Poster Abstract Book

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In the spirit of scientific exchange, we would also like to give those who are unfortunately unable to attend this conference the opportunity to share their work. The following poster presentations are therefore available online.

S01	The Virtual Screening for Potential Allosteric Inhibitors Targeting PIF-Pocket of MAST Protein Kinases [Link to poster]
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P01 Integrating Public Datasets for Local Property Prediction in Low-Data Regimes

E. Wieczorek, B. Jago, S. Manning, P. Morese, B. Bellenie, A. Scarpino

The Institute of Cancer Research, 32 Oakleaf Avenue, SM2 5GP, Sutton, UK

The early stages of drug discovery involve iterative optimization of multiple molecular properties, including potency, physicochemical characteristics, and ADMET endpoints. Local property prediction models can support compound design and selection within a project-specific chemical series; however, their performance is often constrained by limited data availability, particularly in early project phases. When larger in-house datasets are not available, public datasets can be used to enhance the model performance. However, the differences in assay conditions and chemical space coverage may introduce noise and distributional mismatch, limiting the benefit of straightforward data integration.

In this work, we systematically evaluate strategies for integrating public datasets with proprietary in-house data to improve local property prediction models. Models are developed on an in-house PROTAC dataset from a single project, with the dataset from Peteani et al. used as the public data source.[1] We benchmark multiple modeling approaches and compare direct data pooling with transfer learning strategies, including pretraining on public data followed by fine-tuning on internal data. Model performance is assessed with time-based splits for realistic prospective evaluation and across varying amounts of internal training data to reflect different stages of project maturity.

Our results show that naïve pooling of public and in-house data or transfer learning can degrade predictive performance, particularly when the public data is not well aligned with the project chemistry. In contrast, best performance is achieved when public datasets are carefully curated to include only chemically relevant compounds, highlighting the importance of relevance over sheer data volume. Moreover, we find that the addition of external data is most impactful in the middle stages of the project, with no performance gains seen either very early or very late in the project.

[1] Peteani, G., Huynh, M.T.D., Gerebtzoff, G. et al. Application of machine learning models for property prediction to targeted protein degraders. Nat Commun 15, 5764 (2024).

P02 Modelling Macrocyclic Peptide PCSK9 Inhibitors with Alchemical Free Energy Calculations

A. Kalpokas[a], M. Mackey[b], J. Michel[a]

[a] EaStCHEM School of Chemistry, University of Edinburgh, Edinburgh EH9 3FJ, UK
[b] Cresset, New Cambridge House, Bassingbourn Road, Litlington, Cambridgeshire, SG8 0SS, UK

Free energy perturbation (FEP) methodologies are widely used in drug discovery campaigns to optimise the binding affinity of small molecule ligands. Recently, macrocyclic peptides have emerged as an increasingly attractive modality alongside these traditional therapeutics. They possess the unique ability to bind to large, flat, and featureless binding sites inaccessible to small molecules, whilst maintaining the oral bioavailability often lacking in antibodies. However, modelling macrocycles with FEP methodologies presents significant challenges. These campaigns frequently involve complex scaffold changes that extend beyond traditional R-group modifications, and often utilize both canonical and non-canonical amino acids, thus necessitating specialized parametrization protocols to handle such diverse chemical space.

In this work, we address these challenges by benchmarking against the seminal Tucker et al. study [1], which details the development of novel macrocyclic peptide inhibitors targeting PCSK9. We present open-source, state-of-the-art relative binding free energy (RBFE) protocols capable of robustly handling the complex scaffold modifications found in this dataset, such as ring-breaking, linker reconnection, and cross-linker addition for example. Furthermore, we evaluate and refine automated parametrization protocols to accurately model these chemically diverse inhibitors. Taken together, this work broadens the domain of applicability of FEP methodologies in drug discovery.

[1] Tucker et al. A Series of Novel, Highly Potent, and Orally Bioavailable Next-Generation Tricyclic Peptide PCSK9 Inhibitors. J. Med. Chem. 2021, 64 (22), 16770–16800. https://doi.org/10.1021/acs.jmedchem.1c01599.

