverse outcomes for patients.

Methods: The aim of this study is to determine the new therapeutics with in silico analysis against AXL. The generation of pharmacophore model and pharmacophore-based screening were performed by using a reference compound that has previously reported as an inhibitor of AXL in TNBC cell lines. For this purpose, various small molecule chemical databases were screened to find new analogs as potential candidates. Furthermore, the pharmacokinetic and drug-likeness properties were investigated in in silico analysis. Following the screening, molecular docking study was carried out by Glide/SP method.

Results and Discussion: As a result of these studies, the resulted compounds have been identified with high binding energies than reference compound. Hydrogen bonding interactions were observed with various amino acid residues such as Met623 and Asp627 between protein-ligand complex.

Conclusions: Thus, these results have showed that these molecules may be evaluated in in vitro cancer studies and used for the development of new analogs of AXL kinase inhibitor. This study was supported by Çanakkale Onsekiz Mart University, The Scientific Research Coordination Unit, Project number: TYL-2022-3990 and by The Scientific and Technological Research Council of Turkey (TÜBİTAK, 2210C scholarship program).

Keywords: AXL, molecular docking, pharmacophore, screening

{In-silico} Study on the Effect of Pro 120 Ser Mutation on NPC-2 Protein

Kamer Nisa BAZ[1], Mehmet ÖZBİL[1]

[1]Institute of Biotechnology, Gebze Technical University

Kamer Nisa BAZ / Institute of Biotechnology, Gebze Technical University

Introduction: Niemann-Pick Type C is a disorder results from mutations in either NPC-1 or NPC-2 genes, which cause accumulation of cholesterol in the lysosomal system. A P120S mutation in NPC-2 protein causes failure for binding cholesterol and stimulate cholesterol transfer. Although the mutation is known, in-silico analysis hasn't been performed. The aim is to observe the effect of P120S mutation on NPC-2 protein computationally.

Methods: The crystal structure NPC-2 protein was obtained from PDB (ID:6W5V). Wild type (WT) and P120S mutant NPC-2 was simulated for 100 nanoseconds by using YASARA Structure software and YASARA2 force field. Then, RMSD, RMSF, Rg and SASA analysis were performed. Also, cholesterol was docked to crystal WT NPC2, WT NPC2 from MD, and mutant NPC2 from MD, by using YASARA Structure software.

Results and Discussion: According to analysis, P120S mutation causes decrease in RMSD, thus, stabilising the protein structure. Also, based on RMSF analysis, mutation decreased the flexibility in three regions that interact with each other and form cholesterol binding site. Therefore, the elasticity change in these regions may affect cholesterol binding, transport and binding of NPC-1 and NPC-2 proteins. In docking study, cholesterol binding affinity of mutant protein was slightly worse than crystal WT NPC2. However, the proper cholesterol binding to WT NPC from MD couldn't be observed due to crowded environment formed by residues. This result is a verification of induced fit mechanism of cholesterol binding.

Conclusions: In summary, it is computationally shown that P120S mutation of NPC-2 protein could modify the binding site of cholesterol to NPC-2 protein.

Keywords: The Niemann-Pick Type C disease, in-silico molecular dynamics, in-silico molecular docking

In silico discovery of potential azole-containing mPGES-1 inhibitors by virtual screening, pharmacophore modeling and molecular dynamics simulations

L alehan Özalp[1], İlkay Küçükgüzel[1], Ayşe Ogan[1]

[1]Marmara University

Lalehan Özalp / Marmara University

Introduction: Inhibition of microsomal prostaglandin E2 synthase-1 (mPGES-1) is promising for designing novel nonsteroidal antiinflammatory drugs, as they lack side-effects associated with inhibition of cyclooxygenase enzymes (Bülbül, 2019). Azole compounds are nitrogen-containing heterocycles and have a wide use in medicine and are considered as promising compounds in medicinal chemistry (Bhagat J,, 2021).

Methods: Structure-based virtual screening was performed to screen over 1 million azole compounds (Figure 1). Receiver operator characteristic (ROC) curves were used to evaluate the selectivity of each program. Furthermore, scoring power of Autodock4 and Autodock Vina was assessed by Pearson's correlation coefficients. Pharmacophore models were generated and Güner-Henry score of the best model was calculated as 0.89. The best compound was subjected to 100 ns molecular dynamics simulations.

Workflow of screening a large set of compounds followed in the present study, with number of compounds remained at each stage
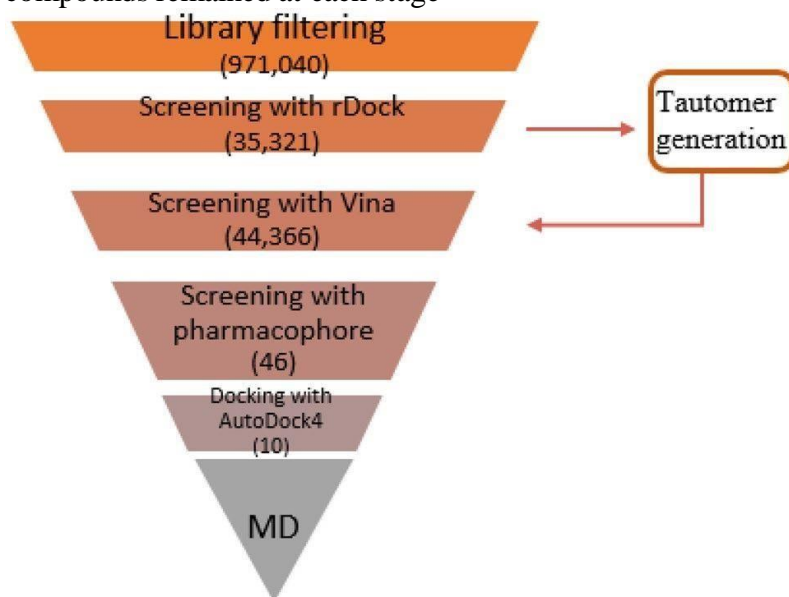
Results and Discussion: Binding modes of the final 10 azole compounds were analyzed and further investigation of the best binding (− 8.38 kcal/mol) compound was performed using molecular dynamics simulation, revealing that furazan1224 (ZINC001142847306) occupied the binding site of the substrate, prostaglandin H2(PGH2) and remained stable for 100 ns. Continuous hydrogen bonds and hydrophobic interactions with amino acids in the active site supported the stability of furazan1224 throughout the trajectory. Hydrogen bonds analysis supports this as stable hydrogen bonds interactions were observed with amino acids in the binding site, including Leu121, Arg126. Pharmacokinetic profile (Table 1) showed that furazan1224 lacks the risks of inhibiting cytochrome P450 3A4 enzyme and central nervous system-related side-effects.

Conclusions: Furazan1224 (ZINC001142847306) is promising as a potential mPGES-1 inhibitor regarding its stability in the enzyme cavity and considerably safe pharmacokinetic profile.

Pharmacokinetic properties of the best candidates for mPGES-1 inhibitor in the study.

ID	GI absorption [1]	BBB permeant [2]	P-gp substrate [3]	CYP1A2 inhibitor [4]	CYP2C19 inhibitor [5]	CYP2C9 inhibitor [6]	CYP2D6 inhibitor [7]	CYP3A4 inhibitor [8]
furazan1224	High	No	Yes	No	Yes	No	No	No
furazan3510	High	No	Yes	No	No	No	No	No
furazan1199	High	No	Yes	Yes	No	No	Yes	Yes
furazan909	High	No	Yes	No	No	No	No	No
furazan856	High	No	No	No	No	No	No	No
furazan1014	High	No	Yes	Yes	No	No	No	No
oxadiazole1769	High	No	Yes	No	No	No	No	No
triazole1047	Low	No	No	No	No	No	No	No
oxadiazole1006	High	No	No	No	No	No	No	No
oxadiazole1011	High	No	No	No	No	No	No	No

[1] Gastrointestinal absorption
[2] Blood-brain barrier permeability
[3] P-glycoprotein substrate
[4] Cytochrome P450 1A2 inhibitor
[5] Cytochrome P450 2C19 inhibitor
[6] Cytochrome P450 2C9 inhibitor
[7] Cytochrome P450 2D6 inhibitor
[8] Cytochrome P450 3A4 inhibitor

Keywords: Anti-inflammatory drug, mPGES-1, virtual screening, molecular dynamics, pharmacophore modeling

Tacrine-Hydrazone Compound as Multi-Target Agent for The Treatment of Alzheimer's Disease and Type II Diabetes Mellitus: Design, Synthesis and Bioactivity Studies

Verda Begüm Tezcan[1], Zeynep Deren Bülbül[1], Eylül Özen[1], Gülşah Bayraktar[2], Şirin Uysal[2]

[1]İzmir Bahçeşehir 50th Years Anatolian High School
[2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ege University, Izmir, Turkey

Verda Begüm Tezcan / İzmir Bahçeşehir 50th Years Anatolian High School

Introduction: Alzheimer's Disease (AD) is a progressive neurodegenerative disorder that is characterized by impairment of cognitive functions, memory loss, difficult in learning and performing daily routine activities [1]. According to Report, the prevalence of the disease has increased day by day and people suffering from AD is estimated to triplicate by the end of 2050, worldwide [2]. AD pathophysiology has a complex nature that makes diagnosis and treatment challenging. Acetylcholine is hydrolysed by acetylcholinesterase (AChE) to choline and acetate. Since acetylcholine levels are decreased in AD and its level can be increased by AChE inhibitors to improve cognitive function [5,6]. Studies have displayed that there is a relationship between AD and type II diabetes mellitus (T2DM). Besides, epidemiological studies have shown patients with AD are more vulnerable to developing impaired fasting glucose and T2DM.

Methods: In this study, we designed a tacrine derivative as a multitarget agent for the treatment of both AD and T2DM. For this purpose, we synthesized 9-(2-(2-chlorobenzylidene)hydrazinyl)-1,2,3,4-tetrahydroacridine compound (EBZ) and evaluated for AChE and α-glucosidase inhibitory activity. Besides, we investigated voltametric antioxidant capacity. Molecular modeling study was also carried out for the compound EBZ on AChE.

Results and Discussion: The synthesized EBZ encoded "9-(2-(2-chlorobenzylidene)hydrazinyl)-1,2,3,4-the compound "tetrahydroacridine" in vitro conditions both against the enzyme AChE and α-Glucosidase it has shown high inhibitory activity against the enzyme, but also electrochemical in the determination of antioxidant capacity, it also exhibited high antioxidant capacity.

EBZ Molecule
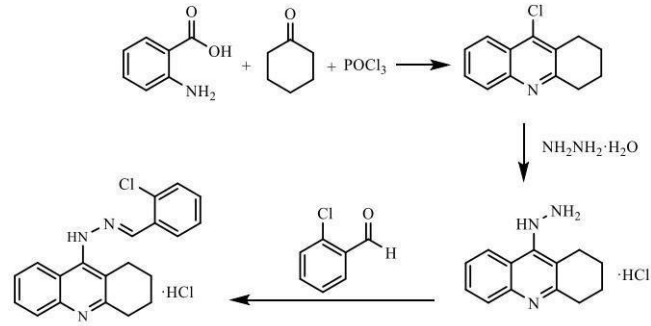
EBZ kodlu bileşiğin genel sentez şeması

Conclusions: The results suggested that compound EBZ can be highlighted as a promising compound for the treatment of both AD and T2DM.

Keywords: Alzheimer's Disease, Type II Diabetes, Acetylcholinesterase, α-Glucosidase inhibitor, synthesis

Pathogenicity prediction of cancer-related variants with protein sequence, structure, dynamics-based features

Metin Yazar[1], Pemra Özbek Sarıca[2]

[1]Istanbul Okan University
[2]Marmara University

Metin Yazar / Istanbul Okan University

Introduction: Single nucleotide variations (SNVs) or variants are the common origin of alterations in human genome having exclusive functional roles in cell such as gene expression, disease susceptibility, and protein-protein interactions. These alterations might cause structural and dynamic impacts on proteins. Cancer is a heterogenous disease including abnormal cell growth with possibility of spreading to other parts of human body. Many cancer-related variants have been deposited in open variation databases such as ClinVar, COSMIC and LOVD. To interpret, classify, and predict the functional consequences of these variants, protein sequence, structure and dynamic based features can be used.

Methods: In this study, we aimed to evaluate these features of cancer-related variants and implemented a machine learning methodology to predict the pathogenicity of the variants. For this purpose, cancer-related variant dataset was curated from ClinVar and filtered based on their review status, molecular consequences, and variation types. Variants were mapped into their 3D protein structures using UniProt SIFTS database. These PDB structures were then mutated and minimized.

Results and Discussion: Sequence-based features including hydrophobicity, biochemical characteristics, polarity, polarizability and PSIC scores; structure-based features including DSSP scores and states, relative ASA values, residue exposure level and radius of gyration and dynamics-based features such as frustration change, distance to hinge residues, QSASA and SASA values were used to train the machine learning algorithm. The performance of our machine learning method was benchmarked against HUMSAVAR datasets.

Conclusions: Our results point out that combination of sequence, structure and dynamics-based features could increase the predictive power for pathogenicity of the cancer-related variants.

Keywords: cancer-related variants, ClinVar, protein structure, machine learning, cancer proteomics

Computational approach for inhibition of ATPases acting antagonistically in Type IV Pilus of Neisseria meningitidis by FDA-approved natural drugs

Aslıhan Özcan[1], Kerem Yalkut[1], Berna Sarıyar Akbulut[1], Pemra Özbek[1]

[1]Faculty of Engineering, Department of Bioengineering, Marmara University, Istanbul, Turkey

Aslıhan Özcan / Faculty of Engineering, Department of Bioengineering, Marmara University, Istanbul, Turkey

Introduction: The Gram-negative diplococcus Neisseria meningitidis is one of the most common causes of bacterial meningitis across the world. Meningococcal meningitis is deadly in 50% of the cases if left untreated, and 10-20% of the survivors may suffer from brain damage, hearing loss, or disability. Despite the availability of effective antibiotics, it may still cause serious medical problems. Type IV Pilus (T4P) plays a key role in the virulence of a variety of bacterial diseases. In N. meningitidis, it is required for bacterial aggregation, twitching motility, adhesion, and signal transduction with host cells, and a very recent study indicated that T4P in N. meningitidis could be an important anti-virulence target against meningococcal diseases. To this end, retraction ATPase (PilT) and assembly ATPase (PilF) protein of N. meningitidis were studied in detail.

Methods: The structures of the ATPases were modelled using homology modelling and the binding regions of the target structures were determined. FDA-approved natural drugs were screened via computational docking as potential inhibitory molecules. Ligands with binding energies better than -8.0 kcal/mol for both structures were accepted to be potential inhibitors. Among these, drug molecules with the most suitable biological activities were determined and selected for further molecular dynamics studies.

Results and Discussion: The results of computational studies show that reserpine and diabeta might have the potential to be used for meningococcal diseases caused by N. meningitidis.

Conclusions: We believe that the results of this study will provide the basis for future in vivo antivirulence drug development research.

Keywords: Drug discovery, molecular docking, anti-virulence, Neisseria meningitidis, Type 4 pili

PP-11

Novel Antipyrine Derivatives as Antioxidant Reagents: Synthesis, In-Silico Pharmacokinetics, Molecular Docking Studies, An Implication In Identifying The Nitric Oxide Synthase Inhibition

Melek Gul[1], Ebru Batı Ay[2], Mukaddes Budak[1]

[1]Department of Chemistry, Faculty of Arts and Sciences, Amasya University
[2]Medicinal and Aromatic Plants Program, Suluova Vocational School, Amasya University

Melek Gul / Department of Chemistry, Faculty of Arts and Sciences, Amasya University

Introduction: In recent years, a wide variety of heterocyclic compounds have been selected as the key, and studies have increased rapidly in the field of their derivatization into structures that will show biological activity.

Methods: The aminoantipyrine compound, which is still used as an active drug substance, is one of the structures chosen as the main skeleton in the modelling of molecules that will show new biological activity. In addition, heterocyclic, aromatic or non-aromatic structures with different ring member numbers (4,5,6) such as furan, thiophene, piperidine, pyrrole, pyridine, pyrimidine, piperazine, isoxazole were included in the modelling, and it was possible to obtain new compounds with different properties and diversity

Results and Discussion: In this study; In the first step, imine derivatives of the main skeleton of antipyrine were synthesized. Furan and thiophene heteroaromatic rings, which are thought to increase the diversity in the structure in terms of biological activity, were selected. The success of a drug depends on its pharmacokinetics characteristics in the body. In silico research of the pharmacokinetic methods helps in reducing the probability of its failure at the drug development stage of lead compounds. In this analysis ADMET, drug-likeness as interested in pharmacokinetic parameters, can predict.

Molecular docking interaction representation of aminoantipyrine analogues
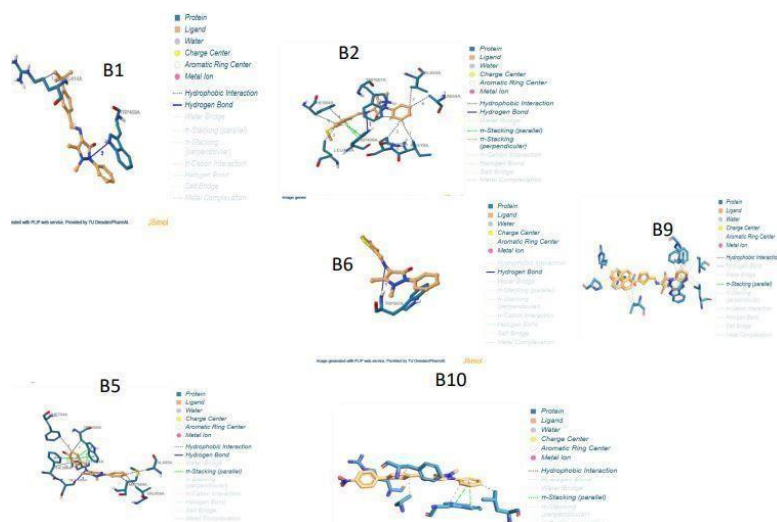
Conclusions: Analogues of antipyrine have been designed, synthesized and characterized by spectroscopic methods. We investigated invitro antioxidant activity, in-silico docking study and some pharmacokinetic parameters. The results of the pharmacokinetic study suggested that synthesising antipyrine analogues have the tendency to be considered as lead-drugs.

PP-12
The combinatorial drug repurposing strategy enhances cytotoxicity in hepatocellular carcinoma

derya yildiz[1], engin ulukaya[1], nazlihan aztopal[1]

[1]istinye university

derya yildiz / istinye university

Introduction: Since most hepatocellular carcinoma (HCC) patients diagnose at an advanced stage and develop resistance to chemotherapy, there is a need for new treatment models. Drug repurposing can thus be a potential strategy to treat HCC. In this regard, network pharmacology is an emerging approach to predict the synergistic activity of repurposed drugs. Thus, this research aims to analyze the repurposing potential and cytotoxic activity of drug/combination efficiency regarding two FDA-approved therapeutic agents, Valproic Acid (VPA) and Niclosamide (NIC), in the HepG2 cell line.

Methods: For repurposing potential, we collated the targets of two drugs from drug gene interaction database and Crossbar, collected signaling pathways related to all the genes from KEGG database. Then, we analyzed protein interactions via STRING database. For cytotoxic potential, we treated HepG2 cells with VPA (1 mM-0.25 mM) and NIC (1 μM-0.25 μM) for 24-72 hours, either by concurrent or sequential application (6-12h). We assessed cell viability by SRB assay and defined the anti-growth effect (GI50, TGI) and cytotoxicity (LC50) of drugs alone or in combination.

Results and Discussion: The target genes of both drugs exerted high interaction regarding STRING database. Indeed, the combinatorial therapy synergistically decreased cell viability compared to the drugs alone. The sequential application strategy was more cytotoxic than concurrent, considering LC50 values. Furthermore, pre-treatment by NIC exerted significant anti-proliferative activity at relatively lower doses than pre-treatment via VPA based on GI50 values.

Conclusions: Network pharmacology and cytotoxicity analyzes of this combination strategy suggest that it may be an alternative treatment model for HCC patients in the future.

Keywords: Hepatocellular carcinoma (HCC), Drug Repurposing, Cytotoxicity, Niclosamide, Valproic Acid

PP-13
Transcriptional regulation of YY1 with a novel G-quadruplex stabilizer

Hazal SARI[1], Beyza BAŞAR[1], Hanım Beyza DOĞAN[1], Fatma SEÇER ÇELİK[1], Sündüs ERBAŞ ÇAKMAK[1]

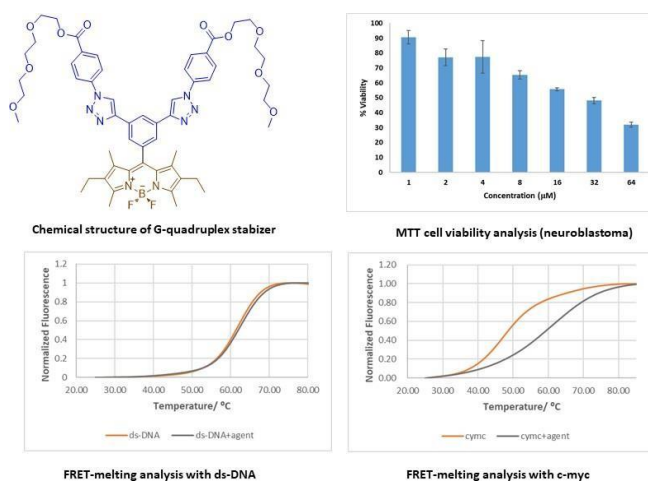[1]Konya Food and Agriculture University

Hazal SARI / Konya Food and Agriculture University

Introduction: Yin Yang 1 (YY1) is a mammalian transcription factor and regulates the expression of many genes involved in cell proliferation, apoptosis and DNA repair. Overexpression of this protein is reported in many cancers such as ovarian, lung, breast cancers. The promoter regions of the YY1 protein are known to be rich in guanine, and we can form G4 structures. In the research, transcriptional regulation of YY1 is aimed with a novel G-quadruplex stabilizer and its potential therapeutic applications will be investigated.

Methods: Compounds were synthesized, purified by chromatographic method and characterized using NMR, and HRMS spectrometry. Viabilities were analyzed using an MTT assay. The interaction of ligand and G-4 structure were analyzed by the FRET-melting test. Effect on YY1 involved cellular pathways is being analysed using qPCR method on neuroblastoma cells.

Results and Discussion: FRET-melting analyses with G-quadruplex forming oligomers (c-myc, bcl-2) and ds-DNA indicated selective stabilization of G-quadruplex with the ligand at 1 μM concentration. Cell viability is shown to decrease significantly in the presence of agent. Effect of the agent on the expression of YY1 and downstream genes is being investigated.

FRET-melting, structure of agent and MTT assay.

Chemical structure of G-quadruplex stabizer

MTT cell viability analysis (neuroblastoma)

FRET-melting analysis with ds-DNA

FRET-melting analysis with c-myc

FRET-melting profiles of 2 mM alone or in the presence of 1mM oligomers, and with first (dsDNA) and second (cymc). The G-quadruplex structure is seen in each of the graphs.

Conclusions: Selective stabilization of G-quadruplex structure by the agent is observed with significant cytotoxicity induction in neuroblastoma cells. Transcriptional regulation of YY1, which is aimed here, would suppress the downstream pathway and have potential therapeutic effect on cancer.

Keywords: G-quadruplex, YY1

Quantum Chemical, Molecular Docking, Molecular Dynamics and ADMET Studies of Potent Anticancer Diimine-Dioxime Agents

Zeliha Nur YILMAZ[1], Bülent DEDE[1]

[1]Süleyman Demirel Üniversitesi Fen Bilimleri Enstitüsü

Zeliha Nur YILMAZ / Süleyman Demirel Üniversitesi Fen Bilimleri Enstitüsü

Introduction: Rational drug design is one of the pre-clinical approaches in the classical drug development process. While methods like Q-SAR and pharmacophore analysis are used in chemoinformatic studies, molecular docking and molecular dynamics (MD) simulations are used in bioinformatic studies. The structure of the protein and ligand in the electronically is very important in molecular docking studies.

Methods: Five diimine-dioxime molecules, which were previously synthesized and characterized by our research group, were used in this study. The optimized geometries, HOMOs-LUMOs and MEP's diagrams of the molecules were calculated quantum chemically. Quantum chemical calculations were performed using the DFT method at the B3LYP/6-311G(d,p) level. Molecular docking simulations were carried out by using AutoDock Vina 1.1.2 program. In molecular docking studies, PDB ID: 2XIR and PDB ID:1M17 proteins were chosen as the receptor structure. MD calculations for 100 ns were performed to examine the stability of the Ligand4-1M17 complex. Toxicity parameters, druglikeness and ADME parameters of all studied ligands were calculated using ProTox-II and SwissADME web-servers.

Results and Discussion: It was determined that the best protein-ligand interaction was between Ligand4-1M17, and the binding energy of this complex was found to be -9.8 kcal/mol. Data from HOMO-LUMO and MEP's obtained as a result of quantum chemical calculations were used to explain the interaction sites of ligands with selected proteins. MD simulations indicated the stability of the complex for the best protein-ligand pose.

Conclusions: All the results obtained revealed that Ligand4 has the potential to be used in studies investigating the anticancer properties of compounds.

Keywords: anticancer, quantum chemical calculation, molecular docking, molecular dynamics simulation

PP-15
Discovery of HDAC6 selective inhibitors by deep machine learning methods

Berna Dogan[1], Tolga Corbaci[1]

[1]Bahcesehir University

Tolga Corbaci / Bahcesehir University

Introduction: Modifications of histone proteins controls gene expression. Histone acetyltransferase (HAT) and histone deacetylase (HDAC) enzymes catalyze histone acetylation and deacetylation process. Disease conditions are observed when HDAC enzymes are out of balance. Among the histone deacetylase isoforms, HDAC6 especially stands out. HDAC6 enzyme can over-function in some common diseases such as different types of cancer, Alzheimer's and Parkinson's diseases. However, approved HDAC inhibitors target more than one isoform of the enzyme. The discovery of molecules selective for HDAC6 enzyme, may allow for the reduction of generally dose-dependent side effects and increase the effectivity of the molecules.

Methods: Many small molecules have already been tested against HDAC isoforms and the bioactivity values are acquired which enables usage of machine learning approaches as such deep learning models that predict selectivity are created and tested. A new approach is proposed that combines continuous and binary models to achieve high accuracy. Continuous machine learning models are used to fill out missing activity values for different HDAC isoforms. This information fed to another model: deep belief networks based on Restricted Boltzmann machines (RBMs). RBMs are unsupervised machine learning algorithms and utilized in pre-training step. Deep Belief Network model is used to screen virtual molecule libraries.

Comparasion of Different Machine Learning Models

Model	Accuracy	Sensitivity	Specificity	AUC
Deep Belief Network	0.88	0.79	0.91	0.93
Random Forest	0.86	0.72	0.92	0.91
Artificial Neural Network	0.85	0.70	0.91	0.90
Support Vector Machine	0.79	0.29	0.98	0.88

Results and Discussion: RBM models outperformed other models. Our algorithm identified molecules with diverse structures as Selective.

t-SNE Graph
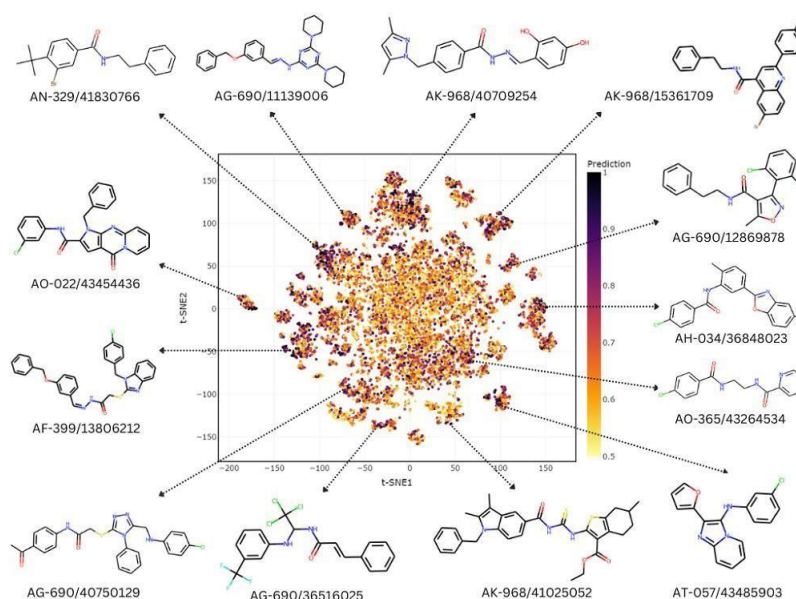
t-SNE graph of molecules predicted as Selective. Molecules with distinct structures sampled from different clusters were displayed.

Conclusions: Proposed method could be applied to other target structures where selectivity is important, many molecules can be screened virtually, facilitating the detection of selective molecules to be tested experimentally.

Keywords: Virtual Screening, Quantitative Structure Activity Relationships, Deep Learning, Molecule Filtering, Drug Design

Structural studies of IDH1

Betul Ertem[1], Kardelen Sabanoglu[2], Helin Gumusboga[1], Hasan Demirci*[1]

[1]Koç University
[2]Yildiz Technical University

Betul Ertem / Koç University

Introduction: The mutant isocitrate dehydrogenase 1 (IDH1) is a promising drug target for several cancer types.

Methods: Here we use use x-ray crystallography and alpha fold to unravel the crystal structure of mutant IDH1.

Results and Discussion: We unraveled the crystal structure of IDH1 at ambient temperature.

Conclusions: The structure of mutant IDH1 provides structural insights for drug development purposes.

Keywords: X-ray crystallography, IDH1, drug development, alphafold

Prediction of CYP450–related pharmacokinetic drug-drug interactions using Graph Convolutional Neural Network

Muhammad Ammar Zahid[1], Muhammad Uzair Zahid[2], Abdelali Agouni[1]

[1]College of Pharmacy, Qatar University
[2]Department of Computer Sciences, Tampere University, Finland

Muhammad Ammar Zahid / College of Pharmacy, Qatar University

Introduction: The increasing complexity of diseases and rapid development of pharmaceuticals have increased the development and use of multi-drug combinations prone to metabolic interactions. The evaluation of such interactions is a time-consuming and costly process due to experimental challenges. Therefore, in-silico methods are required to make accurate and reliable predictions and to accelerate the efforts. Deep learning methods have proved their superiority over conventional QSAR methods to efficiently train predictive models on large datasets.

Methods: We have used a compact Graph Convolutional Neural Network to predict metabolic drug-drug interactions. We used Graph Convolutional layers to automatically learn representations from molecular data using molecular structures. The method was implemented using DeepChem, a machine learning library developed in Python and TensorFlow. Five-folds cross-validation was used to evaluate the model and for tuning hyper-parameters. The top scoring models were used for external validation and making predictions for the FDA-approved drugs.

Results and Discussion: Evaluation metrics show that the models are practical and reliable. However, the performance of models predicting the enzyme substrate status of drugs is affected by the small size of the training datasets.

Conclusions: In this study we used the publicly available datasets to construct practical and reliable model to predict metabolic drug-drug interactions. In the future, we aim to deploy a consensus model as a web-application. Such predictive model will not only help to make better decisions regarding development and use of combination drug therapy but also help researchers to predict the metabolism of new chemical entities during early stages of clinical development.

Keywords: Neural Network, Machine Learning, Metabolic, Drug-drug interaction, Graph Convolutional

R448Q Mutation In The Transcription Factor CTCF: Novel Insight Into Structure - Function Relationship From In Silico Analysis

Esma Nur YAZ[2], Kıvanç KÖK[1]

[1]Dept.of Biostatistics and Medical Informatics, International School of Medicine, Istanbul Medipol University
[2]Master of Science Program Biomedical Engineering and Bioinformatics, Graduate School of Engineering and Natural Sciences, Istanbul Medipol University
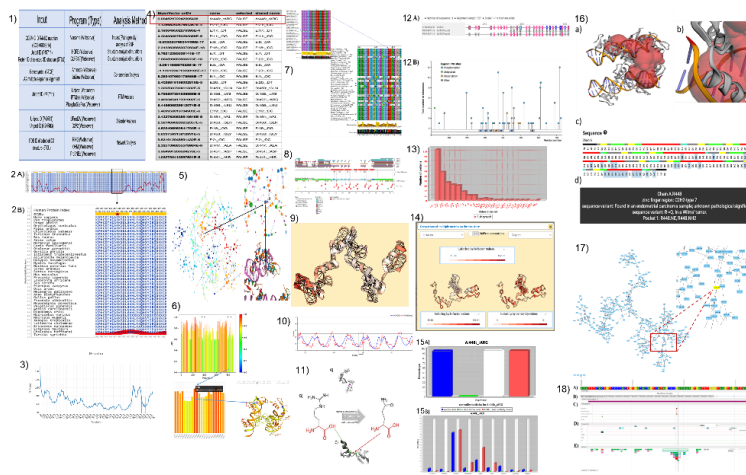
Esma Nur YAZ / Master of Science Program Biomedical Engineering and Bioinformatics, Graduate School of Engineering and Natural Sciences, Istanbul Medipol University

Introduction: CCCTC-binding factor (CTCF) is an evolutionary conserved tumour suppressor candidate protein. This study was carried out to estimate the loss of function that may occur in the protein because of examining the R448Q mutation occurring in the ZF-7 region of CTCF, which consists of 11-zinc fingers and DNA structure.

Methods: To answer this question, to investigate the effect of the R448Q mutation on protein function and stability using in silico tools. In addition to mutation effects, residual interaction network analyses are included in the study, along with analyses of disordered regions, B factors and conservation analysis.

Results and Discussion: Conserved sequences are important for the preservation of the structural and functional properties of the protein, and based on this, it was concluded that the mutation in the 448th amino acid located in the ZF7 region can cause significant functional-structural changes, since it is located in the conserved structure of the protein. The obtained OHM results showed that the ACI value of the 448th amino acid was observed as 0.87 as a result of the analysis of the residues in the active site residue region. In this study, especially the 448th amino acid was examined, and the B-factor value obtained as a result of ProSNEx analysis was 54,26. In addition to the disorder analyzes performed in this study, the order of the 448th amino acid was supported by the B-factor value.

Results

1) General informations about tools and inputs are used. 2A)The sequence of the CTCF protein is shown with the evolutionary most conserved region among known organisms and the relative substitution line represented in red, where the change occurs. 2B) In each gene's entry in Aminode, the product of an Aminode Acid Evolutionary Constrained Analysis to detect the most conserved regions. 3) B-factor scores are representing as blue line and mutation region core is indicated by red box. 4) The list indicates the eigenvector values of CTCF protein edges considering on amino acids using CytoNCA package by Cytoscape 3.9.1 version. The ARG amino acid value is signed by red box. 5) Representations of RIN analysis indicated that relationship between amino acids. 6) OHM Allosteric Couple Intensity Results 7A)Conservation level of amino acids at and near the 448th and logo representation. 7B) The representations of CTCF protein obtained from ECR analysis in organisms according to their frequencies were made by Jalview. 8) D2P2 is predicted disorder regions and PTMs on the CTCF protein. Predicting disorder agreement region is made by green, blue and White colors are representing strong, weak and none disorder agreements. 9)Representation B-factor values on CTCF structure. 10) CTCF disorder tendency is shown on the graph. R448Q mutation region is dictated by the black box. Red line represents IUPred2 results and blue line represents ANCHOR2's. 11) The representation of the mutant and mutated CTCF protein. A) Overview of the protein in ribbon-presentation. The protein is coloured grey, the side chain of the mutated residue is coloured magenta and shown as small balls. B) The schematic structures of the original (left) Arginine (R) amino asit and the mutant (right) Glutamine (Q) amino acid. The backbone, which is the same for each amino acid, is colored red. The side chain, unique for each amino acid, is colored black. C) Close-up of the mutation. The protein is coloured grey, the side chains of both the wild-type and the mutant residue are shown and coloured green and red respectively. 12A) PTM results obtained from iPTMNet from post-transcriptional analyzes are included. The data show that there are PTMs occurring not at amino acid 448th but in adjacent regions. 12B) Data from PhosphoSitePlus did not detect PTMs at amino acid 448th, but there were significant PTMs detected in adjacent regions. Phosphorylation at the 450th amino acid is an example. 13) RING amino acids eigenvector value distribution according to the amino acid numbers are drawn using by CytoNCA. 14)The B-factor value obtained as a result of ProSNEx. Comparing b-factor values (left) and degree centralities (right) regarding on CTCF structure. 15)Centralities measured by CentiScape package. A) Representing Arg amino acid centrality measures in details. B) Edges centrality distribution graph. 16) : a) Display of active information of the 5T0U protein. The red regions represent the active sites of the protein. The protein contains both DNA and zing finger structure. b) It is shown in which region of the protein the R448 amino acid is located. c) The amino acid sequence in the A chain part of the protein is shown. Here, "R" corresponds to the 448th amino acid. shown at the end of the sequence and as the blue region. According to the outputs from CastP, the investigated mutation is located in the active part of the protein. d) The sequence has disease and variation information available in the literature for each amino acid and works integrated with Uniprot. Information about the R448Q mutation is in the table. 17) 5T0U Edges network 18) Pathogenicity and variant analysis of the R448 locus of the CTCF protein are shown. A) Shows base pairs and locations. B) Exonic direction and structure of transcripts. C) Binding sites and functional regions are shown. D) Known variant pathogenicity of the regions are displayed E) Shows known variants 1) General informations about tools and inputs are used. 2A)The sequence of the CTCF protein is shown with the evolutionary most conserved region among known organisms and the relative substitution line represented in red, where the change occurs. 2B) In each gene's entry in Aminode, the product of an Aminode Acid Evolutionary Constrained Analysis to detect the most conserved regions. 3) B-factor scores are representing as blue line and mutation region core is indicated by red box. 4) The list indicates the eigenvector values of CTCF protein edges considering on

amino acids using CytoNCA package by Cytoscape 3.9.1 version. The ARG amino acid value is signed by red box. 5) Representations of RIN analysis indicated that relationship between amino acids. 6) OHM Allosteric Couple Intensity Results 7A)Conservation level of amino acids at and near the 448th and logo representation. 7B) The representations of CTCF protein obtained from ECR analysis in organisms according to their frequencies were made by Jalview. 8) D2P2 is predicted disorder regions and PTMs on the CTCF protein. Predicting disorder agreement region is made by green, blue and White colors are representing strong, weak and none disorder agreements. 9)Representation B-factor values on CTCF structure. 10) CTCF disorder tendency is shown on the graph. R448Q mutation region is dictated by the black box. Red line represents IUPred2 results and blue line represents ANCHOR2's. 11) The representation of the mutant and mutated CTCF protein. A) Overview of the protein in ribbon-presentation. The protein is coloured grey, the side chain of the mutated residue is coloured magenta and shown as small balls. B) The schematic structures of the original (left) Arginine (R) amino asit and the mutant (right) Glutamine (Q) amino acid. The backbone, which is the same for each amino acid, is colored red. The side chain, unique for each amino acid, is colored black. C) Close-up of the mutation. The protein is coloured grey, the side chains of both the wild-type and the mutant residue are shown and coloured green and red respectively. 12A) PTM results obtained from iPTMNet from post-transcriptional analyzes are included. The data show that there are PTMs occurring not at amino acid 448th but in adjacent regions. 12B) Data from PhosphoSitePlus did not detect PTMs at amino acid 448th, but there were significant PTMs detected in adjacent regions. Phosphorylation at the 450th amino acid is an example. 13) RING amino acids eigenvector value distribution according to the amino acid numbers are drawn using by CytoNCA. 14)The B-factor value obtained as a result of ProSNEx. Comparing b-factor values (left) and degree centralities (right) regarding on CTCF structure. 15)Centralities measured by CentiScape package. A) Representing Arg amino acid centrality measures in details. B) Edges centrality distribution graph. 16) : a) Display of active information of the 5T0U protein. The red regions represent the active sites of the protein. The protein contains both DNA and zing finger structure. b) It is shown in which region of the protein the R448 amino acid is located. c) The amino acid sequence in the A chain part of the protein is shown. Here, "R" corresponds to the 448th amino acid. shown at the end of the sequence and as the blue region. According to the outputs from CastP, the investigated mutation is located in the active part of the protein. d) The sequence has disease and variation information available in the literature for each amino acid and works integrated with Uniprot. Information about the R448Q mutation is in the table. 17) 5T0U Edges network 18) Pathogenicity and variant analysis of the R448 locus of the CTCF protein are shown. A) Shows base pairs and locations. B) Exonic direction and structure of transcripts. C) Binding sites and functional regions are shown. D) Known variant pathogenicity of the regions are displayed E) Shows known variants

Conclusions: In this study, inferences were obtained that the candidate tumor suppressor CTCF protein may have determinative effects in cancer using in silico analysis methods.