P03 The Discovery of Novel E3 Ligase Ligands with Proximers

J. Longden[a], D. Dandekar[a],R. Karki[b], P. Gribbon[b], A. Ausekar[a]

[a] Evolvus, Altenhoferallee 3, 60438, Frankfurt am Main, Germany
[b] Fraunhofer Institute for Translational Medicine and Pharmacology, Schnackenburgallee 114, 22525, Hamburg, Germany

Targeted protein degradation (TPD) has recently emerged as a promising new drug modality. In TPD chemical substances are used to recruit proteins of interest to an E3 ligase for degradation, thus perturbing it's activity. These compounds are heterobifunctional and extremely diverse, they include small molecules capable of binding to both a target and an E3 ligase at the same time e.g. Thalidomide, and large chimeras of multiple small molecules, each binding to a target protein or E3 ligase and joined by a chemical linker. TPDs are of great interest to the pharmaceutical industry because they provide a mechanism to target previously undruggable proteins. However, to date the vast majority of TPDs have utilised just two E3 ligases for ubiquitination; cereblon or VHL. There is thus an unmet need to identify novel E3 ligases and the small molecules that can bind them.

Evolvus specializes in the curation of life science datasets and the scouting of new data. Proximers describes the chemical structures and bioactivity, including ADMET properties, of protein degraders reported in patents. Here we describe the use of Proximers for the training of pharmacophore-based machine learning models that can identify novel chemical compounds that bind to E3 ligases and also predict which E3 ligase the compound binds to. These models can be used for the virtual screening of compound collections or for focused library design.

[1] Karki, R. et al. Pharmacophore-based machine learning model to predict ligand selectivity for E3 ligase binders 2023 ACS Omega 8(33): 30177-30185
[2] Karki, R. et al. Pharmacophore-based ML model to filter candidate E3 ligands and predict E3 ligase binding properties 2024 Informatics in Medicine Unlocked 44: 101424

P04 Protective Effects of Muntingia Calabura Leaves Extract on Cisplatin Induced Myelosupression and Chemobrain in Wister Rats

S. Dutta[a], R. Shanmugam[a], L.P. Priyanka Dwarampudi[b]

[a] TIFAC CORE in Herbal Drugs, AYUSH, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Ooty – 643001, Tamil Nadu, India
[b] Department of Pharmacognosy, JSS College of Pharmacy, Ooty, India

Background: The gift to humanity for acquiring a healthy lifestyle is the use of medicinal herbs, which have tremendous therapeutic and basic relevance. Muntingia calabura has great value in all indigenous traditional medical systems, including folkloric Ayurveda, for therapeutic and dietary purposes to restore lost vitality and vigour.

Aim & Objective: To evaluate the protective effects of ethanolic extract of Muntingia calabura against cisplatin-induced myelosuppression and chemobrain in albino Wistar rats.

Methods: The dried powder of Muntingia calabura leaves was powdered and defatted using petroleum ether. The marc left over was extracted with ethanol using a Soxhlet apparatus. The experimental rats were treated with ethanolic extract of Muntingia calabura for 21 days according to protocol. Rats were administered cisplatin on the 1st, 3rd, 5th, and 7th day to induce bone marrow toxicity and neurotoxicity. Blood samples were collected from all animals on the 1st, 7th, 14th, and 21st day, one hour before administration of the drugs, and hematological parameters were determined; behavioral activity of rats was assessed. On the 21st day, under anesthesia, all rats were sacrificed. Brain and bone marrow samples were collected for histopathological examination. Hematological parameters (RBC, WBC, platelets, hemoglobin, hematocrit, eosinophils, basophils, neutrophils, lymphocytes, monocytes, bleeding time, and clotting time) were determined, and the Morris water maze test, open field test, and rota-rod test were performed.

Results & Discussion: Administration of cisplatin alone significantly reduced hematological parameters on the 7th, 14th, and 21st days and prolonged bleeding and clotting times in toxic control animals compared to normal animals. Treatment groups administered Muntingia calabura extract exhibited a significant rise in hematological parameters and reduced bleeding and clotting times compared to toxic controls. In the Morris water maze test, cisplatin increased escape latency and reduced the number of crossings and time spent in the target quadrant in toxic controls, but treatment with the extract improved these alterations. In the open field test, the number of squares crossed was reduced and there was a significant increase in rearing, fecal pellets, and immobility time in toxic controls, but the extract reversed cisplatin-induced chemobrain effects. Toxic controls showed reduced time to fall in the rota-rod test, but administration of the extract significantly increased muscle strength in treated animals.