PP-19
Towards Selective Stabilization of G-Quadruplex DNA/RNA Structures with Structurally Optimized Ligand

Maide Önder[1], Hatice Tekin[1]

[1]Konya Food and Agriculture University

Maide Önder / Konya Food and Agriculture University

Introduction: Guaine rich regions of nucleic acids spontaneously form Hoogsteen hydrogen bonds and stack into G-quadruplex structures. G-quadruplex structures found in some important genomic regions like promoter of oncogenes which makes them attractive targets for chemotherapeutic strategies. In the project scope, a BODIPY-based ligand, which can fit between G-quadruplexes because of its planer structure and therefore stabilize them, is designed and efficacy is examined.

Methods: A small BODIPY-based cationic ligand was synthesized and characterized. FRET DNA melting analysis was performed with using labelled oligomers such as double stranded DNA, telomere, and fragments of oncogene promoters to examine binding affinity of ligand to G-quadruplex.

Results and Discussion: The results of the FRET DNA melting analysis demonstrated that the binding of ligand to the G-quadruplex structures considerably enhances the melting temperature of several DNA oncogenes, namely c-Kit and c-Myc, as ligand concentration rises. However, the melting temperatures for Bcl-2 and h-Telo are slightly decrased, and neither Tert nor dsDNA showed any appreciable changes.

FRET analysis results of two different ligands
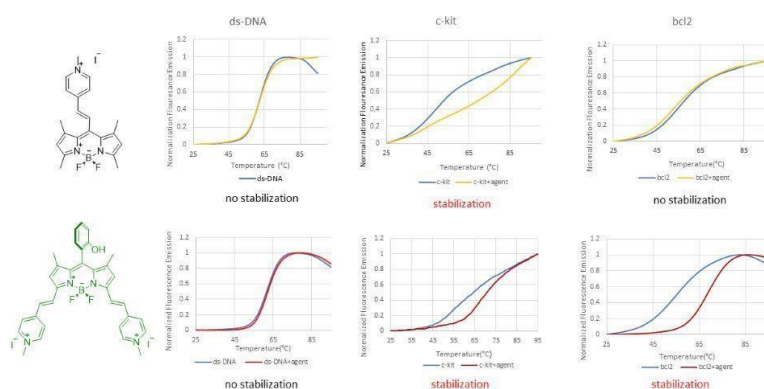
Conclusions: In this research, the simple-structured BODIPY-based ligand stands out with regard to targeting specific oncogenes, in this case c-Kit and c-Myc, and as a result, it provides a novel method for stabilizing G-quadruplex structures for potential chemotherapeutic uses. The project's next stages include an toxicity analysis, an examination of the impact on gene expression, and an examination of biological activity.

Keywords: BODIPY, G-quadruplex stabilizer

PP-20
INVESTIGATION OF THE STRUCTURAL DIFFERENCES BETWEEN WILD-TYPE AND MUTANT FORMS OF MutSα HETERODIMER WITH MOLECULAR DYNAMIC SIMULATIONS

Clara Xazal Buran[1], Elhan Taka[1], Mert Gür[1]

[1]İstanbul Technical University

Clara Xazal Buran / İstanbul Technical University

Introduction: Colon cancer is very common in Turkey and in the world endanger human health. Studies reveal that the causes of some hereditiary colon cancers are mutations in proteins that are involved in repairing DNA mismatches. MutSα which is heterodimer structure formed by MSH2 and MSH6 proteins is one of the mismatch repair protein. MutSα move on DNA, identifies mismatched bases, binds mismatch region, and initiating DNA repair. Certain mutations that occur in MutSα protein prevent the function of protein, and cause cancer. Only some of the mutations in MutSα have been associated with hereditiary colon cancer, but the effect of some mutations on protein function and efficiency is not yet known.

Methods: Samples taken from individuals with a family history of colon cancer to obtained mutations as a result of genetic screening tests (Levent Doğanay, Ümraniye Training and Research Hospital) have been reported to our lab. Ala733Thr, Arg577Cys, and Ser1279Asn mutations were detected and the effects of these mutations on DNA-free MutSα were investigated by performing whole atom Molecular Dynamics (MD) simulations with cell nucleus's physiological conditions.

Results and Discussion: It was observed that the root mean square deviation (RMSD), heat capacity and root mean square fluctuation (RMSF) in certain domains of the mutant protein were higher than the wild- type protein.

Conclusions: In this study, the effects of mutations in the DNA-free MutSα protein on protein structure and dynamics were investigated by performing molecular dynamics simulations, and it was concluded that mutant proteins showed different thermodynamic and structural properties than wild type.

Keywords: Molecular Dynamics Simulations, Colon cancer, Protein structure and dynamics, MutSα, DNA repair proteins

PP-21
NEW HEXAHYDROQUINOLINE DERIVATIVES AND THEIR CYTOTOXIC PROPERTIES ON HePG2 CELLS

Göksun Demirel[1], Anıl Yirün[1], Gökalp Çetin[4], Aylin Balcı Özyurt[6], Deniz Arca Çakır[7], Terken Baydar[2], Rahime Şimşek[3], <u>Pınar Erkekoğlu</u>[2]

[1]ÇUKUROVA UNIVERSITY FACULTY OF PHARMACY DEPARTMENT OF TOXICOLOGY
[2]HACETTEPE UNIVERSITY FACULTY OF PHARMACY DEPARTMENT OF TOXICOLOGY
[3]HACETTEPE FACULTY OF PHARMACY DEPARTMENT OF PHARMACEUTICAL CHEMISTRY
[4]ERZINCAN BINALI YILDIRIM UNIVERSITY FACULTY OF PHARMACY DEPARTMENT OF PHARMACEUTICAL CHEMISTRY
[5]HACETTEPE UNIVERSITY VACCINE INSTITUTE DEPARTMENT OF VACCINE TECHNOLOGY
[6]Bahçeşehir University, Faculty of Pharmacy, Department of Pharmaceutical Toxicology
[7]Hacettepe University, Vaccine Institute, Department of Vaccine Technology, Ankara, TURKEY

Pınar Erkekoğlu / HACETTEPE UNIVERSITY FACULTY OF PHARMACY DEPARTMENT OF TOXICOLOGY

Introduction: Inflammation is the underlying cause of many diseases such as cardiovascular and autoimmune diseases, and cancer. Recently 1,4-dihydropyridine (1,4-DHP) compounds were found to be effective in reducing inflammation which contributes to development of inflammation associated diseases. Hexahydroquinolines are condensed derivatives of the 1,4-DHP ring and have various biological activities including anti-inflammatory activity.

Methods: In this study, five compounds having 1,4,5,6,7,8-hexahydroquinoline structure were synthesized with various ester groups in 3rd position and biphenyl substituents in 4th position. The structure of the synthesized compounds was elucidated by spectral methods and their cytotoxic properties were determined by MTT test to identify the cytotoxic properties of these compounds in human hepatoma cell line (HepG2 cells) as liver is the primary target organ for many drugs.

Results and Discussion: For MTT assay, these compounds were applied to HepG2 cells at a concentration range of 5 - 200 µM. MTT results showed that inhibitor concentration 50 (IC50) values of these five compounds were between 138 – 650.9 µM and inhibitor concentration 20 (IC20) values of compounds were between 66 – 384 µM. We demonstrated that novel compounds have cytotoxic effects at very high doses compared to the human blood concentrations of their available drug analogues.

Conclusions: Further studies on different cell types should be conducted to better understand their antioxidant and potential anti-inflammatory effects.

Keywords: Hexahydroquinolines, antiinflammatory drug, MTT test, cytotoxicity, HepG2 cells

PP-22

Molecular Docking and in Silico ADMET Analyses of Novel Fedratinib Derivatives as Potent JAK2 Inhibitors

Harun Nalçakan[1], Gülbin Kurtay[1], Tuğba Güngör[2]

[1]Ankara University
[2]Çanakkale Onsekiz Mart University

Harun Nalçakan / Ankara University

Introduction: Janus kinase (JAK) family members, JAK1, JAK2, JAK3, and TYK2, are non-receptor cytoplasmic tyrosine kinases that transmit cytokine signals through the JAK-STAT pathway. Therefore, JAKs have emerged as potential inhibitory targets for the treatment of numerous diseases due to their ability to control the transcription of a vast number of genes, including those involved in immunological, inflammatory, and cancer processes. Among these kinases, JAK2 is shown to have a crucial role in cell proliferation and survival, making it an appealing target for cancer therapy. Consequently, many JAK2-inhibiting drugs have emerged as prospective cancer therapeutics. As a pioneering example, Fedratinib, a JAK2-selective inhibitor, was authorized by the FDA in 2019 to treat high-risk myelofibrosis in adults.

Figure 1. (left) The scope of molecular structures of fedratinib and designated derivatives (right) Binding pose of Fed20 (-9.6 kcal/mol) with JAK2 (PDB ID: 6VNE).
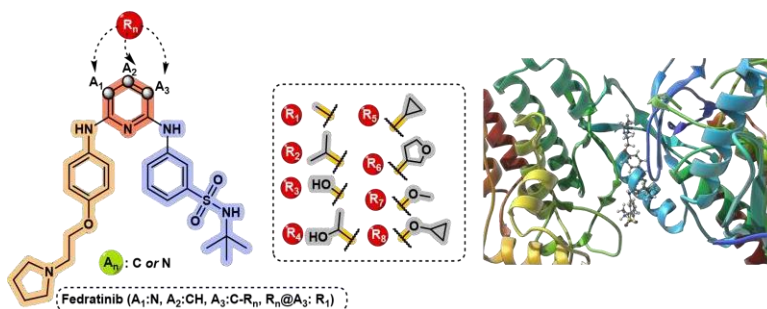
Methods: This work intends to provide a comprehensive computational study by modifying the pyrimidine unit of fedratinib and generating 27 new pharmacological candidates (Fed1-27). To this aim, Gaussian 09 (DFT/B3LYP/6-31G(d,p)) was employed to optimize the geometry of target molecules, while GaussView 5.0.8 was used to display them. SwissADME and POM studies were then performed to explore ADMET properties and drug-likeness. Investigated molecules were also subjected to molecular docking analysis (SAMSON platform/2022-R2, OneAngstrom/AutoDock Vina Extension) to assess their possible inhibitory action on JAK2 (PDB ID: 6VNE).

Results and Discussion: Fed1-27 binding scores with JAK2 ranged between -7.8 and -9.6 kcal/mol. Fed20 had the lowest binding score, which was revealed to be -9.6 kcal/mol, whereas fedratinib had a binding score of -8.4 kcal/mol.

Conclusions: This study aimed to disclose the pharmacokinetic properties of newly tailored fedratinib derivatives as potent JAK2 inhibitors.

Keywords: Fedratinib, Janus Kinase, JAK2, Molecular docking, ADMET

<div align="center">

PP-23
Alphafold Based Pathogenicity Prediction of Missense Variants

</div>

Mustafa Filik[1], Enes Dursun[1], Uğur Sezerman[1], Emel Timuçin[1]

[1]ACIBADEM University

Mustafa Filik / ACIBADEM University

Introduction: Classification of clinically important variations is an important and recurrent topic in molecular diagnostics. Recently classifiers that leverage structural information showed improved performed over those that solely rely one sequence-based attributes, reflecting the significance of protein structure as an important descriptor for this problem. Despite their superior performance, structure-based predictors are generally limited to the cases that were structurally characterized. This limitation would be resolved by the extensive structure predictions recently made by AlphaFold2 (AF).

Methods: Prompted by this prospect, we have developed a novel pathogenicity predictor that use both sequence and structural information from AF structures. We have implemented an Extreme Gradient Boosting ensemble algorithm on a large dataset of more than 20 K variations from the ClinVar database. For hyper-parameter tuning and model selection, a nested cross-validation approach was applied. The resulting model, named as AlphaFold-based Pathogenicity Predictor (AFbPP) was tested on a blind dataset alongside with four different established predictors.

Results and Discussion: AFbPP has outperformed all four predictors in the blind dataset resulting in an AUROC of 0.80 while the second best performer which also used structural information showed an AUROC of 0.76.

Conclusions: Our results underscored the structural attributes obtained from AlphaFold predictions as useful attributes for the variant classification problem in addition to sequence-based features.

Keywords: Missense Variant, Pathogenicity Prediction, Machine Learning, Alphafold, Bioinformatics

Investigation of OXA enzyme inhibitors using computational tools

Ilgaz Taştekil[1], Fatma Gizem Avci[3], Berna Sariyar Akbulut[2], Pemra Ozbek Sarica[2]

[1]Marmara University Institution of Pure and Applied Sciences
[2]Marmara University Engineering Faculty Deparment of Bioengineering
[3]Uskudar University Department of Bioengineering

Ilgaz Taştekil / Marmara University Institution of Pure and Applied Sciences

Introduction: Increasing amount of nosocomial infectious cases due to the antibiotic resistances developed by different bacterial species is alarming in recent years. Pseudomonas aeruginosa, Acetinobacter baumannii, Klebsiella pneumoniae and Enterobacteriaceae species account for the development of resistive mechanisms against either conventional or new generation β-lactams through different classes of β-lactamases they synthesize in their metabolism for vital cellular functions. Among them, class D β-lactamases are alarming ones within all other classes. More than 800 class D β-lactamase structures have been identified up to date having similar 3D structures albeit varying amino acid sequences. In contrast to their structural similarities, class D β-lactamases different hydrolytic activities and efficiencies against antibiotics when compared either within themselves or with class A β-lactamases. Among class D β-lactamases, OXA-10, OXA-23 and OXA-48 consist of both similar and varying properties such as their 3D structures, functional mechanisms and substrate profiles.

Methods: In this study, three different types of OXA enzymes are investigated through virtual library screening of two different drug libraries. Molecular Dynamics (MD) simulations will follow the molecular docking application in the further stages of the study.

Summary of the Study
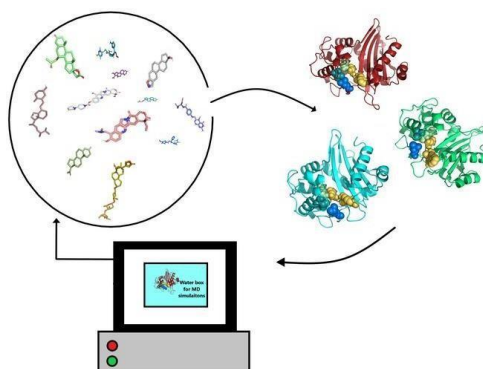
Results and Discussion: Molecular docking applications and MD simulations are in process now.

Conclusions: Candidate molecules obtained from computational analysis will provide valuable data for the experimentalist in the field.

Keywords: OXA enzymes, Molecular docking, Virtual library screening, md simulations, drug

Design and Synthesis of New Coumarin-Bistriazole Hybrids as Potential Drug Candidates

Busra Arvas[1], Cigdem Yolacan[1], Feray Aydogan[1]

[1]yildiz technical university

Busra Arvas / yildiz technical university

Introduction: Coumarin derivatives are natural or synthetic heterocyclic molecules with oxygen. They are considered as pharmacological flavonoids. Coumarin derivatives have attracted researchers' attention due to their wide range of biological activity such as antitumor, anticoagulant, antioxidant, antiviral, antiinflamatory, antimicrobial, antibacterial, etc [1,2]. Triazoles can be used as binders on the peptides or aromatic rings and may exert bioisosteric effects. They can bind to a biological target with a high affinity by hydrogen bonding, dipole-dipole and π-stacking interactions. This demonstrates the unquestionable importance of triazoles in pharmaceutical chemistry [3].Recently, medicinal chemists have focused on combination of two or more pharmacophores in one molecule to produce an hybrid molecule. These hybrid molecules can show enhanced or even new biological activities.

Methods: After the synthesis of the coumarin skeleton, alkylation reactions on the 5- and 7-positions of the coumarin skeleton were performed. Then, the synthesis of azide derivatives was carried out by the reaction of obtained alkylation products with NaN3. Finally, 1,2,3- triazole ring was obtained by click reaction of synthesized azide derivatives and dipolarophils.

Results and Discussion: Coumarin ring formation and alkylation reactions were performed by well known and easily applicable methods. To construct the 1,2,3-trizole rings, click reactions were accomplished under mild conditions in good yields. The structures of all new coumarin-bistrizole hybrides were confirmed by their spectral data.

Conclusions: In conclusion, a serie of new coumarin-bistriazole derivatives with the potential to display a variety of biological activities have been designed and synthesized.

Structure of coumarin-bistriazole hybrids
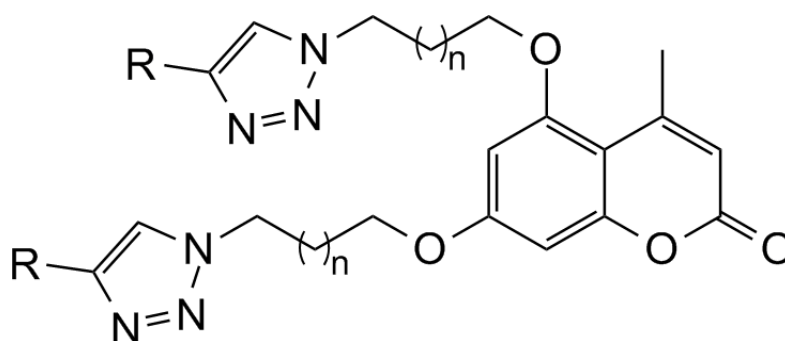
Keywords: Coumarin, triazole, biological activity, heterocyclic compound, organic synthesis

Dissecting the Effect of Viscosity of Deep Eutectic Solvents on the Structure and Dynamics of Thermostable Lipases

Zeynep Kavalcı[1], Emel Timuçin[1]

[1]Acibadem University

Zeynep Kavalcı / Acibadem University

Introduction: Deep eutectic solvents (DESs), a subgroup of ionic liquids, are more environmentally-friendly and less expensive alternatives of organic solvents that are extensively used in biocatalysis processes. Furthermore, DESs media has been successfully applied to lipase reactions which carry paramount importance for many industrial processes. From this perspective, understanding how lipases behave in DES and how the physicochemical properties of the DES solvents affect the lipase's stability and activity is crucial to the efforts of successful industrial applications of lipases.

Methods: In this study, we have implemented molecular dynamics simulations of a thermostable lipase in two different DES compositions formed by the choline/chloride (ChCl) as the hydrogen bond acceptor and either glycerol or ethylene glycol as the hydrogen bond donor. We have generated four lipase systems that were solved in two different DESs with different ChCl molar ratios that resulted in different viscosities. All systems were run for 300 ns at different temperatures.

Results and Discussion: The trajectories were analyzed to assess how the DES composition and alternating molar ratios affect the lipase structures. Results showed as the molar ratio of hydrogen bond donor gets higher, i.e. higher viscosity, the lipase mobility decreased. As such, even at 373 K, we observed an almost frozen lipase backbone for the more viscous DES solvents.

Conclusions: These in silico insights suggested that tailoring DES molar ratios as a viable strategy to optimize lipase stability in DES media.

Keywords: Thermoalkalophilic lipases, Molecular dynamic simulations, Biocatalysis, Deep eutectic solvent, Thermostability

The Development of Antagonists for Knockdown of Axl Overexpression

Begüm Nisa Kasaplı[1], Pınar Siyah[2], Serdar Durdağı[3]

[1]Department of Molecular Biology and Genetics, Faculty of Engineering and Natural Sciences, Bahçeşehir University, Istanbul, Turkey
[2]Department of Biochemistry, Faculty of Pharmacy, Bahçeşehir University, Istanbul, Turkey
[3]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Bahçeşehir University, Istanbul, Turkey

Begüm Nisa Kasaplı / Department of Molecular Biology and Genetics, Faculty of Engineering and Natural Sciences, Bahçeşehir University, Istanbul, Turkey

Introduction: Axl is a protein that participates in the receptor tyrosine kinase (RTK) pathways that encourage development, progression, and metastasis of cancer. Axl has primarily been inclusive in cell proliferation and migration and is found in nearly all tissues and cell membranes. Axl belongs to the Tyro3, Axl, and Mer (TAM) subfamily. While they all contribute to immunity, Axl has also been involved in cancer. Hereby, the number of recent studies indicates that targeting Axl has gained prominence due to the increasing findings of its significant correlation with a poor prognosis and drug resistance. The high affinity ligand for activating TAM subfamily proteins is growth arrest specific 6 (Gas6). TAMs overexpression is associated with more aggressive cancer stages, lower presumptive patient survival rate, metastasis, and acquired drug resistance. As a result, the Gas6 and Axl complex has been identified as a trigger for aberrant cell proliferation and metastatic process in many cancer types.

Figure 1. The Crystal Structure of Gas6 in Complex with the Ig-like Domain of the Axl Receptor
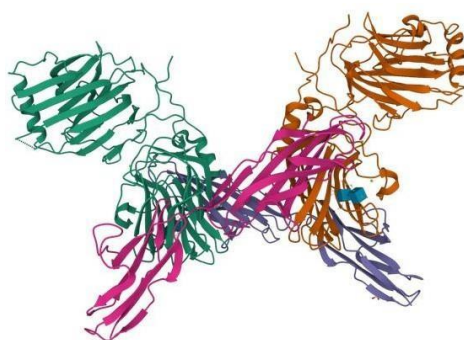
The green and orange chains are chains of the Gas6 protein and are known as chains A and B, respectively. The purple and pink chains are chains of the Axl protein and are known as chains C and D, respectively.

Methods: In this study, it is intended to review current therapeutics that target the Gas6 and Axl pathway in cancer and advance them by using FDA-approved drugs. X-ray crystallography structures (2C5D; PDB ID) whichwere imported from Protein Data Bank (PDB) are used as receptor (Figure 1).

Results and Discussion: The scores obtained as a result of dockings targeting Axl (chain D) were evaluated according to ligand efficiencies. Ligands with high efficiency were acceptedas the best scores (Table 1).

Table 1. Best Docking Scores According to their Efficiency

Compound	Docking Score (kcal/mol)	Ligand Efficiency
Netarsudil	-7.416	-0.218
Istradefylline	-7.313	-0.261
Procaine benzylpenicillin	-7.124	-0.310

Conclusions: We proposed the drug candidates which reduces the overexpression of the Axl might be effective in preventing cancer development and metastasis.

Keywords: Axl, metastasis, proliferation, therapeutics, suppression

PP-28

Development new generation of imatinib using structural biology techniques at ambient temperature

Gözde Karakadıoğlu[1]

[1]Koc University

Gözde Karakadıoğlu / Koc University

Introduction: Chronic myeloid leukemia (CML) is a kind of blood cancer and most CML patients have been associated with a chromosomal anomaly with the BCR-ABL fusion oncogene. Imatinib mesylate is the first small molecule developed to target the BCR-ABL fusion protein. Despite a high response rate in CML patients with imatinib therapy, almost one-third of patients still have an inadequate response to imatinib. In other words, due to mutations in region of imatinib binding-pocket or other of the BCR-ABL, resistance to imatinib has emerged in CML patients.

Methods: In this study, ABL kinase domain gene was purchased from Genscript Biotech. The gene was inserted to pET11a vector plasmid constract. These strains has been used to express the gene encoding our target protein. To be able to procure further purified protein, we were used Ni-NTA affinity chromatography. The purified protein solution was added to crystal screen conditions in Terasaki plates. Then, X-ray diffraction images were collected from the formed crystals in order to acquire the best 3D structure. These diffraction datas were collected from XtalCheck module (Rigaku Oxford Diffraction) at ambient temperature.

Results and Discussion: We will have revealed the structures determined at ambient temperature and high resolution with the help of X-ray crystallography technique. Additionally, we will have re- evaluated structures and designed new target small molecule with approaching from the perspective of integrative structural biology.

Conclusions: The results propose that may developed a new generation of imatinib that is more specific, high affinity and resistant to possible mutations to treat CML disease and improve patients' lives.

Keywords: Chronic myeloid leukemia, Imatinib, BCR-ABL, X-ray crystallography

Synthesis, Purification and Application of Isotopic Derivatives of Various Pharmaceutical Active Ingredients Analytical Determination Methods

Gizem Nur Ayan[1], Sezin Erarpat[1], Kumsal Eroglu[1], Omer Tahir Gunkara[1], Sezgin Bakirdere[1]

[1]Yildiz Technical Univesity

Gizem Nur Ayan / Yildiz Technical Univesity

Introduction: The phenytoin substance we are working on is a drug active ingredient used in the treatment of epilepsy. Within the scope of this study, the isotopic derivative of phenytoin (phenytoin-d2) will be used for the determination of the phenytoin by quadruple isotope dilution (DIS) method. Quantitative determinations of selected analyte within the scope of the project will be performed using gas chromatography-mass spectrometry (GC-MS). By using the dispersive liquid-liquid microextraction method to enrich the analytes in the sample solution, trace detection limits for analytes will be obtained. Optimization studies of the important parameters of the DSSME-GC-MS method will be carried out and the limit of detection (LOD), limit of determination (LOQ) and linear range will be determined.

Methods: Phenytoin was synthesized using benzil and urea as a starting materials. Both starting materials weighted to the round bottom flask and ethanol was added as a solvent. KOH was added to the reaction mixture. Then mixture refluxed, reaction finished after TLC control. Crude solid crystalized with EtOH. Likewise, deutero phenytoin was synthesized using urea- d4. It was analyzed in the GC-MS system and analytical studies were carried out.

Synthesis of Phenytoin
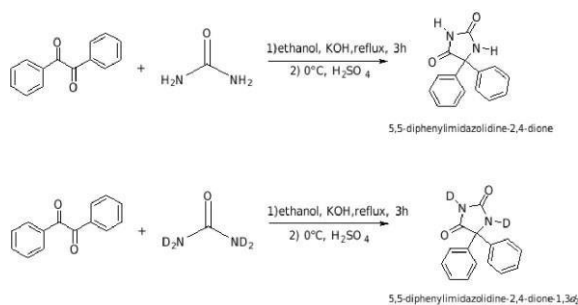
Results and Discussion: The synthesis stages of the phenytoin substance have been successfully completed and the results of the studies using the DLLME method in the GC-MS system have been analyzed.

Conclusions: As a result, novel phenytoin deutero derivatives synthesized in this project. QID-DSSME-GC-MS method will be applied with newly synthesized d2-derivatives of phenytoin, and trace level analytes will be determined with high accuracy and precision.

Keywords: phenytoin, dispersive liquid liquid microextraction, GC-MS, drug active ingredient, epilepsy

Synthesis of Bisindolylmaleimide Based Potential Antitumor Compounds

Şura YILMAZ[1], Mustafa Yavuz ERGÜN[1]

[1]Dokuz Eylul University

Şura YILMAZ / Dokuz Eylul University

Introduction: Possible changes in the cell's signal transmission play an active role in the tumor development process. As a result of revealing the role of molecules involved in signal transduction and signaling pathways in carcinogenesis, identifying inhibitory agents specific to these pathways may open new horizons in cancer treatment. Protein Kinase C (PKC) enzymes signal through multiple pathways and control the expression of genes involved in cell cycle progression, tumorigenesis, and metastatic spread.PKC consists of two lobes, N-terminal and C-terminal. These two lobes are connected by a flexible hinge region where the ATP-Mg complex is located.In silico studies, it was determined that the bisindolylmaleimide molecule functions as a part of adenine by mimicking ATP in PKC. In studies, it was observed that the effectiveness against PKC increased with the deterioration of the planarity. It has been observed that Bisindolilmaleimide with distorted planarity is more effective than Staurosporine in planar structure.

Methods: SP-1: First, indole was derivatized, and then derivatized bisindolyllmaleimide was obtained.SP-2: Bisindolylmaleimide was synthesized from indole. Then, mono-substituted bisindolylmaleimide derivatives were synthesized by derivatization.

Results and Discussion: 1H-NMR, 13C-NMR, and FTIR analyses of the synthesized derivatives were performed. As a result, four molecules synthesized with the desired yield and purity were obtained. Bioinformatics tools were used for molecular docking. Colon cancer cells were used to test the biological activity of these molecules.

Conclusions: Studies on the continuation and development of these promising studies in targeted cancer treatment will continue.

Keywords: cancer, bisindolylmaleimid, protein kinase c, targeted cancer treatment, Arcyriarubin A

PP-31

Investigation of Breast Cancer Cell Responses to the Fullerenol-Dexamethasone Dual Therapy

Betul Uzulmez[1], Gulcihan Gulseren[1]

[1]Institute of Sciences

Betul Uzulmez / Institute of Sciences

Introduction: Cancer is the majority common cause of death in the world. The research has focused on rational drug designs to increase the success of the therapeutic agent. Owing to this research and nanobiotechnological developments, successful approaches such as long half-life, multi-agent presentation and reduced systemic toxicity have been revealed by providing molecule activation with targeted functionalities. In this study, fullerenol molecules was selected to investigate the nanomaterials-cancer mechanics with two different breast cancer cell line (MCF-7 and MDA-MB-231). In addition, the effects co-administration of fullerenols with the synthetic glucocorticoid dexamethasone, which is used in the clinic with the effects of increasing drug penetration into cancer tissue and protecting healthy tissue from chemotherapeutic side effects, were investigated at the nanoparticle-cell interaction level. Cancer is the most common cause of death in the world.

Methods: Synthesis and Characterization of Fullerenol Cell Culture Experiments Gene Expression AnalysisStatistical Analysis

Results and Discussion: Cellular death and survival mechanisms on cells that vary according to dose, exposure time and cell type was evaluated by various metabolic, morphological and gene expression analyzes. MDA-MB-231 cells induced an apoptotic death response to fullerenol and dexamethasone co-administration. In addition, MCF-7 cells appear with a new spheroid formation process that maintains vital activities besides slowed metabolism by showing increased cellular sphere formation potential with co-administration.

florescence microscopy
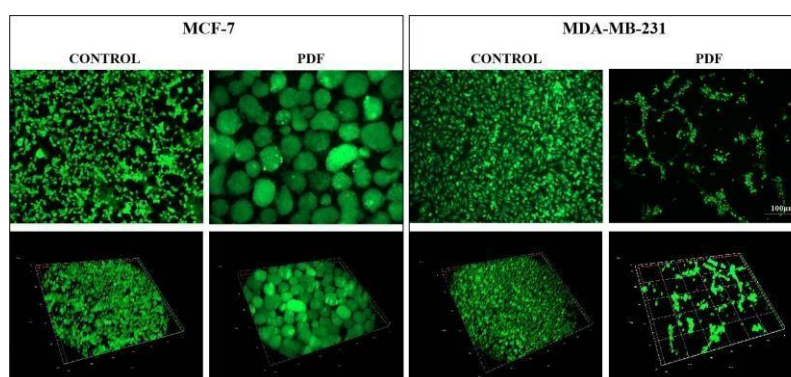
Cellular responses of co-administration.

Conclusions: The findings obtained, the fact that the same application produces results in direct death or development of new life forms in different cells is presented as a contribution to the development of new awareness for cancer treatment.

Keywords: Fullerenol, dexamethasone, anticancer activity, mammosphere formation and spheroids

PP-32
Deep Learning Based Drug Repurposing Study for JAK2 Inhibitors

Mehmet Ali Yucel[1], Oztekin Algul[2]

[1]Mersin University
[2]Erzincan University

Mehmet Ali Yucel / Mersin University

Introduction: The Janus Kinase 2 (JAK2) has become the crucial target for myeloproliferative neoplasm. The deep neural network (DNN) methods have been used successfully in drug discovery. Drug repurposing has gained increasing interest as an alternative strategy to de novo drug design. In this study, the DNN classification model was developed for JAK2 inhibitors. FDA-approved drugs were screened and, findings were supported by a molecular docking study.

Methods: Datasets were obtained from ChEMBL and the ZINC database. Neural networks consist of an input layer, two hidden layers (256,256), a dropout, and an output layer. Keras and RDKit libraries were used for model building and generating fingerprints. The molecular docking study has been conducted with the JAK2 enzyme. The 3-dimensional structure of the JAK2 inhibitor ruxolitinib in complex with the JAK2 enzyme (PDB ID:6VGL) was retrieved from the RSCB protein databank. The docking process was carried out by Autodock Vina.

Results and Discussion: The DNN model was evaluated with several metrics shown in Table 1. The DNN model predicted lansoprazole as active in the FDA dataset. In molecular docking results, lansoprazole showed a better affinity score than ruxolitinib which is approved for JAK2 inhibition (-9.1 kcal/mol and -8.3 kcal/mol, respectively).(Figure 1) In the literature, there is no study to support that lansoprazole may inhibit JAK2. However, there is a study shows that pantoprazole blocks JAK2/STAT3 pathway.

The interactions of ruxolitinib and lansoprazole with JAK2
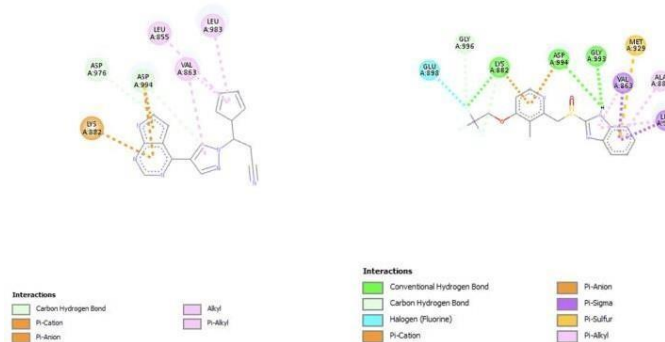
Evaluation scores of the DNN model

Model	Accuracy	F1 score	Matthews Correlation Coefficient	ROC-AUC
DNN	0.83	0.80	0.67	0.84

Conclusions: Our study showed that lansoprazole may have inhibitor activity for the JAK2 enzyme. In conclusion, these findings seem sufficient to start comprehensive studies.

Keywords: Deep learning, Drug repurposing, JAK2, Lansoprazole

PP-33
An in Silico study of the Antiviral Activity of Mediterranean Herbs and Spices Against Multiple Targets of SARS-CoV-2

Jean-Pierre Brincat[1], Frederick Lia[1], Gulsah Akbas[2], Jenya Dursun[2], Merve Tosun[2], Seyma Aydinlik[2], Yuksel Cetin[2]

[1]Institute of Applied Sciences, Malta College of Arts, Science and Technology, Paola, Malta
[2]TUBITAK, Marmara Research Center, Life Sciences Medical Biotechnology Unit, Gebze/Kocaeli, 41470, Turkey

Jean-Pierre Brincat / Institute of Applied Sciences, Malta College of Arts, Science and Technology, Paola, Malta

Introduction: Strategies to combat the COVID-19 pandemic caused by the SARS-CoV-2 virus including vaccines, monoclonal antibodies, and small-molecule inhibitors. So far, the search for antiviral small-molecule inhibitors has mostly focused on repurposing existing drugs. This aim of this study was to use in silico methods to determine potential small-molecule inhibitors for two important targets, ACE2 and 3CLpro, for SARS-CoV-2.

Methods: The RSCB PDB database entry 6LU7 was selected following a detailed literature review. This protein was downloaded, pre-processed, minimized energetically, and the bound inhibitor was removed from the active site. A GRID was prepared using the default options. A "catalytic water molecule" sits in the active site of the enzyme and is known to influence binding. However, articles in literature state claim that this molecule can be displaced by suitable ligands. In order to take this into consideration, the whole process was repeated with and without this water molecule. A total of 5121 ligands were docked and possible tautomers and stereoisomers were generated for a total of 13544 structures. These were then minimized energetically using the OPLS force-field. Docking was performed using Glide for all the ligands with the default options under standard precision. Post-docking minimization was performed.

Results and Discussion: Several compounds were found to have a high docking score including: Cyanidin-3-O-arabinose chloride, Cyanidin 3-O-rhamnoside, Kaempferol-3-O-pentoside, Quercetin 3-O-rhamnoside, Quercetin-3-D-xyloside known inhibitors of 3CLpro, such as salvianolic acid were also docked with a high score.

Conclusions: The results obtained can serve as a basis for the selection of compounds for acquisition and in vitro testing.

Keywords: Mediterranean Herbs and Spices, Antiviral Activity, Antioxidant Potential, In silico methods, SARS-Cov-2

Trace Levels in Blood and Urine of Colchicine Active Substance Used in the Treatment of Gout and Behçet's Disease, Also Used in the Treatment of COVID-19, with the HPLC system determination

Rabia Kutlu[2], Buse Tuğba Zaman[1], Sezin Erarpat[1], Ömer Tahir Günkara[1], Sezgin Bakırdere[1]

[1]Yıldız Technical University
[2]İstanbul University

Rabia Kutlu / İstanbul University

Introduction: Colchicine is an important drug agent used for diseases such as Gout, Behçet's disease, Familial Mediterranean Fever, COVID-19.High-performance liquid chromatography (HPLC) of colchicine with trace levels of biological substances such as blood and urineTo develop an analysis method with high accuracy and sensitivity in order to perform the determination in.

Colchicine
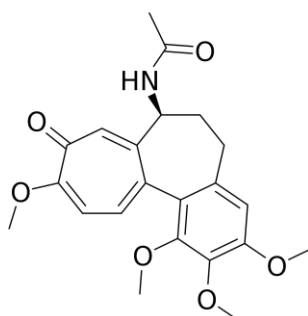
Methods: The active ingredient of colchicine was extracted with methanol from commercial drugs. Whether the active compound was transferred to methanol was determined by TLC controls. Trials of preconcentration of the analyte in very small concentrations in human body fluids (blood and urine) were carried out using the dispersive liquid-liquid microextraction method, which is an analytical determination method. The organic phase obtained after the extraction process was decided as a result of the trials and sent to the HPLC system.

Results and Discussion: Recovery trials of the DSSME-HPLC method will be studied in blood and urine samples. Colchicine standard solution will be added to the prepared samples at the determined concentration and developed DSSME-HPLC new analysis method will be applied. A test study will be carried out on the accuracy and reproducibility of the method by determining the percent recovery results.

Conclusions: Colchicine substance, the new analysis method developed by studying the recovery trials of the DSSME-HPLC method in blood and urine samples was applied, the percent recovery studies were determined and the analysis was developed by performing test studies for the accuracy and reproducibility of the method.

Keywords: Colchicine, Organic Synthesis, drug active ingredient, HPLC analysis

Synthesis, pharmacokinetic and biological evaluation of 5-aminoquinoline-triazole hybrid derivatives

Irem Kulu[1]

[1]Gebze Technical University

Irem Kulu / Gebze Technical University

Introduction: The discovery of new drugs against cancer is a very difficult and time-consuming process. Therefore, combining core structures with known effects can produce more effective structures in a shorter time by synthesizing hybrid molecules is of great interest to the synthetic chemist. In this regard, we aimed to prepare hybrid molecules that have 5-aminoquinoline and 1,2,3-triazole rings for the construction of new drug-like molecules.