Conclusion: The findings imply that ethanolic extract of Muntingia calabura has important protective qualities against cisplatin-induced bone marrow toxicity and chemobrain in albino Wistar rats. Further study should be undertaken to determine the mechanism of action responsible for the protective properties.

[1] Srirangan P, Sabina EP. Protective effects of herbal compounds against cyclophosphamide-induced organ toxicity: a pathway-centered approach. Drug and Chemical Toxicology. 2025 Jan 23:1–43.
[2] Gamal NK, El Naga RN, George MY. Mechanisms and protective strategies in cognitive impairment induced by combination of doxorubicin and cyclophosphamide. Archives of Pharmaceutical Sciences, Ain Shams University. 2024 Jun 1;8(1):109–21.
[3] Chawansuntati K, Hongjaisee S, Sirita K, Kingkaew K, Rattanathammethee K, Kumrapich B, Ounjaijean S, Kongkaew A, Lumjuan N. Effects of quercetin and extracts from Phyllanthus emblica, Morus alba, and Ginkgo biloba on platelet recovery in a rat model of chemotherapy-induced thrombocytopenia. Heliyon. 2024 Jan 30;10(2).
[4] Sivakami S, Thangapushbam V, Rama P, Jothika M, Sundaram R, Arumugam N, Almansour AI, Santhamoorthy M, Muthu K. Green synthesis of silver nanoparticles from Muntingia calabura fruits extract and its anticancer, cytotoxic, antioxidant, antibacterial and photocatalytic activity. Chemistry of Inorganic Materials. 2025 Aug 26:100112.
[5] Garingo AG, Maumay AP, Dango GW, Derilo RC, Subong JD. Cytotoxic and genotoxic properties of Saraisa (Muntingia calabura) bark extract. International Journal of Advanced Research and Publications. 3:8–13.

P05 ROCS X, When Billions Aren't Enough

L. Eberlein, M. Krier, G. Stahl, A. Lee, M. Geballe

OpenEye, Cadence Molecular Sciences, Santa Fe, 87508, USA

OpenEye's ROCS X, deployed on the Orion cloud molecular design platform, is engineered to search ultra-large chemical spaces, ranging from billions to trillions of molecules, for hit identification in drug discovery. ROCS X leverages reaction informatics to construct 2D and 3D synthon libraries of synthetically accessible molecules derived from over 7 million building blocks, enabling the creation of a virtual space for trillions of compounds. By operating in an unenumerated form, ROCS X avoids the prohibitive costs of full enumeration. Instead, ROCS X applies novel query strategies and shape-based scoring of ROCS and FastROCS to efficiently identify high-quality hits. ROCS X integrates multi-armed bandit models, Bayesian active learning, and reaction-driven sampling to prioritize and explore diverse, chemically tractable space. It supports both ligand-based and pocket-derived queries (via SZMAP), enabling the discovery of structurally novel hits that are synthetically feasible.

Developed in collaboration with a pharmaceutical partner, ROCS X has already yielded approximately 150 new synthesizable compounds not found in vendor catalogs on their drug discovery projects, demonstrating its real-application impact. For medicinal chemists, ROCS X provides a powerful and fast approach to find novel synthesizable molecules. By uniting cheminformatics, cloud-scale computation, and AI-guided search, ROCS X redefines early-stage drug discovery by enabling efficient exploration of trillion-scale chemical space.

P06 Computational Explorations of Halogenase Substrate Scope

B. A. J. Connaughton[a], J. B. O. Mitchell[a], M. Bühl[a], O. Holodaieva[a], R. J. M. Goss[a], A. S. J. S. Meyb[b]

[a] EaStCHEM School of Chemistry, University of St Andrews, St Andrews, Fife, KY16 9ST, UK
[b] EaStCHEM School of Chemistry, University of Edinburgh, Edinburgh, EH9 3FJ, UK

Cyanophage viruses disrupt photosynthesis in oceanic cyanobacteria by altering the bioactivity of molecules in the host through halogenation. The VirX1 enzyme facilitates these reactions and offers a route to the regioselective halogenation of a range of aromatic substrates,[1] unlike on harmful reagents.[2] While it has historically been understood that only activated aromatics can be halogenated enzymatically, a recent study indicates that unactivated aromatics may be also.[3]