Methods: Newly synthesized all quinoline-triazole hybrid compounds were subjected to FTIR, 1HNMR, 13CNMR, and MALDI-MS spectroscopic characterization methods. Furthermore, these derivatives (8a–g) were explored for their anti-cancer activity toward Human urinary bladder carcinoma (T24) cells through cell viability, fluorescent imaging, and colony formation analyses. The frontier molecular orbital energies gap and chemical behavior indices based on HOMO and LUMO energy values were analyzed via in-silico methods.

Results and Discussion: It was found that 8 f was the most promising molecule by giving a good response with a 10–30% decrease in cell viability in a dose-dependent manner. Further fluorescent imaging and colony formation analyses were performed on only 8f and gave good results. It was found that 8f was the most promising molecule by giving a good response with a 10–30% decrease in cell viability in a dose-dependent manner. The predicted ADME properties of all new compounds obeyed Lipinski's rule of five which indicates that they have drug-like properties.

Conclusions: All in vitro and in silico results are in agreement that derivative 8f has potent anticancer activity and could serve for further investigation to enhance its potential biological activities.

Keywords: Quinoline, triazole, Anticancer activity, Pharmacokinetic properties

MOLECULAR DOCKING STUDIES REVEAL TOXIN BINDING DIFFERENCES THAT ENABLE SELECTIVITY FOR SODIUM CHANNELS

Selin Sezer[1], Saliha Ece Acuner Zorluuysal[1]

[1]İstanbul Medeniyet University

Selin Sezer / İstanbul Medeniyet University

Introduction: Voltage-gated sodium (NaV) channels are transmembrane ion channel proteins and are potential drug targets for many conditions such as chronic pain, epilepsy, and cardiac arrhythmias. Animal toxins have recently been discovered to target NaV channels and natural toxins have high potential as selective modulators. It has been recently shown that toxin binding differences enable specific binding in sodium channels. At least eight different binding sites, mainly voltage sensor domains 2 and 4, have been proposed in NaV channels and six of them are toxin binding sites. This study aims to reveal the selective binding mechanisms of three toxins; namely, Hm1a and Pre1a peptides found in tarantula venom and Hj1a peptide found in scorpion venom, by modeling their interactions with the target NaV channels by molecular docking.

Methods: Structures of 7 NaV channels and three toxins were used for molecular docking studies performed by HADDOCK and AutoDock Vina. The resulting complexes were statistically analyzed to identify the differences in binding energies and non-polar interactions between NaV channels and toxins.

Results and Discussion: In line with the literature, ASP1018, GLU1021, GLU1080 amino acids in NaV1.1 DIV(S1-S2) loop region, as well as LYS282, were found to be important binding sites for toxins. Analysis of the complex structures of NaV channels with different toxins explains the specific binding mechanism.

Conclusions: Molecular docking studies can reveal the differences in toxin binding residue preferences and the mechanism of selective toxin binding of NaV channels.

Keywords: Voltage gated sodium channels, toxins, molecular docking, protein interactions

A QSAR STUDY ON NOVEL 2,4-DIAMINOQUINAZOLINE DERIVATIVES TOWARD DESIGNING NEW LEAD COMPOUNDS FOR THE POTENTIAL TREATMENT OF SPINAL MUSCULAR ATROPHY

Gülben Sabuncu Gürses[1], Safiye Sağ Erdem[1], Melek Türker Saçan[2]

[1]Marmara University, Faculty of Science, Chemistry Department, Göztepe, Istanbul Turkey
[2]Bogazici University, Institute of Environmental Sciences, Istanbul, Turkey

Gülben Sabuncu Gürses / Marmara University, Faculty of Science, Chemistry Department, Göztepe, Istanbul Turkey

Introduction: Spinal Muscular Atrophy (SMA) is a neuromuscular disease that leads to muscle weakness and atrophy, resulting from low levels of SMN protein. Quinazoline-based compounds are promising since they were found to increase the SMN protein levels. We generated robust and valid quantitative-structure-activity-relationship (QSAR) models to predict SMN promoter activity of new candidate chemicals using experimental SMN promoter activity of quinazoline derivatives in the literature.

Methods: Geometry optimizations of dataset compounds were performed with M06-2X/6-31G(d) method using SPARTAN16 software. Numerous 0D-3D descriptors were obtained using Dragon 7.0.2 software. QSARINS 2.2.1. program was used for the training/test set division of dataset, for the selection of descriptors, and for the generation of validated QSAR models. The best models were selected using the multicriteria decision-making tool of the QSARINS and used to predict the SMN2 promoter activity values of 50 candidate chemicals that fell into the applicability domain (AD) of the generated models.

Results and Discussion: The three selected six to seven-descriptor QSAR models meet fit, internal, and external validation criteria. The predictive performance of all models was checked using the test set. The predicted SMN2 promoter activity values of noval chemicals within the AD of the generated QSAR models were obtained and lead candidates with high SMN2 promoter activity were highlighted.

Conclusions: This study contributes to the literature with several robust and predictive QSAR models using SMN2 promoter activity values of 2,4-diaminoquinazolines and predicting the SMN2 promoter activity of candidate chemicals that have no SMN2 promoter activity values. We thank Prof. Gramatica and Dr. Chirico for providing QSARINS.

Keywords: QSAR, SMN protein, SMA, DIAMINOQUINAZOLINE

PP-38

Synthesis and human monoamine oxidase inhibitory activity of novel C2-, C3- and C4-substituted phthalonitriles

Haytham Elzien Alamin Ali[2], Lalehan Özalp[1], Özkan Danış[1], Zafer Odabaş[1]

[1]Marmara University
[2]University of Khartoum

Lalehan Özalp / Marmara University

Introduction: Having two isoforms (MAO-A and MAO-B), monoamine oxidase (MAO) enzyme catalyzes the oxidative deamination of exogenous and endogenous amines(Herraiz et al., 2018). Selective inhibitors of MAO-B are critical for the treatment of Alzheimer's (Gökhan-Kelekçi et al., 2007) and Parkinson's disease (Abel, 1995) . Reversible inhibitors lack the adverse effects of irreversible inhibitors(Baker et al., 2000). Therefore, development of selective reversible MAO-B inhibitors still draws attention. C3-, C4- substituted phthalonitriles showed good MAO-B inhibitory activity and selectivity in literature (Manley-King, 2012). Here, we synthesized novel five C-3, C-4 and one C-2, C-3 substituted phthalonitrile derivatives and investigated their inhibitory activities against human MAO-A and MAO-B for the first time.

Methods: Diazenyl phthalonitriles (compounds 1–6) were synthesized (Scheme 1). The inhibitory activities of the test compounds on MAO activity were investigated by determining their effects on the production of H_2O_2 from p-tyramine and were expressed as IC50 values. Phthalonitrile compounds were subjected to geometry optimization by using Gaussian with M062X method and 6-31G(d,p) basis set. All compounds were docked to the crystalstructures of MAO-A (PDB ID: 2Z5X) and MAO-B (PDB ID: 2XFN) using Autodock4. Druglikeness profile was computed with Molinspiration software for each compound.

Results and Discussion: Compound 5 displayed the highest MAO-B selectivity. Compound 3 displayed the highest MAO-B activity, however, was not found to be the most selective phthalonitrile. Compound 1 displayed good inhibitory activity towards both isoforms. Compound 6, the only C2-, C3- substituted phthalonitrile derivative, showed the lowest MAO-B inhibitory activity.

Binding mode of Compound 5 in MAO-B.
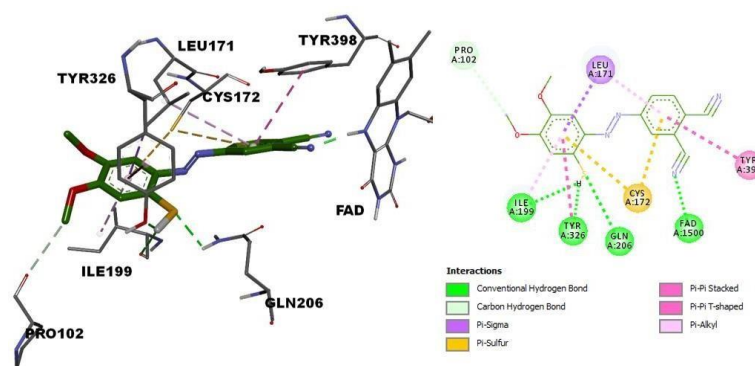
Gibbs free energy of binding, calculated inhibition constants and Selectivity Index (SI) for phthalonitrile derivatives in the study.

Compound	MAO-A Lowest Binding Energy (ΔG, kcal/mol)	Ki[a] (μM)	MAO-B Lowest Binding Energy (ΔG, kcal/mol)	Ki[a] (μM)	SI[b]
1	-7.86	1.72	-10.03	0.044	39.09
2	-8.40	0.69	-8.87	0.31	2.22
3	-6.79	10.5	-11.17	6.48×10^{-3}	1620
4	-7.43	3.57	-9.34	0.14	25.50
5	-8.24	0.91	-10.71	0.014	65
6	-8.82	0.34	-7.21	5.18	0.07

Conclusions: Compound 5 is promising as a potential selective MAO-B inhibitor.

Development of a new generation and high-throughput detection kit for monkeypox virus infection

Tuğba İLHAN[1], İlayda GÜLER[1], Apdul Sametcan VAR[1], Idris ARSLAN[1]

[1]Zonguldak Bülent Ecevit University Biomedical Engineering Zonguldak Türkiye

Tuğba İLHAN / Zonguldak Bülent Ecevit University Biomedical Engineering Zonguldak Türkiye

Introduction: Monkeypox virus is an enveloped double-stranded DNA virus that belongs to the Orthopoxvirus genus of the Poxviridae family. However, it is a viral zoonosis with symptoms similar to those seen in the past in smallpox patients, although it is clinically less severe. Although the smallpox vaccination eradicated smallpox in 1980s, monkeypox has recently emerged as the most important orthopoxvirus for public health.

Methods: To develop a diagnostic kit for a infectious diseases makes a vital role contribution to fight against the pathogens. To date, no knockout treatment or vaccination for monkeypox virus, but some detection kits are available. Herein, we have developed a IgG/IgM monkeypox virus detection kit (whole blood/serum/plasma) through in combination of recombinant DNA technology, molecular docking algoritms and CRISPR-Cas technologies. Our detection kit is based on a lateral flow immunochromatographic assay.

Results and Discussion: The aim of the project was to develop a new monkeypox viral detection kit based on recombinant DNA technology, molecular docking algoritms and CRISPR-Cas methods. However, assays for clinical performance and validation are still in progress. But, the preliminary results are so promising.

Conclusions: We have just developed a new, efficient and high-throughput monkeypox detection kit for fighting a viral enfection. After clinical assays it will be commercially available

Keywords: monkeypox virus, detection kit, IgG/IgM, monkeypox virus

PP-40
Synthesis and Evaluation of Functionalised Polycyclic Benzo[4,5]-Imidazo[1,2-a]-Pyrimidin-4-yl Structure

Mohamed Amari[1], Fairouz Abboub[1], Mokhtar Fodili[2]

[1]Faculty of Chemistry, USTHB, BP 32 El Alia 1611 Bab Ezzouar, Algiers, Algeria.
[2]Laboratory of organic chemistry and natural substances, ZianeAchour University, BP 3117 Ain El Chih, Djelfa, Algeria.

Mohamed Amari / Faculty of Chemistry, USTHB, BP 32 El Alia 1611 Bab Ezzouar, Algiers, Algeria.

Introduction: The choice of these two nuclei is mainly based on their biological [1], pharmacological [2] and agrochemical [3] activities, as well as on their environmental involvement through complexation with heavy metals [4]. With this in mind, and with the aim of continuing our research on the reactivity of 4-hydroxy-2-pyrones [5-7]

Methods: To prepare our series of products, an equimolar quantity (10 mmol) of the precursor 4-hydroxy-6-methylpyran-2-one 1 and of 2-aminobenzimidazole 2 must be dissolved in 20 ml of alcoholic solution (Scheme 1). The reaction mixture is stirred under reflux for various times determined by thin layer chromatographic monitoring. As soon as one of the reagents has completely disappeared, the solution is left to cool, the precipitate which forms is then recovered by filtration under filtered vacuum and then recrystallized from ethanol.

Scheme 1
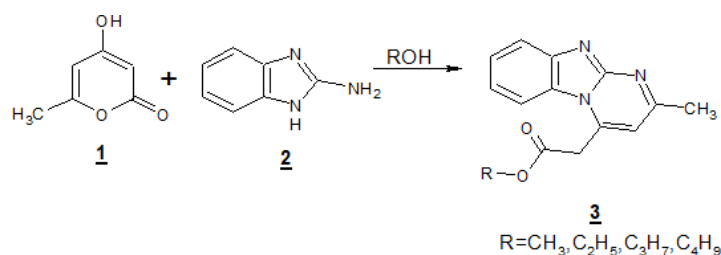
Results and Discussion: The reaction made it possible to isolate for each solvent a single compound whose structure was identified by 1H, 13C and IR NMR spectroscopic methods and elemental analysis.

Conclusions: The opening of the pyranic ring of 4-hydroxy-6-methyl pyran-2-one 1 in the presence of aminobenzimidazole 2 in different alcohols for various times, evolves by an esterification reaction towards the pyrimidine nucleus fused to benzimidazole 3. We found that the yields of the reactions studied depend on the nature of the solvent used. The results obtained confirm the interest of deacetylateddehydroacetic acid for the synthesis of new pyrimidine compounds.

Keywords: Dehydroacetic Acid, Benzimidazole, Pyrimidine

<div align="center">

PP-41

Development of Novel Diagnostic and Therapeutic Agents for Use in Hypoxic Cancer

</div>

Aminesena Başer[1], Gülşen Türkoğlu[1], Fatma Seçer-Çelik[1], İlkyaz Yılmaz[1], Sündüs Erbaş-Çakmak[1]

[1]Konya Food and Agriculture University

Aminesena Başer / Konya Food and Agriculture University

Introduction: Cancer is a complex disease and diagnosis-treatment of this disease requires discrimination of the region from healthy tissue using specific cancer markers. A common marker for solid cancer microenvironment is reduced oxygen level, known as hypoxia. In the project novel diagnostic probe and therapeutic agents are developed based. A probe and photodynamic agent show their effect through an induced spectral shift by the actions of elevated reductive enzymes of hypoxic cancer cells. One other agent is designed to bind to G-quadruplex rich oncogene promoters, including hypoxia regulator hif1a transcription factor, and change expression of certain genes.

Methods: Compounds were synthesized, purified by chromatographic methods and characterized using NMR and HRMS spectrometry. Viabilities were analyzed using MTT assay. Fluorescence imaging of the probe was done under normoxia and hypoxia conditions. Hypoxic environment was created by either in hypoxia chamber or through $CoCl_2.6H_2O$ treatment. PDT actions were investigated by $1O_2$ trap molecule and PI staining. G-quadruplex binding was analysed by FRET-melting assay. Gene expression analysis was done by qPCR method and cell migrations were analysed using wound healing method.

Results and Discussion: Hypoxia probe was shown to be nontoxic at the application dose and display enhanced emission under hypoxia. PDT agent produces cytotoxic $1O_2$ efficiently in its active form. PI staining indicates increased cell death in hypoxic cells. Efficient G-quadruplex stabilization compared to ds-DNA was recorded.

<div align="center">

Working principles of agents and their results

</div>
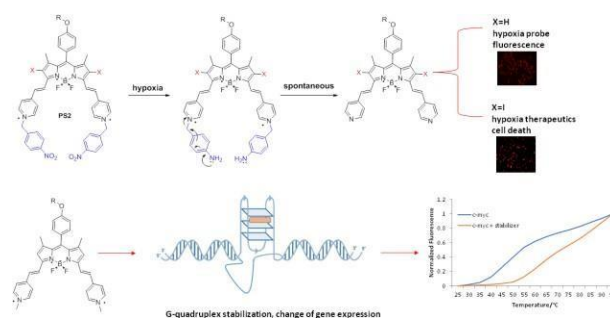
Conclusions: In the project novel hypoxia sensors and hypoxia-dependent therapeutic agents were developed and their activities were proved in hypoxic cells. Authors acknowledge the support by TÜBİTAK 1001, Grant No: 221Z058.

Keywords: cancer, hypoxia, gene regulation, fluorescence, photodynamic therapy

PP-42
**Investigation of Tomentosin β-Amino Alcohol Derivatives Interactions with
Topoisomerase II Enzyme Using Molecular Docking Method**

Ahmet Çağan[1], Akın Akıncıoglu[1], Tuba Aydın[1]

[1]Ağrı İbrahim Çeçen Universty

Ahmet Çağan / Ağrı İbrahim Çeçen Universty

Introduction: It is known that tomentosin (1) has cytotoxic effects on colorectal adenocarcinoma, lung cancer (Michalakea et al. 2019), leukemia (Yang et al. 2021) and many other cancer cells.

β-Amino Alcohol Derivatives
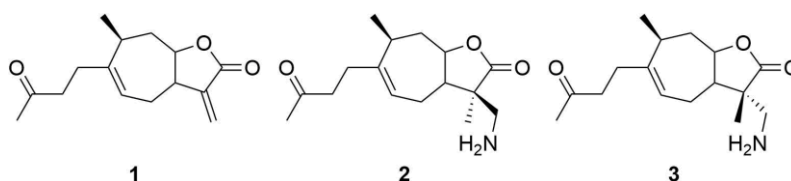
Methods: In addition, β-Amino alcohols are a broad class of compounds with a wide variety of bioactivities such as antiplasmodial, antileishmanial, antiproliferative, antimicrobial (Bai et al. 2011), and anti-cancer.

Results and Discussion: In this study, the interactions of β-amino alcohols substituted tomentosin analogs 2 and 3 with the enzyme topoisomerase II (PDB ID: 4FM9) were examined using the molecular docking method.

Conclusions: In order to understand the anticancer effect for compounds 2 and 3, the relationship with the 4FM9 topoisomerase II enzyme was investigated. Affinity values of -6.8 and -7.1 (kcal/mol) were calculated for compounds 2 and 3, respectively.1.Michalakea, E., Graikou, K., Aligiannis, N., Panoutsopoulos, G., Kalpoutzakis, E., Roussakis, C., & Chinou, I. (2019). Isolation and structure elucidation of secondary metabolites of two Greek endemic Inula species. Biological activities. Phytochemistry Letters, 31, 155-160.2.Yang, L., Xie, J., Almoallim, H. S., Alharbi, S. A., & Chen, Y. (2021). Tomentosin inhibits cell proliferation and induces apoptosis in MOLT-4 leukemia cancer cells through the inhibition of mTOR/PI3K/Akt signaling pathway. Journal of Biochemical and Molecular Toxicology, 35(4), e22719.3.Bai, B., Li, X. Y., Li, Y., & Zhu, H. J. (2011). Design, synthesis and cytotoxic activities of novel β-amino alcohol derivatives. Bioorganic & medicinal chemistry letters, 21(8), 2302-2304.

Keywords: tomentosin, docking

{Aspergillus Carneus} Metabolite Averufanin induced cell cycle arrest and apoptotic cell death on cancer cell lines via inducing DNA Damage

Deren Demirel[1], Ferhat Can Özkaya[3], Weaam Ebrahim[4], Emel Sokullu[2], İrem Durmaz Şahin[2]

[1]Koc University Research Center for Translational Medicine (KUTTAM), Sariyer, Istanbul, Turkey
[2]Koc University, School of Medicine, Sariyer, Istanbul, Turkey
[3]Aliaga Industrial Zone Technology Transfer Office, Aliaga, 35800 İzmir, Turkey
[4]Department of Pharmacognosy, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt.