We investigate the substrate scope of VirX1 with respect to activated and unactivated aromatics, beginning with an investigation of tryptophan and phenylalanine. Using docking and molecular dynamics simulations, we equilibrate the enzyme-substrate system and sample conformational space. These sampled structures are then used as a starting point for hybrid quantum mechanical/molecular mechanical calculations (with DFT at the M06-2X/def2-QZVPP/xTB level)[4,5] which enable us to build reaction energy profiles and investigate the feasibility of a given substrate in VirX1-facilitated halogenation. Additionally, we explore the use of experimental data in machine learning techniques to predict the reaction success of a given substrate.

[1] D. S. Gkotsi et al., Nat. Chem., 2019, 11, 1091–1097.
[2] X. Teng et al., Bioorg. Med. Chem. Lett., 2005, 15, 5039–5044.
[3] N. E. Avalon et al, JACS, 2024, 146, 18626–18638.
[4] Y. Zhao and D. G. Truhlar, Theor. Chem. Account, 2008, 120, 215–241.
[5] C. Bannwroth. S. Ehlert and S. Grimme, J. Chem. Theor. Comput., 2019, 15, 1652–1671.

P07 Query Matters: How Selection Strategies Influence Active Learning in Drug Discovery

H.J. Williams[a], D.S. Palmer[a], S.D. Pickett[b], A. Baxter[b]

[a] Department of Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow, G11XL, Scotland
[b] GlaxoSmithKline R&D Pharmaceuticals, Stevenage, SG1 2NY, UK

We present SimDMTA, an in silico framework designed to simulate the Design–Make–Test–Analyze (DMTA) cycle used in preclinical drug discovery. Using docking scores as a proxy for biological assays, the simulations allow factors controlling the efficiency of the DMTA cycle to be explored in a manner that would not be feasible using traditional experiments due to time and cost constraints. In this workflow, a machine learning model predicts docking scores, selects compounds using various query strategies, docks selected molecules, and retrains iteratively. Starting from a broad chemical space, the model actively samples molecules derived from a 3,5-dimethyl-4-phenylisoxazole scaffold, an active warhead for the Bromodomain 4 (BRD4) BD1 binding site, to refine its predictions. Our results show that uncertainty-based sampling significantly outperforms greedy and hybrid approaches in both hit discovery and the ability of the model that predicts docking scores to generalize beyond its training set. Notably, by the final iteration, 37 of the top 50 ranked compounds were within the top 1% of the chemical space of all evaluated compounds. Strategies that include some random selection correct systematic biases more rapidly, but are less effective at predicting top-performing molecules. These findings underscore the value of incorporating molecular diversity and uncertainty into design strategies. While such strategies may deprioritize those molecules with the highest absolute predictions in early rounds, they markedly accelerate model refinement, ultimately leading to more effective hit identification in discovery driven by active learning.

[1] Query Matters: How Selection Strategies Influence Active Learning in Drug Discovery Huw J. Williams, Stephen D. Pickett, Andrew Baxter, and David S. Palmer, Journal of Chemical Information and Modeling Article ASAP
DOI: 10.1021/acs.jcim.5c02504

P08

Peptide Deformylase as a Target for the Antibacterial Activity of Imidazolium Cations

V. Rastija[a], G.K. Šarić[a], M. Vraneš[b], S. Papović[b]

[a] Faculty of Agrobiotechnical Sciences Osijek, Josip Juraj Strossmayer University of Osijek, Vladimira Preloga 1, HR-31000 Osijek, Croatia
[b] Faculty of Science, University of Novi Sad, 21000 Novi Sad, Serbia

Deformylation is a crucial step in bacterial protein biosynthesis since the most mature proteins do not retain the N-formyl group or the terminal methionine residue. Peptide deformylase (PDF) is a bacterial metalloenzyme that deformylates N-formylmethionine; therefore, it is essential for bacterial growth and a potential target for research of the mechanism on antibacterial activity [1]. Recently, we have investigated antimicrobial effects of newly synthesized imidazolium-based ionic liquids against beneficial soil bacteria Bacillus mycoides and plant pathogen Pseudomonas syringae. To elucidate the possible mechanism of antibacterial action, we performed molecular docking of imidazolium cations into the actinonin binding site of PDF (PDB: 1G2A). The highest free binding energy was achieved by the imidazole cation with the longest alkyl chain, 3-dodecyl-1H-imidazol-3-ium (-7.12 kcal/mol). The results obtained are in accordance with the results of the performed in vitro antibacterial study, where the 3-dodecylimidazolium 2-hydroxybenzoate showed pronounced inhibitory activity against beneficial and pathogenic soil bacteria.