Deren Demirel / Koc University Research Center for Translational Medicine (KUTTAM), Sariyer, Istanbul, Turkey

Introduction: Cancer is one of the leading causes of death worldwide, accounting for nearly 10 million deaths in 2020. Current treatment methods include hormone therapy, γ-radiation, immunotherapy, and chemotherapy. Although chemotherapy is the most effective treatment, there are major obstacles posed by resistance mechanisms of cancer cells and side-effects of the drugs, thus the search for novel anti-cancer compounds, especially from natural sources, is crucial for cancer pharmaceutics research. One natural source worthy of investigation is fungal species. In this study, the cytotoxicity of 5 metabolic compounds isolated from filamentous fungus Aspergillus Carneus. Arugosin C, Averufin, Averufanin, Nidurifin and Versicolorin C were analyzed.

Methods: NCI-SRB assay on 10 different cell lines of breast cancer, ovarian cancer, glioblastoma and non-tumorigenic cell lines were conducted. Averufanin showed highest cytotoxicity with lowest IC50 concentrations especially on breast cancer cells. Therefore, Averufanin was further investigated with PI Cell Cycle Assay, MUSE Apoptosis Assays and Western Blot to enlighten cell death mechanism induced and molecular mechanism of action.

Results and Discussion: Results indicated that Averufanin induced cell cycle arrest and apoptotic cell death on cancer cell lines via inducing DNA Damage.

Projected Cellular Mechanism of Action of Averufanin Compound
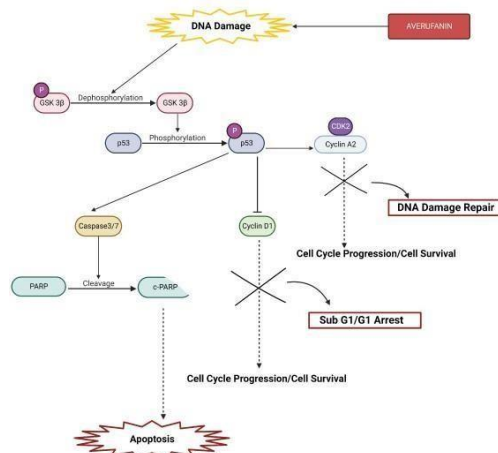
Conclusions: Consequently, this study shows that Averufanin can be contemplated and further explored as a new therapeutic strategy in breast cancer.

Synthesis of Various Organic Molecules and Smart Liquid-Liquid Microextraction Method Together with Slotted Quartz Tube Flame Atomic Absorption Spectrophotometer for the Determination of Trace Amounts of Metals in Biological Systems and Wastewater

Paye Naz Diridiri[1], Doç.Dr. Ömer Tahir GÜNKARA[1], Sezin ERARPAT[1], Prof.Dr. Sezgin BAKIRDERE[1]

[1]Yildiz Technical University

Paye Naz Diridiri / Yildiz Technical University

Introduction: In this study, it is aimed to develop an analytical method with high accuracy and sensitivity in which metals (Cd, Co, Ni, Cu) in biological systems can be determined at trace levels with an economical and simple method.

Methods: In this context, it is aimed to synthesize organic molecules to be used in the determination of cadmium metals, to apply the Smart Liquid-Liquid Microextraction technique, and then to determine them with high sensitivity in the Slotted Quartz Tube integrated Flame Atomic Absorption Spectrophotometer system.

Results and Discussion: As ligands calixarene, which is a phenolic-based macrocyclic compound consisting of repeat units of the phenol and methylene group, dating back to the nineteenth century, and other organic molecules will be used.

Calix[4]arene molecular structure
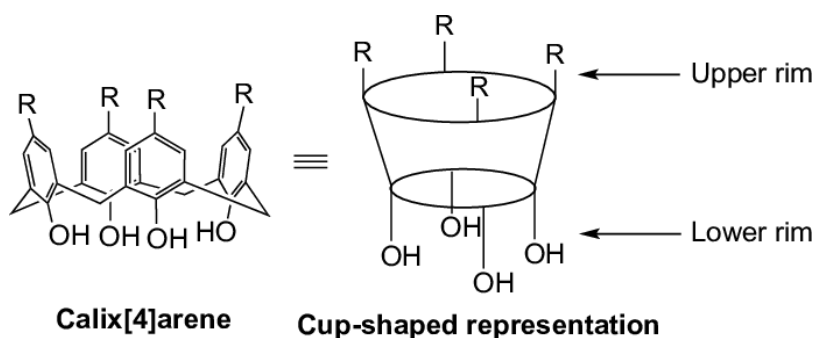
Hamid, Shafida & muhamad bunnori, Noraslinda & Ishola, Afeez & Ali, Yousaf. (2015). Applications of calixarenes in cancer chemotherapy: Facts and perspectives. Drug Design, Development and Therapy. 9. 2831. 10.2147/DDDT.S83213.

Conclusions: Thanks to its cyclic structure, functional groups can be attached to calixarenes, and other organic molecules used. Thus, these organic molecules gain the ability to accept guest species such as alkali and alkaline earth metal ions, lanthanide ions and silver ions.

Keywords: Flame Atomic Absorption Spectrophotometer, Biological Systems, Calixarenes, Metal selective ligands

PP-45
The Mechanism and Energetics of the Dynein Priming Stroke

Mert Golcuk[1], Sema Zeynep Yılmaz[1], Ahmet Yildiz[2], Mert Gur[1]

[1]Department of Mechanical Engineering, Istanbul Technical University (ITU), 34437, Istanbul, Turkey
[2]Physics Department, University of California, Berkeley, CA, USA

Mert Golcuk / Department of Mechanical Engineering, Istanbul Technical University (ITU), 34437, Istanbul, Turkey

Introduction: Dyneins are AAA+ motors that move progressively straight to the minus end of the microtubule (MT). The dysfunctionality of dyneins has been associated with numerous neurodegenerative diseases and disorders, and play important roles in cell division and motility. Understanding how dynein generates motility and force on MTs is essential to develop novel chemical inhibitors/modifiers of dynein function for the treatment.

Methods: We performed all-atom conventional (cMD), steered, and umbrella sampling (UMD) molecular dynamics simulations of dynein to elucidate the conformational transition and energetics of the dynein priming stroke, where linker moves from straight to bent conformation. The full-length human dynein-2 motor domain structure in complex with ADP.Vi (PDB ID:4RH7) was selected as the starting structure. Structure was solvated in a water box and ions were added (System size:781,332 atoms).

Results and Discussion: Free energy surfaces constructed for the dynein motor domain show that the priming stroke is an energy neutral process separated by a 5.7 kT energy barrier from the straight conformation. Also, our simulations showed that fully extended straight post-power stroke conformation of the linker is not possible for a closed ring due to steric clash at its AAA4 module, and linker adopts two conformational states at the surface of a closed AAA+ ring.

Conclusions: We investigated the mechanism and energetics of linker movement between its bent and straight conformations. The free energy surface obtained via UMD and cMD simulations of the dynein motor domain showed that the priming stroke is an energetically neutral process when the catalytic ring is in its closed conformation.

Keywords: Dynein, Molecular Dynamics, Mechanochemical Cycle, Umbrella Sampling

PP-46

Accelerated MD simulations elucidate that conformational preference of AR antiandrogens contributes to agonism/antagonism

Ebru Akkus[1], Muslum Yildiz[1], Abdulkadir Kocak[1]

[1]Gebze Technical University

Ebru Akkus / Gebze Technical University

Introduction: Affecting millions of men all over the world, prostate cancer (PCa) is a complex disease that can develop from the prostate gland, a male reproductive accessory organ (Rebello et al., 2021). The disease progresses with elevated concentrations of androgen levels. The treatment includes but not limited to use antiandrogens, acting as antagonists to androgen receptor (AR) signaling. However, long term use of these small drugs causes AR to develop resistance by mutations. Furthermore, these mutations can convert antagonist molecules to behave as agonists, enhancing the cancer progress. Although the mechanism of agonist to antagonist conversion is yet to be fully elucidated, studies have shown that the Helix-12 (H12) repositioning might account for agonistic/antagonistic conformations. Widely used first generation antiandrogens such as bicalutamide (BIC) and second generation antiandrogens such as enzalutamide (ENZ) are known to switch to agonistic behavior upon mutations such as F876L, T877A and W741L. To the best of our knowledge, there is no mutations reported responsible for agonistic behavior of one of the most recent antiandrogens, darolutamide (DAR).

Methods: Using Accelerated Molecular Dynamics simulations in AMBER22, we have investigated several antiandrogens in mutations of AR.

Results and Discussion: We reveal that darolutamide, a second generation antiandrogen, possesses conformational change throughout MD simulations.

Conclusions: We reveal that conformational change in antiandrogen structures might contribute for agonistic/antagonistic behavior.

Keywords: androgen receptor, accelerated MD, darolutamide, antagonist, AR mutation

PP-47

Regulating the Expression of Oncogenes or Genes Associated With Cancer Energy Metabolic Switching Through Tissue/Site Specific DNAAlkylation and Stabilization

H. Beyza Doğan[1], Beyza Başar[1], Gülnur Şener[2], Cihad Özdemir[1], Aminesena Başer[1], Nezahat Gökçe Özsamur[1], Fatma Seçer Çelik[1], Sündüs Erbaş Çakmak[1]

[1]Konya Food and Agriculture University
[2]Sabancı University

H. Beyza Doğan / Konya Food and Agriculture University

Introduction: DNA alkylation or stabilization of DNA secondary structures are recently attracting attention as a therapeutic tool for cancer. In this study, novel DNA secondary structure stabilizers are developed for site specific DNA alkylation or cell specific gene regulation. DNA alkylation potential as well as effect on the expression of oncogenes, genes associated with energy metabolism were investigated under normoxia and/or hypoxia.

Methods: Ligands were synthesized, purified by using chromatographic methods and characterized by 1H NMR, 13C NMR and HRMS spectroscopy. Stabilization G-quadruplex DNA structures were tested by FRET melting assay. DNA alkylation was checked by gel electrophoresis. Cell viability was performed by MTT assay in MCF-7 cells. Hypoxic microenvironment was mimicked by CoCl2.6H2O induced accumulation of HIF1α. Gene expression analysis will be done by qPCR.

Results and Discussion: It has been proven that the molecules stabilize the G-quadruplex but not the ds-DNA. These agents were shown to be non-toxic to cells both in hypoxia and normoxia below 2 µM. Agent conjugated with the alkylating chlorambucil moiety display a significant change in DNA melting curves of certain oligomers which is attributed to site specific alkylation of G-quadruplexes of certain oncogenes as opposed to ds-DNA.

Figure
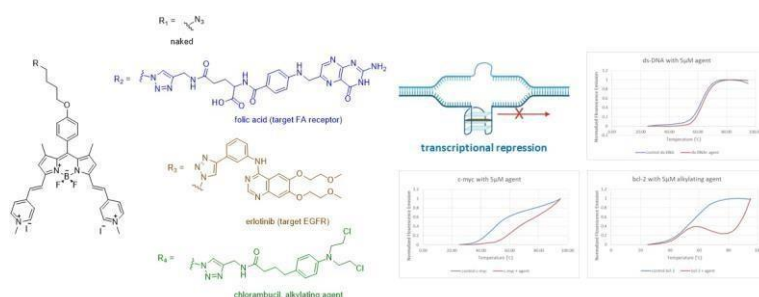
BODIPY- based agents conjugated with different ligands display a significant change in DNA melting curves of certain oligomers with G-quadruplex.

Conclusions: Novel G-quadruplex stabilizers can reduce the expression of oncogenes and genes associated with cancer energy metabolic switching providing a novel tool for potential cancer therapies.

Keywords: G-quadruplex, DNA alkylation, DNA stabilization, Cell targeting

Investigation of Reaction Mechanism of Human Lysosomal Cathepsin A Enzyme in silico

Berkehan Kura[1], Nurcan Şenyurt Tüzün[1]

[1]ITU

Berkehan Kura / ITU

Introduction: This research is finding barriers of activation mechanism of human Cathepsin A enzyme. Model studies have been successfully computed. 3 sets of calculations have been planned. Simplest model calculations are finished and will be reported. Middle sized model has some other important parts of the enzyme such as the oxianion hole. Structures are optimized and some barriers are examined. Having critical bond lenghts and angles from this data, we have modeled the active site of enzyme with cluster method. Presently calculations are proceeding with cluster method.

Methods: For stage 1 and stage 2 calculations, m062x0 functional and 6-311++G(d,p) basis set are used with implicit solvent (water) calculations with PCM method. For the cluster calculations, b3lyp functional in gas phase is used. The basis set for cluster calculations are hybrid. A standart basis set 6-31g(d) is used. For the atoms that can have a minus charge in ligand and protein 6-31+g(d) basis set is used. For the important hydrogens that are doing important H-bond interactions 6-31g(d,p) basis set is used.

Results and Discussion: For stage 1 calculations, a maximum barrier above 31kcal/mol is computed. It should be noted that this is a very simple model which does not include the catalytic aminoacid Asp372. With introduction of Asp372 and the oxianion hole, calculations showed the barriers reduced around 23 kcal/mol. With stage 3 cluster calculations we have found some mechanistical differences with stage 2 calculations indicating stage 3 calculations are indeed neccessary. Stage 3 calculations are still being computed.

Conclusions: Computations are required for final conclusions.

Keywords: DFT, Cluster, Cathepsin A, Carboxypeptidase, Enzyme

An Overview of Bioanalytical Assays and Techniques Used at Antibody-Drug Conjugate (ADC) Characterization

İsmail Emir Akyıldız[1], Sezer Acar[2], Sinem Raday[2], Dilek Demirel[2], Özge Erdem[2]

[1]Marmara University
[2]Balparmak R&D Center

İsmail Emir Akyıldız / Marmara University

Introduction: Antibody-drug conjugate (ADC) biotherapeutics are an emerging type of pharmaceutical that conduct multiple monoclonal antibodies combined with a linker that designs to enable the transportation and selective release of cytotoxic drugs in close proximity to tumors.

Methods: ADCs typically incorporate both large and small molecule characteristics and the inherent complexity of the mAb, combined with the added variability introduced by the drug, presents challenges in terms of bioanalysis. Hence, multiple bioanalytical obstacles should be overcome for ADCs.

Results and Discussion: ADC characterization includes structural confirmation, purity, homogeneity, and stability assays. Total antibody assays, total conjugated ADC assays, free drug assays, immunogenicity assessments, and anti-drug antibody assays are some of the well-known tests. To confirm ADC identity, binding assays, DAR profiling, charge determination, and peptide mapping should also be performed. LBA assays for efficacy, SDS-PAGE for MW characterization, SEC for aggregate analysis, charge determination using IEX or CE, and Circular Dichroism to confirm conformational changes are the mainly used techniques. Recently, chromatographic techniques are ubiquitous. LC-HIC-UV, RP-LCMS, using either a QTOF, ion mobility QTOF or an Orbitrap, and MALDI-TOF are the most used ones. UPLC-QTOF for deglycosylated ADCs can provide direct measurements of DAR. They can also be profiled by harnessing HIC LC-UV/MS. Orthogonal separation as 2D-LC combining HIC and RP in tandem can also be evaluated for resolving the ADC isomers. Hybrid techniques are also discussed such as LBA-LC-MRM.

Conclusions: Although, MS systems are versatile and gaining more attention, more than a single technique must be in use sequentially for the comprehensive characterization of ADCs.

Keywords: Antibody-Drug-Conjugates, Bioanalysis, Multi-Attribute-Monitoring, Cancer

IN SILICO CHARACTERIZATION OF THE KLEBSIELLA PNEUMONIAE TETRAHYDRODIPICOLINATE N-SUCCINYLTRANSFERASE (DapD) ENZYME AND IDENTIFICATION OF NOVELANTIMICROBIALS VIA HIGH-THROUGHPUT SCREENING

Seda Nematipour[2], Safiye Sag Erdem[2], Ozal Mutlu[3]

[1]Marmara University
[2]Marmara University Chemistry
[3]Marmara University Biology

Seda Nematipour / Marmara University Chemistry

Introduction: Antimicrobial resistance represents one of the biggest threats facing modern medicine. Resistance to a wide range of antibiotics has been acquired by Klebsiella pneumoniae strains over the last few decades. We chose dapD (2,3,4,5-tetrahydropyridine-2,6-dicarboxylate N-succinyltransferase) as a target since it is a verified druggable target considering gene essentiality.

Methods: The enzyme does not have a verified 3D structure in Protein Data Bank therefore we generated the 3D structure with homology modelling and performed high throughput virtual screening against a world approved drugs library of 9967 ligands downloaded from ZINC15 database. HTVS was performed using Schrodinger Glide.

Results and Discussion: Glide Gscore (ligand binding free energy) highest limit was chosen as -8 kcal/mol. Out of 9967 ligands 33 was found to have better Gscore than -8 kcal/mol. The active site residue interactions of these ligands were analyzed with ligand interaction diagram. We propose these ligands as potential antibacterial lead compounds.

Conclusions: Klebsiella Pneumoniae dapD was used first time as an antimicrobial target in a repurposing study. The results can contribute to potential repurposing and/or ligand design studies.

Keywords: klebsiella pneumoniae, homology modelling, htvs, antimicrobial resistance, dapD

A DFT Study On The Mechanism Of Catalytic Asymmetric Synthesis Of Chiral Amines As Drug Building Blocks

Merve Kopar[1], Nurcan Şenyurt Tüzün[1]

[1]Istanbul Technical University

Merve Kopar / Istanbul Technical University

Introduction: Asymmetric synthesis of chiral amines are one of the important building blocks or constituents of pharmaceutical products. In that respect, obtaining enantiopure products, especially by enzymes is a very demanding area of organic synthesis, due to their environmentally friendly approach. For this purpose, a significant amount of work with IREDs with high R/S selectivity stands out. The aim of this study is to investigate the mechanism of enzymatic asymmetric chiral amine synthesis via in silico methods. For this purpose, Stackebrandtia nassauensis (SnIR), an imine reductase is investigated in the study.

Methods: Calculations were started with a quantum mechanical model study in order to determine the appropriate coordinates and geometries for the reaction between the substrate and the model of reacting NADPH. Then, critical residues of SnIR and other IREDs in the literature were examined and dockings were performed for the selection of critical residues to create a quantum mechanical model cluster of the enzyme. Coenzyme, enzyme and substrate interactions were examined in these imine reductase enzymes and utilized in further cluster formation. After cluster formation, hydride transfer reaction was investigated using 1-methyl-3,4-dihydroisoquinoline as substrate.

Results and Discussion: Transition state structures were found for both S and R enantiomers and the barriers from DFT calculations were compared to account for the experimental enantioselectivity.

Conclusions: The preliminary calculations gave a lower barrier for R enantiomer than S, contrary to the experimental findings. However, the cluster approach will be further refined.

Keywords: Chiral Amines, Imine Reductases, Asymmetric Synthesis, Enzymes, Pharmaceutical Products

Small Molecular inhibitors of Aurora kinase B; From Structural Insight to Mechanism Based Design

Sajda Ashraf[1]

[1]TrustLife

Sajda Ashraf / TrustLife

Introduction: Aneuploidy, one of the eight hallmarks of cancer, arises following the dysfunctional segregation of chromosome during cell division1. Aurora kinase B is a protein that play critical role in the attachment of the mitotic spindle to the centromere2. Over expression of this protein in various cancers prompt us to identify new leads against the target as a possible strategy to control cancer associated abrupt cell division.

Methods: By utilizing integrated computational techniques, including homology modeling, 3D-QSAR and pharmacophore-based virtual screening, we proposed some novel compounds as potential Aurora kinase B inhibitors. Additionally, highly significant 3D-QSAR model was developed with cross validation value (q2) of 0.602 and linear regression value (r2) of 0.936. These values reflect statistical reliability of our generated model. Moreover, the obtained best pharmacophore model was used for virtual screening against a database of over 30 million drug like molecules which were randomly selected from large commercially available databases i.e. Chembridge, National Cancer Institute's (NCI), Maybridge and ZINC database.

Results and Discussion: The results suggested that the identified compounds retained the interactions with binding residues. Binding energy decomposition identified residues Glu155, Trp156 and Ala157 of site B and Leu83 and Leu207 of site C as major contributors to binding affinity, complementary to 3D-QSAR results. To best of our knowledge, this is the first comparison of WaterSwap field and 3D-QSAR maps.