[1] Clements J. M. et al. Antimicrob Agents Chemother. 2001, 45, 563-570.
Funding: This work was supported by the Croatian Science Foundation under the project number HRZZ-IP-2024-05-6164, “Innovative Approaches in the Development of Imidazoles for Plant Protection”

P09

SAR Study of Imidazolium Cations as Antibacterial Agents against Plant Pathogenic and Beneficial Bacteria

G.K. Šarić[a], V. Rastija[a], M. Vraneš[b], S. Papović[b]

[a] Faculty of Agrobiotechnical Sciences Osijek, Josip Juraj Strossmayer University of Osijek, Vladimira Preloga 1, HR-31000 Osijek, Croatia
[b] Faculty of Science, University of Novi Sad, 21000 Novi Sad, Serbia

Imidazolium-based ionic liquids (ILs) have previously shown strong inhibitory activities against human pathogenic bacteria[1]. To develop novel plant protection agents, a novel ILs were tested against plant pathogenic bacteria Pseudomonas syringae, and beneficial soil bacteria, Bacillus mycoides, as well. Among the tested compounds, 3-dodecylimidazolium 2-hydroxybenzoate showed pronounced inhibitory activity against both bacteria. A structure-activity relationship (SAR) study was performed to shed light on the most important structural characteristics for the enhanced antibacterial effects. Structures of the eleven imidazolium cations have been optimized, and then, molecular descriptors were calculated by the DRAGON program. The one-parameter linear regression (LR) equations were generated by the QSARINS program. The best LR equation for the antibacterial activity against P. syringae was obtained with the number of total secondary C atoms(sp3) (nCs) (R^2 = 0.956); while for the effect against B. mycoides with the presence/absence of C-N at topological distance 8 (B08[C-N]) (R^2 = 0.948). Both models support the experimental results that the longer alkyl chain length is a prerequisite for better antibacterial effects of Ils.

[1] Vraneš M B. et al. Molecules 2025, 30, 4346.
Funding: This work was supported by the Croatian Science Foundation under the project number HRZZ-IP-2024-05-6164, “Innovative Approaches in the Development of Imidazoles for Plant Protection”

P10

Benchmark Assessment of 3D Protein-Conditioned Molecule Generators

N. Sanjrani[a,b], D. Coupry[a], P. Pogany[a], D. Palmer[b]

[a] GSK, Medicines Research Centre, Stevenage, UK
[b] Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow, UK

To understand the benefits and drawbacks of 3D combinatorial and deep learning generators, a novel benchmark was created focusing on the recreation of important protein–ligand interactions and 3D ligand conformations. Using the BindingMOAD data set with a hold-out blind set, the sequential graph neural network generators, Pocket2Mol and PocketFlow, diffusion models, DiffSBDD and MolSnapper, and combinatorial genetic algorithms, AutoGrow4 and LigBuilderV3, were evaluated. It was discovered that deep learning methods fail to generate structurally valid molecules and 3D conformations, whereas combinatorial methods are slow and generate molecules that are prone to failing 2D MOSES filters. The results from this evaluation guide us toward improving deep learning structure-based generators by placing higher importance on structural validity, 3D ligand conformations, and recreation of important known active site interactions. This benchmark should be used to understand the limitations of future combinatorial and deep learning generators.

[1] Natasha Sanjrani, Damien E. Coupry, Peter Pogány, David S. Palmer, and Stephen D. Pickett Journal of Chemical Information and Modeling 2025 65 (15), 8006-8021
DOI: 10.1021/acs.jcim.5c01020

P11

Ensemble-Based Conformational Modelling For Macrocycles: From X-Ray Refinement to Lead Optimisation

B. Wong[a], H. Tandon[a], K.G. Kroeck[a], A.N. Jain[a], A.E. Cleves[a], M. Öeren[a], M.D. Segall[a]

[a] GSK, Medicines Research Centre, Stevenage, UK

Protein-ligand structures are invaluable for structure-guided drug design; however, conventional refinement methods, optimised for protein modelling, do not capture the conformational complexity of flexible ligands, especially macrocycles. This can lead to a systematic overestimation of bound-state strain, sometimes by more than 10 kcal/mol, an error large enough to misdirect design decisions.

We introduce xGen™, an ensemble-based fitting and refinement method that avoids reliance on single-conformer models and atom-specific B-factors. xGen generates ligand models with improved agreement to electron density and substantially reduced conformational strain. These improvements enable more accurate strain quantification and are particularly important for macrocyclic systems, where reliable conformational modelling and strain estimation are critical for achieving improved optimisation outcomes.

Applied to ~3,000 protein-ligand complexes from the PDB, xGen demonstrates that ensemble occupancies capture conformational heterogeneity more effectively than atom-specific B-factors, enabling accurate representation of even macrocycles as low-strain ensembles. Notably, per-atom strain showed a strong inverse correlation with ligand efficiency, establishing strain as a quantitative predictor for lead optimisation.

We demonstrate the practical impact through a macrocyclic PD-1/PD-L1 inhibitor peptide project that progressed from lead to clinical candidate. Starting with a crystal structure of the complex and NMR data for the unbound ligand, we employed an integrated workflow combining deep conformational search, docking, and accurate strain estimation to identify the clinical candidate within the top 10% of synthesised analogues. This translates to a potential of 90% saving in synthetic efforts. Quantitative strain assessments emerged as the dominant predictor of ligand efficiency, enabling confident prioritisation of the most promising compounds.

By providing realistic conformational ensembles and actionable strain metrics, this approach enables better design decisions earlier in the drug discovery process.

[1] Jain, A. N. et al. xGen: Real-Space Fitting of Complex Ligand Conformational Ensembles to X-ray Electron Density Maps. J. Med. Chem. 2020, 63, 10509-10528
[2] Jain, A. N. et al. Complex peptide macrocycle optimization: combining NMR restraints with conformational analysis to guide structure-based and ligand-based design. JCAMD. 2023, 37, 519-535

P12 High-Throughput Solubility Screening Reveals Antibody-Specific Responses to Pharmaceutical Excipients

Z. Han[a], G. Licari[b], A. Evers[c], P. Sormanni[c], T.P.J. Knowles[c]

[a] Yusuf Hamied Department of Chemistry, University of Cambridge, Cambridge CB2 1EW, U.K.
[b] Merck
[c] University of Cambridge

Understanding the effects of formulation excipients on protein solubility is a key part of physical chemistry and pharmaceutical sciences. While excipients are routinely employed to reduce the self-association of biologic drugs, their mechanisms of action remain poorly understood and are often assumed to be broadly nonspecific. Using a high-throughput combinatorial droplet microfluidic platform, we systematically survey and quantify how common pharmaceutical excipients affect the solubility of a diverse panel of therapeutic monoclonal antibodies (mAbs). We show that, while excipients are generally solubilizing, their effects vary substantially across different mAbs, with excipient-specific solubilization scores spanning dynamic ranges of approximately 7-fold to >200-fold across the antibody panel. Histidine, arginine and sodium chloride, in particular, engage in interactions characterized by unique molecular specificity, whereas sucrose effects are largely governed by nonspecific, solvent-mediated interactions. Correlating excipient performance with dynamical mAb molecular features from solvated full-length homology models allows us to dissect and quantify the relative contributions of molecular features governing excipient-mediated solubilization. We envision this new physicochemical understanding lays the groundwork for rational excipient selection and bespoke formulation design, with direct implications for accelerating protein therapeutic development for preclinical scenarios.