Conclusions: Overall, this integrated strategy provides a basis for the development of new and potential AK-B inhibitors and is applicable to other protein targets.

Keywords: Auror Kinase B, Molecular docking, 3D-QSAR, MD-Simulation, Binding Free Energies

Affinity determination of antisense oligonucleotides specifically designed for conserved regions of the SARS-CoV-2 genome by in-silico analyses

Eylül Aydın[1], Ufuk Amanvermez[1], Berk Ergun[2], İlayda Şahin[3], Sezer Akyöney[4], Özkan Özdemir[1], Özden Hatırnaz Ng[5]

[1]Department of Genome Studies, Graduate School of Health Sciences, Acibadem Mehmet Ali Aydinlar University, Istanbul, Türkiye
[2]Geniva Informatics and Health Ltd.
[3]Department of Medical Biotechnology, Graduate School of Health Sciences, Acibadem Mehmet Ali Aydinlar University, Istanbul, Türkiye
[4]Department of Biostatistics and Bioinformatics, Graduate School of Health Sciences, Acibadem Mehmet Ali Aydinlar University, Istanbul, Türkiye
[5]Department of Medical Biology, School of Medicine, Acibadem Mehmet Ali Aydinlar University, Istanbul, Türkiye

Eylül Aydın / Department of Genome Studies, Graduate School of Health Sciences, Acibadem Mehmet Ali Aydinlar University, Istanbul, Türkiye

Introduction: In Turkiye, as millions were affected, thousands of people lost their lives due to COVID-19. New treatment approaches are needed due to procurement, the uncertainty of immunity, and new variants. Antisense-oligonucleotides (ASOs) inhibit RNA translation to prevent critical protein synthesis by targeting viral RNA genome/transcripts, disrupting the viral life cycle. Peptide-conjugated phosphorodiamidate morpholino oligonucleotides, third-generation-ASOs, target viral genes without affecting the host, reducing the negative side effects. Here, we aim to develop a suitable therapy with inhalation delivery, following a stepwise in-silico analysis approach to determine the affinity of ASOs explicitly designed for SARS-CoV-2.

Methods: The most conserved regions were identified by multiple-sequence-alignment using MAFFT for 4.5 million sequences (GISAID, January 2022). Then, the top 2000 with >99.9% conservation were checked for GC content, Tm value, and secondary structures. Suitable primers were tested for binding to SARS-CoV-2 with high-affinity and human genome with low-affinity, prioritizing those having no correspondence to a coding and/or regulatory region in the human genome.

Results and Discussion: For primers with an affinity for the human genome, tissue- and single-cell-gene expression was checked from GTEx. It was considered that the related regions were outside the coding regions/not expressed in the lung since our therapy relies on inhalation. For modeling, RNAfold and RNAup were used for RNA-secondary-structure and RNA-RNA-interaction-prediction, respectively. Docking scores obtained from simulations were compared based on value and consistency between the top 10 models.

Conclusions: A ranking system was developed and after PCR validation of the top 6, thethree most efficient were selected as ASO-based-therapy candidates. Supported-by-TUBİTAK, No:121S921

Keywords: SARS-CoV-2, COVID-19, docking, antisense oligonucleotides, RNA interference

PP-54

Ph-responsive hydrogel beads for controlled drug delivery of indomethacin

BOUSLAH MOKHNACHI NAIMA[1], BOUKHADRA SAFIA[1], BOUNABI LEILA[1], KHERFI HAMZA[1], OUAZIB FARID[1], BAA NESMA[1]

[1]University of Sciences and Technology Houari Boumediene, USTHB,

BOUSLAH MOKHNACHI NAIMA / University of Sciences and Technology Houari Boumediene, USTHB,

Introduction: Colonic drug delivery is significantly important for treatment of diseases associated with colon such as colon cancer, colonic polyps, treatment of inflammatory bowel as well as for the delivery of antiasthmatic and antihypertensive drugs. Hydrogels beads are three-dimensional, cross-linked networks of hydrophilic polymers that can potentially be used for the development of "smart" delivery systems, which are capable of control release of the encapsulated drug at a targeted colon site.This study was devoted to the development of microbeads based on sodium alginate (Alg) or sodium alginate / polyvinyl pyrrolidone blend (AG / PVP) as drug delivery systems of indomethacin drug.

Methods: The free and drug loaded hydrogel microbeads based on sodium alginate (Alg) or sodium alginate / polyvinyl pyrrolidone blend (AG / PVP) were synthesized by the ionotropic gelation method using CaCl2 as crosslinking agent.

Results and Discussion: Swelling behaviour of unloaded and indomethacin-loaded microbeads in different media, at regular time was strongly influenced by the pH of the medium and the highest swelling rates were reached in simulated intestinal fluid . The drug, the unloaded beads and the drug loaded beads were characterized by FTIR spectroscopy, (DTA) and (TGA) thermal analysis. DTA study showed that the melting peak of indomethacin was removed in all formulations suggesting an amorphisation of the drug in the beads. The release kinetics from the Alg/IND and Alg-PVP/IND beads revealed that the Alg beads ensure a slower release of the drug.

Conclusions: The study confirmed controlled release of the drug from microbeads providing longer duration of action in chronic diseases.

Keywords: Swelling, Drug release, Indomethacin, polymeric system, pH-sensitive Hydrogel

Elaboration of pH-sensitive Calcium alginate/poly(vinyl alcohol) hydrogel beads Study of The antioxidant activity and antibacterial properties

HADJ-HAMOU Assia Siham[1], TOUZOUT Zineb[1], ABDELLAOUI Naima[1], ABDELLAOUI Karima[4]

[1]University of Sciences and Technology Houari Boumediene, Polymer Materials Laboratory, Department de macromolecular chemistry, Faculty of chemistry, BP 32, El Alia, Algiers Algeria 16111.
[2]University of Sciences and Technology Houari Boumediene, Polymer Materials Laboratory, Department de macromolecular chemistry, Faculty of chemistry, BP 32, El Alia, Algiers Algeria 16111.
[3]University of Sciences and Technology Houari Boumediene, Polymer Materials Laboratory, Department de macromolecular chemistry, Faculty of chemistry, BP 32, El Alia, Algiers Algeria 16111.
[4]University of Sciences and Technology Houari Boumediene, Reaction Engineering Laboratory. Faculty of Mechanical engineering and Process engineering, BP 32, El Alia, Algiers Algeria 16111.

HADJ-HAMOU Assia Siham / University of Sciences and Technology Houari Boumediene, Polymer Materials Laboratory, Department de macromolecular chemistry, Faculty of chemistry, BP 32, El Alia, Algiers Algeria 16111.

Introduction: Curcumin (Cur), due to its anticancer, antioxidant and antibacterial properties, has been widely used as an alternative therapeutic agent for various diseases. In this study, new beads formulations based on Sodium Alginate biopolymer (SA) and Poly Vinyl Alcohol (PVA) were successfully prepared by ionotropic gelation method of SA using Calcium Chloride $CaCl_2$ as a cross-linker agent followed by freeze-thawing (FT) cycles for further crosslinking of PVA.

Methods: The encapsulation efficiency and the loading capacity of the prepared beads were evaluated using Cur as the model drug. CA/PVA and CA/ PVA/Cur were characterized by FTIR and UV spectroscopy. The in vitro release study of Cur loaded beads was investigated at 37°C in simulated gastric fluid, simulated intestinal fluid and simulated colonic fluid. The antioxidant activity and the potential antibacterial properties of the elaborated beads against E.coli and S.aureus were also evaluated.

Results and Discussion: The obtained results indicate that the swelling, the degradation and the behavior of the developed beads were influenced by the pH of the test medium and the PVA content. The introduction of PVA into the SA matrix greatly enhanced the physicochemical properties of the elaborated beads. Results also suggested that the antioxidant activity of the loaded beads (CA/PVA/Cur) at composition of (30/70) showed a higher DPPH radical-scavenging activity while the formulation (CA/PVA/Cur) (50/50) proved to be the most effective against the two bacterial strains compared to the other combinations

Conclusions: The good antioxidant activity and antibacterial properties of these materials make them promising for the development of novel drug carrier systems.

Keywords: Curcumin, Biopolymer, Antioxidant and Antibacterial properties, Poly Vinyl Alcohol, Sodium Alginate

PP-56
Deep learning approach to predict selectivity of bioactive compounds retention time of a new RP-HPLC column

FERROUKHI Ouassila[1]

[1]University of Sciences and Technologie Houari Boumediene of Algiers

FERROUKHI Ouassila / University of Sciences and Technologie Houari Boumediene of Algiers

Introduction: Retention time is an important parameter for identification in LC. In recent years, extensive research in the field of Deep Learning (DL) has led to the development of a wide array of machine learning algorithms dedicated to solving complex tasks in the field of analyte identification [1].In this work, a deep Learning-based prediction software equipped with a friendly graphical user interface to predict selectivity of the bioactive molecules towards a new mesogenic ether crown RP-HPLC phase has been developed.

Methods: After the synthesis of the new RP-HPLC column, its characterization was made with proton NMR and the nematic state was determined by DSC. DL using PAH's descriptors based on retention times of the RP-HPLC, built the model algorithms.

Results and Discussion: Thermal study of the new material exhibits transitions in Vant' Hoff plots indicating changes in the structure of the phase, and analytical chromatographic behaviors show molecular shape recognition towards planar and non-planar solutes probably due to the mesogenic state [2].Several training operations were performed on a dataset of PAHs, which is primarily used for building a model that relates defined characteristics of the analytes in the training set to their tR and LnK values, in order to test the efficiency of the code validating the implemented model.

Conclusions: The stationnary phase exhibits successful separation of bioactive compounds with shape recognition. Using deep learning, good values of evaluation metrics indicate that the column can be recommended for the prediction of tr and Lnk of a target compound of known chemical structure.

Keywords: Deep learning, RP-HPLC, mesogenic material, ether crown

PP-57
Discovering Anti-Cancer Molecules Targeting p53-MDM2 Interaction by Drug Repurposing

Alpsu Olkan[1], Ece Erdemoglu[2], Serdar Durdagi[1]

[1]Bahcesehir University School Of Medicine
[2]Mersin University School Of Medicine

Alpsu Olkan / Bahcesehir University School Of Medicine

Introduction: At structural and biological levels the well-characterized p53-MDM2 relationship in many cancer pathways, the inadequacy of selective inhibitors in the literature, and the increasing interest in PPI in drug development studies make the inhibition of this interaction a promising approach to activate p53.In the present study we aimed to propose novel inhibitors with high efficiency and low side effects against MDM2 protein.In this context almost 2360 FDA clinically approved compounds have been retrieved and prepared.Then they were docked with our prepared crystal structure (PDB:1T4F) at the binding cavity that interacts with p53.Top 10 compounds based on docking score were selected for further investigations.Short (10-ns) and long (100-ns) molecular dynamics (MD) simulations were then carried out to examine the structural and dynamic profiles of selected identified compoundsby supporting it with MM/GBSA calculations.Finally based on computational analysis, selected top 6 compounds have been proposed and compared with MDM2-p53 inhibitors in the literature.

Methods: 1.Preparation of protein crystals that were taken from PDB (1T4F)2.Preparation of small molecules through Maestro modeling suite3.Receptor Grid Generation4.Molecular Docking5.Molecular Dynamics (MD)6.MM/GBSA Calculations7.MetaCore/MetaDrug (Anti-cancer activity)

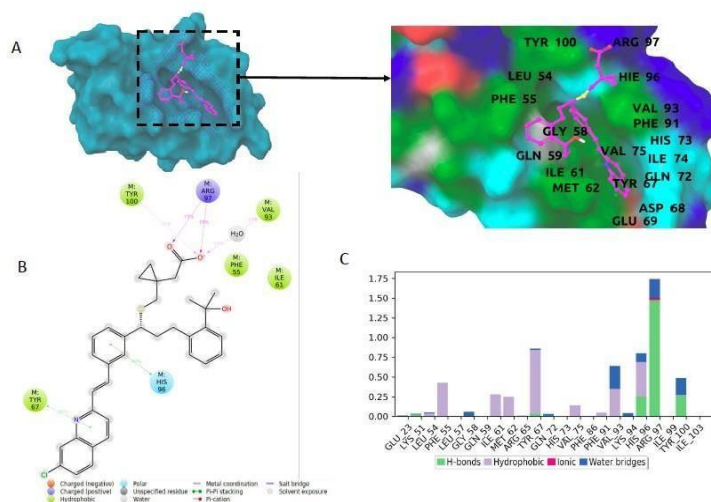**Results and Discussion**: .

Montelukast

Figure 1. (A) Surface representation of the Montelukast at the binding pocket of MDM2. The average frame from 100-ns trajectory was used. (B) 2D ligand interaction diagram of Montelukast at MDM2 binding site. (C) Interaction fractions of binding pocket residues of MDM2 with Montelukast throughout the MD simulations. Results show statistical results of collected 1000-trajectory frames throughout 100-ns MD simulation.

Docking Scores

MOLECULE	DOCKING SCORE (kcal/mol)	MMGBSA results (kcal/mol) (after 10-ns MD simulation)	Standart Deviation of MMGBSA results after 10-ns MD simulation	MMGBSA results (kcal/mol) (after 100-ns MD simulation)	Standart Deviation of MMGBSA results after 10-ns MD simulation	CANCER ACTIVITY (MetaCore/MetaDrug)
Montelukast	-6.90	-81.23	17.01	-80.85	7.41	0.67
Cangrelor	-8.94	-55.25	4.41	-60.43	9.58	0.79
Methylprednisolone	-6.82	-56.30	3.85	-59.53	4.41	0.33
Eltrombopag	-7.34	-61.36	13.05	-58.73	6.73	0.46
Cefoperazone	-6.72	-63.47	13.57	-57.06	6.46	0.58
Pitavastatin	-7.29	-56.90	20.30	-54.22	4.50	0.41
Idasanutlin	-5.71	-69.91	15.24	-74.77	5.65	0.56
Nutlin-3a	-5.71	-61.87	3.92	-60.88	2.97	0.76

Table 1. Docking scores of top-6 compounds at the MDM2 binding site with 2 reference molecules included. These compounds were initially used in short (10-ns) MD simulations. Table also shows average MM/GBSA scores of these compounds from derived 100-trajectories throughout the short (10-ns) and long (100-ns) MD simulations. Prediction of cancer therapeutic activity for the selected hit molecules using MetaCore/MetaDrug was also reported in the table.

Conclusions: In conclusion these calculations have shown that the following 6 compounds can be considered as MDM2 inhibitors:Montelukast,Cangrelor,Methylprednisolone, Eltrombopag,Cefoperazone,Pitavastatin.These compounds might be preclinically investigated,and if the simulation and in-vitro results are confirmed, they could be used as clinical investigation against cancer.Montelukast a leukotriene receptor antagonist,was found as the best compound against MDM2 in our study.At last but not least, this is the first study that shows Montelukast as a promising compound against MDM2 inhibition.

Keywords: Cancer P53 MDM2 Protein-Protein Interaction Drug Repurposing

Virtual Screening of Small Molecule Libraries Against ERCC1-XPF for the Identification of Potent Inhibitors

Salma Ghazy[1], Serdar Durdagi[1]

[1]Bahcesehir University

Salma Ghazy / Bahcesehir University

Introduction: A fundamental characteristic of cancer is its acquired ability to evade chemotherapeutic drugs. Nuclear excision repair is a pathway of choice in repairing DNA lesions brought about by drugs like Cisplatin. ERCC1-XPF complex plays the main role in this pathway, monitoring the healing of intrastrand Pt-DNA adducts in addition to interstrand crosslinks, and double-strand breaks. Unrepaired DNA lesions interrupt mechanisms such as DNA replication and transcription, inducing apoptosis to lead to cancer cell death and tumor diminishing. ERCC1-XPF also shares in preserving genome consistency. The inhibition of ERCC1-XPF – via substituting the side chain of the Phe293 residue on the ERCC1 protein in dimerization form with XPF – enhances chemotherapy and bypasses the resistance mechanism of cancer cells. This study aims to screen small molecule drug libraries to obtain compounds with ERCC1-XPF inhibiting properties through the molecules' binding affinities to the XPF protein's HhH2 domain with interaction sites I, II, and III.

Methods: The predicted binding affinities of compounds were computed by variousmolecular docking scoring functions, including Glide, AutoDock Vina, and GOLD. Next, a neural network model was constructed on Canvas and then evaluated, followed by the calculation of the R2 value for further optimization. Lastly, a molecular dynamics simulation was conducted to observe how a biomolecular system functions and interacts with its environment.

Results and Discussion: The highest docking scores were shown with interaction site II using Glide XP. RMSD values of MD simulations show a maximum value of 4Å.

Conclusions: Results seem promising and further drug libraries will be investigated in detail.

Keywords: MD simulation, Virtual screening, Cancer, Neural Network, ERCC1-XPF

Discovery of new small molecules as RET tyrosine kinase inhibitor to stop the tumor growth of Thyroid cancers and non-small cell lung cancers occurring by RET protein mutations with minimum resistance to inhibitors

EHSAN SAYYAH[1]

[1]Bahçeşehir university Durdagi Lab (HITMER)

EHSAN SAYYAH / Bahçeşehir university Durdagi Lab (HITMER)

Introduction: Gene fusion and point mutations cause to activate RET tyrosine kinase where the gene fusion is responsible for non-small cell lung cancer and papillary thyroid cancers and the point mutation on the RET proto-oncogene, which is the receptor tyrosine kinase, causes multiple endocrine neoplasia type 2A and 2B (MEN2A, MEN2B) and Familial medullary thyroid cancer. Furthermore, small molecules as inhibitors bind to the binding site of RET kinase domain to block their enzymatic activity. On the other hand, a single amino acid change on the RET kinase position can provide resistance to the tyrosine kinase inhibitors, so it is essential to find a compound with activity against RET mutants. So, we hypothesize that with in-silico analysis of protein-protein interaction, we can discover new small molecules that can inhibit the activity of RET, so it can stop the growth of tumor sizes with the lowest resistance to that inhibitor.

Methods: •Text mining (obtain specific fragments of approved molecules)•Create fragment-based molecule libraries•Q-SAR model (using RET-specific molecules got from ChemBL database).•pIC50 Prediction•Cancer QSAR (Metacore) •Preparation of RET protein "Protein Preparation Wizard", "Grid Preparation", and "LigPrep"•Schrodinger virtual screen workflow•MD simulations-Calculate MMGBSA for each simulation.

Results and Discussion: we got good results from the MD simulation but till now we still predict pIC50 values of 3 libraries to get more molecules.

Conclusions: Our methods let us get very good results and till now we get more than 20 molecules but we still continue our research to get more results so from those molecules choose those that are more drug-likeness.

Keywords: RET proto-oncogene, in-silico drug discovery, RET inhibitor, thyroid carcinoma, non-small cell lung cancer

Virtual Screening of Large-Scale Small Molecule Libraries Against Bruton Tyrosine Kinase Effective in Chronic Lymphotic Leukemia

EZGİ SAMBUR[1], Prof. Dr. Serdar DURDAĞI[2]

[1]Health Sciences
[2]PHARMACY FACULTY

EZGİ SAMBUR / Health Sciences

Introduction: It is known that Bruton Tyrosine Kinases (BTKs) play a role in Chronic Lymphotic Leukemia (CLL), Mantle Cell Lymphoma (MCL), Waldenström's Macroglobulinemia, Marginal Zone Lymphoma and Graft Versus Host diseases. BTKs are a family of Tyrosine Kinases that are involved in signal transduction for the development and maturation of B lymphocytes. Overexpression of B cells causes cancer. BTKs are critical in the activation of the B-Cell Receptor (BCR) signaling pathway. Inhibiting the activation of BTKs in this part may be promising for the treatment of Chronic Lymphocytic Leukemia.

Methods: In this context, primarily Ligand Preparation, then Text Mining, then Covalent Docking, MD and MM-GBSA are used.

Results and Discussion: Therefore, in this study, we focus on identifying small molecule therapeutics that target the Human Bruton Tyrosine Kinase. We use the Ibrutinib molecule, which is known to inhibit BTKs, as a query molecule. Ibrutinib is an effective drug, especially used in the treatment of Chronic Lymphocytic Leukemia. In line with the results obtained in this study, Ibrutinib was chosen as the query molecule. Molecules similar to Ibrutinib were obtained by virtual screening methods. Despite the drug resistance to ibrutinib, the development of new hit molecules is promising.

Conclusions: IUPAC text files of molecular fragments at the Ibrutinib was used in the screening of 5 different libraries containing small molecules. More than 2 million molecules were screened. We performed covalent docking experiments on our molecules obtained with text mining. In this context, it is aimed to discover hit molecules that will inhibit BTK's with virtual scanning algorithms.

Keywords: Chronic Lymphocytic Leukemia (CLL), Covalent Docking, MD, Computational Biology, Text Mining

Discovery of novel Allatostatin type-c receptor agonists

Kübra Kahveci[1]

[1]Boğaziçi University

Kübra Kahveci / Boğaziçi University

Introduction: G-protein coupled receptors (GPCRs) are the most prominent receptor family of the cell membrane, and they have diverse roles in various signaling pathways. Due to their significant roles, GPCRs are popular drug targets and suitable candidates for next-generation pesticides. Allatostatin receptor type-c (AstR-C) is a class A GPCR responsible for the regulation of Juvenile Hormone (JH) secretion in insects. JH is vital for growth, development, metamorphosis, and reproduction. To date, only AST-C peptide has been identified for the receptor as a natural ligand. Therefore, AstR-C represents a potential pesticide target against Thaumetopoea pityocampa, the main factor limiting the growth and survival of the Mediterranean pine forests. The study aims to provide novel potent agonists of AstR-C for next-generation pesticide design.

Methods: Virtual screening was performed on previously described orthosteric pocket against ChemDiv libraries to discover potential AstR-C agonists. Molecular dynamics (MD) simulations and MM-GBSA calculations were applied to hit molecules. Biological evaluation of the agonist candidates was performed through TGF-a shedding assay and in vivo lethality tests on larvae.

Results and Discussion: Docking and MD simulations revealed the interactions in the orthosteric pocket. The in silico investigations presented ten agonist candidates. Lethality tests on larvae with promising candidates showed activity with LC50 values ranging from 406.121 to 1000 mg/L.

Conclusions: A combination of in silico and biological methods was conducted to identify new agonists of AstR-C, and four novel agonists of AstR-C have been discovered. Their activity against the receptor has been observed through different methodologies, and these molecules represent next-generation pesticides against Thaumetopoea pityocampa.

Keywords: GPCRs, drug discovery, next-generation pesticides, allatostatin

PP-62

IDENTIFICATION OF THERAPEUTIC MOLECULES THAT WILL INTERACT COVALENTLY AGAINST SARS-COV2 MAIN PROTEASE, SPIKE /ACE2, TMPRSS2 AND RDRP TARGET STRUCTURES USING STRUCTURE AND LIGAND-BASED IN SILICO APPROACHES AND IN VITRO TESTS

Murat Serilmez[1], Serdar Durdağı[1]

[1]Bahçeşehir University School of Medicine Computational Biology and Molecular Simulations Laboratory

Murat Serilmez / Bahçeşehir University School of Medicine Computational Biology and Molecular Simulations Laboratory

Introduction: In the COVID19 pandemic period which affects the whole world, At first there is no specific antiviral drug or vaccine for the treatment of the disease, and new solutions are being investigated in our country and in the world. These proteins are among the most attractive targets for the development of new drugs against SARS-CoV2 because of their important role in the cell entry, replication and transcription of the virus.It is aimed to determine the molecules to be covalently bound in drug screening for important target proteins for SARS-CoV2 (Spike/ACE2, TMPRSS2, Main Protease and RDRP by in silico methods and in vitro tests of the identified molecules

Methods: It was prepared at neutral pH by downloading FDA approved 2360 molecules from Drugbank. The LigPrep module in the Schrödinger Maestro program was used. The ionization process in the force field OPLS3e was performed at pH 7.4 using the Epic module.Covalent reactions were performed. The structures with the best docking score were taken into molecular simulation and MMGBA values are calculated.

3D image of the Natamycin molecule binding to Mpro and 2D ligant interaction diagram in the Mpro binding package
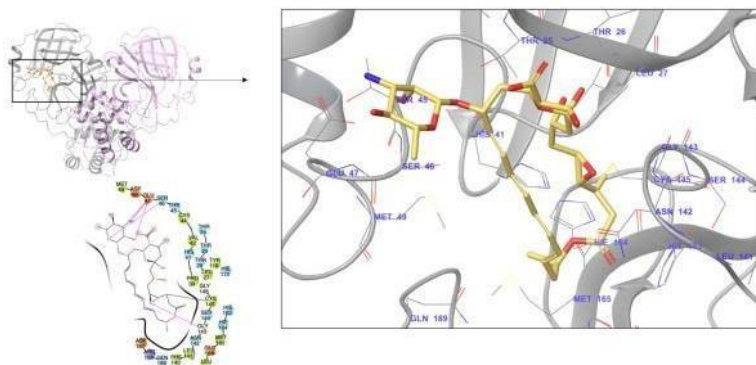
Mpro covalent docking reaction sites

Reaksiyon type	Reaction Sites	Successful covalent docking the number of ligands giving the score
Michael Addition	368	338
Nucleophilic Addition to a Double Bond	3202	1259
Nucleophilic Addition to a Triple Bond	64	62
Nucleophilic Substitution	946	933
Boronic Acid Addition	10	10
Epoxide Opening	32	31
Phosphonate Addition	97	92
Beta Lactam Addition	73	70
Conjugate Addition to Alkene (nitrile activated)	6	6
Conjugate Addition to Alkene (nitrile activated)	1	1
Conjugate Addition to Alkene (nitrile activated)	5	5
Disulfide Formation	18	18

Results and Discussion: Mpro in the target molecules with a high docking score for each covalent reaction Natamycin (-7.881) TMPRSS2 in the target Abarelix(-8.753), Spike ACE2 in the target Leucovorin(-7.021) RdRp in the target Candicidin (-7.817kcal/mol)

Conclusions: Drug repurposing in different indications is remarkable as it becomes less costly in terms of both time and required resources.By measuring the average binding energies during the MD simulation, drugs with high scores and whose interactions with critical amino acids, which are important in inhibition in target structures

Keywords: Covid 19, Mpro, Spike/ACE2, TMPRSS2, Covalent docking

Inhibition of c-MET interactions with downstream proteins for the treatment of cancer

Okan Sezgin[1], Serdar Durdagi[1]

[1]Bahcesehir University

Okan Sezgin / Bahcesehir University

Introduction: The MET gene is a proto-oncogene that is responsible for encoding the mesenchymal-epithelial transition factor. c-MET is a vital receptor for embryonic development, taking part in cell migration. c-MET carries out signal transduction from the extracellular matrix to the cytoplasm by binding with its ligand, the hepatocyte growth/scatter factor (HGF/SF). However, aberrant expression of the MET gene leads to cancer. The c-MET downstream signalling pathway includes PI3K/Akt/PKB, RAS/RAF/ERK/MAPK, and some other functional downstream members which are related to feedback and resistance mechanism of c-MET. Today, one of the biggest challenges for c-MET-targeted cancer therapy is treatment resistance (TR). Thus, it is necessary to create new and combinatorial therapies targeting receptor tyrosine kinases (RTKs). Therefore, we have investigated many c-MET downstream signaling pathways, and its juxtamembrane and extracellular domains.

Methods: we focused on the MET/HGF interactions by considering the hotspots on the surface of the MET and HGF protein. Interfaces and grids are elucidated by the support of literature and the Schrödinger Bioluminate package program. MET and HGF proteins were prepared by Schrödinger Maestro "Protein Preparation Wizard. Grids were formed by Glide: Receptor Grid generation . Enamine and ChemDiv Datasets were prepared by Schrödinger maestro Ligprep. Schrodinger Glide Virtual Screening Workflow was used for MET, HGF and MET-HGF and it includes filtering, Docking HTVS , SP, XP and MM-GBSA. Enamine and ChemDiv datasets were docked to the predicted binding sites and top-scoring molecule complexes were subjected to molecular dynamics simulation (MD) and MM/GBSA.

PP-64

Marin exopolysacharides and thier application in dermocosmetics

Safa Haddad[1], Rafik Marir[1]

[1]National higher school of biotechnology (ENSB), Constantine, ALGERIA.

Safa Haddad / National higher school of biotechnology (ENSB), Constantine, ALGERIA.

Introduction: The marine world can hold inexhaustible resources of bioactive molecules that can present various pharmacological applications. For example the marin exoplysacharide (EPS) matrices that surround bacteria allowing them to organize into biofilms for colonizing surfaces, exhibit different biological properties widely exploited in cosmetology as a natural substitute of hyaluronic acid or collagen, known for their restorative and cutaneous hydration properties.

Methods: the study consists of evaluating the biological properties of exopolysaccharides (EPS) extracted from marine bacteria collected from the coast of ANNABA to determine their potential application in dermocosmetics. After sampling, the morphological identification of the isolated strains was performed. Extraction of EPS from strains grown in biofilm was carried out. The evaluation of the biological properties was performed by the in vitro measurement of the antioxidant activity then by the in vitro evaluation of the depigmenting potential and finally by the in vivo healing effect after laceration on Wistar rats for the assessment of the accelerating potential of the neoformation of the dermal tissues.

Results and Discussion: The identification showed homogeneous colonies of bacilli bacteria. Different fractions of EPS products were isolated. The measurement of the total sugar concentrations of each fraction showing a higher value for the EPS-Solubles, our study focused only on this fraction. Antioxidant properties, and antityrosinases are present in them but with very low potential. The healing effect of EPS revealed a remarkable healing power. the toxicological test allowed us to conclude that our extract of EPS is virtually non-irritating.

Conclusions: These exopolysaccharides are interesting for applications in dermocosmetics.

Keywords: exopolysaccharides, extraction, antioxidant activity, healing activity, dermocosmetic

Construction of new hERG blocker models based on heteroatom numbers from ultra large ligand libraries

Safa Haddad[3], Serdar Durdagi[1], Kader Şahin[2]

[1]Computational Biology and Molecular Simulations Laboratory, Department of Biophysics, School of Medicine Bahcesehir University
[2]Bahçeşehir University, School of Pharmacy Department of Pharmaceutical Chemistry
[3]Graduate school of natural and applied sciences, Bioengineering department

Safa Haddad / Graduate school of natural and applied sciences, Bioengineering department

Introduction: Inhibition of the hERG1 channels has been associated with an increased duration of ventricular repolarization, causing prolongation of the time interval between Q and T waves. LQTS result in cardiovascular problems. Many types of compounds bind to the hERG channels, leading to a blockade. The drug-induced blockade is thought to be a major reason for arrhythmias. Identification of the interactions governing the blockade of cardiac K+ channels is crucial both for the prevention of ion channel block and for the design of ion channel modulators.

Methods: First, small molecule database of inhibitors is created. 3D structures of hERG1 inhibitors and their PIC50 values will be used in the development of pharmacophore models using PHASE. Then, we will be investigating the heteroatom numbers to observe which heteroatom will more contribute, the calculation of the heteroatom number could be realized by CANVAS. In the end, we will create a model of hERG blockers based on the combination of hetatom numbers causing the blockage and realize screening of ultra-large libraries using hERG blocker model.

Results and Discussion: hERG1 inhibitors with their IC50 values are collected from chembl. Pharmacophore model is constructed with 508 hERG blockers. 3D QSAR models are constructed using PHASE and pharmacophore models are generated. The heteroatom numbers will be calculated and the heteroatom that will more influence the blockade will be determined. A model of hERG blockers will be created and a screening of ultra-large libraries is realized.

Conclusions: In the end we will construct ligand-based models based on heteroatom numbers from ultralarge ligand libraries.

Keywords: hERG1 blockers, K+ channel, heteroatoms, blockade, ultra-large libraries

PP-66

Screening of small molecule libraries using combined text mining, ligand- and target-driven based approaches for identification of novel granzyme H inhibitors

Saima Ikram[1], Jamshaid Ahmad[2], Fawad Ahmad[2], Serdar Durdagi[1]

[1]Bahçeşehir University, School of Pharmacy
[2]Peshawar University Pakistan
[3]Bahçeşehir University

Saima Ikram / Bahçeşehir University, School of Pharmacy

Introduction: Granzymes are serine proteases synthesized by CTL and NK cells. Five granzyme genes (GzmA, -B, -H, -K, -M) are present in humans, which are located at three different chromosomal loci. Serine protease binding pocket constitutes a catalytic triad (i.e., His59, Asp103 and Ser197). Granzymes are released into target cells by a specialized process known as granule exocytosis pathway. After internalization, these proteases initiate apoptosis. Their intracellular activity is regulated by specialized inhibitors knows as SERPINs. However, if these proteases are secreted in excess into the extracellular environment, their regulation becomes important as otherwise they start self-damage to the tissues thereby worsening the disease conditions.

Methods: In the current study, we investigated small molecule databases for the identification of potential molecules having the ability to inhibit GzmH by combined molecular simulations, which can ultimately be used as a potential therapeutic agent.

Results and Discussion: Analysis of the interaction fraction of all the studied ligands at the binding pocket of the protein shows that main interactions are constructed via hydrogen bonding and hydrophobic interactions. Compound $C_{19}H_{17}N_7O_4S$ showed the highest average MM/GBSA score (-70.18 kcal/mol). It mainly forms nonbonding chemical interactions with Arg43 (100% throughout the simulations time) and hydrophobic interactions with His59. In addition, a π-cation interaction was observed with Lys42.

Conclusions: There is no any small molecule or synthetic molecule inhibitor reported so far for extracellular GzmH. We have identified 12 potential hit inhibitors of this enzyme from two individual small molecule databases that can be used for drug target.

Keywords: Human granzyme H, SERPINs, Natural killer cells, Molecular docking

Investigation of the role of CLDNs and TRPs proteins and their associated proteins in peritumoral brain edema (PTBE) by evaluating gliovascular unit (GVU) in disrupted blood brain barrier in glioma IDH 1 mutant vs IDH 1 wild type

Anwar Abuelrub[1]

[1]Bahçeşehir university

Anwar Abuelrub / Bahçeşehir university

Introduction: Spinal Muscular Atrophy (SMA) is a neuromuscular condition that results in progressive muscle atrophy and motor neuron loss due to an autosomal recessive mutation. On chromosome 5q13, humans have two distinct SMN protein-coding genes known as SMN1 and SMN2. Where SMNs 1 and 2 are nearly identical. However, SMN2 produces between 70-95% less full-length SMN protein than SMN1. The substitution of a C-T in exon 7 is the cause of SMN2's failure to generate enough full-length SMN protein, due to the exclusion of exon 7, resulting in degraded SMN protein structures.

Methods: Previous research has confirmed that in addition to ligand binding to the 5′ splice site being sufficient to promote SMN2 exon 7 inclusion, the GA-rich region plays a critical role in preserving the medicines' ability to regulate splicing. This GA-rich region of SMN2 would be used as a target, after structure and ligand preparation, molecular docking and molecular dynamics simulations will be held to find the structure-affinity relationship. Besides, MD Trajectory Analysis of the RNA force field will be used to describe the structural and thermodynamic properties of RNA-small drug molecules.

Results and Discussion: The results would be conducted to find the most stable RNA-small complex structure over the longest time possible, to determine the MD trajectory's smallest RMSD.

Conclusions: At the end of this study, is expected to obtain stable small molecules with an increased sufficient potency for regulating splicing, by binding to the GA-rich sequence to induce SMN2 exon 7 inclusion. Leading to elevated levels of SMN proteins.

Keywords: SMA, Alternative Splicing, Exon 7, SMN, Small Molecule.

IN SILICO SCREENING OF THE APPROVED DRUGS, PEPTIDOMIMETICS AND DESIGNING OF NEW PEPTIDES AGAINST AXL-GAS6 TARGET

ilayda tolu[1]

[1]bau

ilayda tolu / bau

Introduction: Axl is one of the members of the TK family. It is mainly responsible for cell proliferation and migration. Axl is also found related to cancer cell metastasis and angiogenesis. Gas6 is the natural ligand of Axl. It binds on the cell membrane receptors and initiates signalling. The aim of this study is to investigate new therapeutic molecules against Axl-Gas6 target by screening approved drugs and compounds in clinical investigation and peptidomimetic databases.

Methods: Protein and ligand preparation, Molecular Docking, Molecular Dynamic simulations, MM/GBSA Calculations.

Results and Discussion: As a result, two peptidomimetic molecules have higher negative binding energies than reference molecules. The results indicate that these small molecules on peptidomimetic and FDA databases and ten designed peptides can be considered good candidates as inhibitors of the Axl-Gas6 complex in the treatment of kidney cancer.

Conclusions: In conclusion, the hit molecules from peptidomimetics and FDA libraries can be used as an inhibitor on the Axl-Gas6 protein complex, and ten peptides can be used as peptide-based inhibitors as mimicking the Gas6 binding on the Axl. The obtained hit compounds against Gas6/Axl protein complex need to be validated by in vitro experiments before being considered in further preclinical investigations.

Keywords: Axl-Gas6 protein complex, peptide design, computer aided drug design, molecular docking, MD simulations

ANALYZING THE DIRECT INTERACTIONS OF VITAMIN E ANALOGUES WITH NADPH OXIDASE-2 (NOX2) BY USING COMBINED MULTI-SCALE MOLECULAR MODELING METHODS

Asena Himmetoglu[1], Saima Ikram[1], Yesim Negis[3], Serdar Durdağı[1,2]

[1]Computational Biology and Molecular Simulations Laboratory, Department of Biophsyics, School of Medicine, Bahçeşehir University, Istanbul, Turkey

[2]Molecular Therapy Lab, Department of Pharmaceutical Chemistry, School of Pharmacy, Bahçeşehir University, Istanbul, Turkey

[3]Faculty of Medicine, Department of Medical Biochemistry, Bahçeşehir University, Istanbul, Turkey

Abstract

NADPH Oxidases (NOX) are multi-subunit enzymes that catalyze the reduction of molecular oxygen to produce superoxide. They contribute to the production of a significant amount of reactive oxygen species in cells, which are involved in cell signaling and immune response. To date, seven members of NOX family have been identified in mammals among which NOX2 is ubiquitously expressed in many cell types such as phagocytes, neurons, microglia, endothelial cells. NOX2 is vital for the immune system, cellular signaling, regulation of gene expression, and cell differentiation, while increased activity promotes a wide variety of pathological processes, including neurotoxicity, neurodegeneration, cardiovascular diseases, and organ failure. Therefore, modulation of NOX2 activity, without affecting the physiological redox state, may prove to be a promising treatment for degenerative diseases as well as an adjunctive agent to prevent their secondary complications. In this study, we aimed to investigate the binding affinities of vitamin E analogs and its physiological metabolites; α, β, δ, γ -tocopherols, α, β, δ, γ -tocotrienols, α-tocopheryl phosphate and α-T-13′-COOH on NOX2 enzyme subunits using in silico molecular modeling approaches. Vitamin E analogs have been proposed as signaling molecules and reflect anti-inflammatory effects that are partly mediated through specific interactions with proteins. Examining the direct interaction of NOX2 with vitamin E analogs also provides important insights for understanding the mechanism of action of vitamin E analogs acting as free radical scavengers; if they are able to prevent the assembly formation of NOX2 rather than directly scavenging free radicals. In this study, a novel structural model of NOX2 is designed by using three critical subunits comprised of p47phox PX domain, cytosolic p22phox tandem SH3 domain, and SH3 domain of p67phox. This newly constructed model considerably advanced our understanding of analyzing the molecular interactions of analogs with NOX2 subunits. The binding capacity of the vitamin E analogues were predicted by using in silico methods and compared with known NOX2 inhibitors available in the database. Among the analyzed molecules, α-tocopherol, α-tocopheryl phosphate, α-T-13-COOH, and β-tocotrienol showed significant interactions.