[1] Z. Han, N. A. Erkamp, R. Scrutton, G. Licari, O. Predeina, A. Evers, P. Sormanni, T. P. J. Knowles, 2026, bioRxiv, DOI: 10.64898/2026.01.29.702671

P13 Molecular Mechanics Demonstrate S-COMT as Promising Therapeutic Receptor When Analysed with Scondary Plant Metabolites

D. Garg, A. Vashishth, M. Jayawant, V. Bastikar

Centre for Computational Biology and Translational Research, Amity Institute of Biotechnology, Amity University Maharashtra, Mumbai, India

Major depressive disorder (MDD) and other psychiatric conditions are debilitating illnesses affecting millions globally. Catechol-O-methyltransferase (COMT), an enzyme that regulates dopamine and norepinephrine breakdown in the brain, has emerged as a potential therapeutic target for these disorders. This study explores the inhibitory potential of plant secondary metabolites against S-COMT using computational techniques. COMT exists in two isoforms: membrane-bound COMT (MB-COMT), primarily found in brain neurons, and soluble COMT (S-COMT), present in peripheral tissues. S-COMT, particularly in the prefrontal cortex, is crucial for regulating neurotransmitters and maintaining cognitive function. Studies suggest S-COMT variants might be linked to the development of depression, schizophrenia, and other psychiatric disorders. Current COMT inhibitors often suffer from limitations, necessitating the exploration of novel therapeutic strategies. This study employed in-silico methods to investigate plant secondary metabolites as potential S-COMT inhibitors. Here, we describe the S-COMT protein structure retrieval and validation, followed by molecular docking simulations to identify plant compounds with the strongest binding affinity to the receptor's active site. Key amino acid residues involved in these interactions were also analysed. Furthermore, molecular dynamics simulations were conducted to assess the stability of the top-scoring protein-ligand complexes over a 100-ns timeframe. The results explored the stability of ligand binding within the active site and its impact on the overall conformation of the S-COMT receptor. Our findings highlight promising therapeutic potential for these plant-derived compounds. Further in vitro and in vivo studies are warranted to validate their efficacy and safety for potential clinical applications in treating S-COMT-related disorders.

Subjects: Bioinformatics and Computational Biology, Proteomics, Neurogenerative Diseases.

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P14 Structural Interaction Fingerprints for Analysis of Nucleic Acid-Ligand Interactions

F. Stefaniak, N.A. Szulc, Z. Mackiewicz, J.M. Bujnicki

Laboratory of Bioinformatics and Protein Engineering
International Institute of Molecular and Cell Biology in Warsaw
ul. Ks. Trojdena 4, 02-109 Warsaw, Poland

Computational methods play a central role in drug discovery and are widely used in virtual screening, structure optimization, and compound activity profiling. Over the past decades, almost all the attention in medicinal chemistry has been focused on protein-ligand binding, and computational tools have been developed with this goal in mind. With the recent discovery of functional RNAs and their potential applications, RNAs have gained considerable attention as potential drug targets. However, the availability of bioinformatics tools for nucleic acids is limited. Here, we present fingeRNAt-a software tool for detecting non-covalent interactions formed in complexes of nucleic acids with ligands. The program detects nine types of interactions, but the scope of detected interactions can be easily extended using a simple plug-in system. In addition, detected interactions can be visualized using the included PyMOL plugin, facilitating the analysis of molecular complexes at medium throughput. Interactions are also encoded and stored as a bioinformatics-friendly Structural Interaction Fingerprint (SIFt) - a binary string where the corresponding bit in the fingerprint is set to 1 if a particular interaction is present and 0 otherwise. This output format, in turn, enables high-throughput analysis of interaction data using data analysis techniques.

We present applications of fingeRNAt-generated interaction fingerprints for visual and computational analysis of RNA-ligand complexes, including analysis of interactions formed in experimentally determined RNA-small molecule-ligand complexes deposited in the Protein Data Bank. We propose similarity based on interaction fingerprints as an alternative measure to RMSD to recapitulate complexes with similar interactions but different folding. We show the application of SIFts accompanied by machine learning methods to predict the binding of small molecules to RNA and to facilitate virtual screening experiments. This approach, combined with Explainable Artificial Intelligence (XAI) methods, allows for understanding the decision-making process behind the predictive models.

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P15

Evaluation of Single-Template Ligand-Based Methods for the Discovery of Small Molecule Nucleic Acid Binders

F. Stefaniak[a], D. Bajusz[b], A. Rácz[c]

[a] Laboratory of Bioinformatics and Protein Engineering
International Institute of Molecular and Cell Biology in Warsaw
ul. Ks. Trojdena 4, 02-109 Warsaw, Poland
[b] Medicinal Chemistry Research Group, HUN-REN Research Centre for Natural Sciences, Magyar tudósok krt. 2, 1117 Budapest, Hungary
[c] Plasma Chemistry Research Group, HUN-REN Research Centre for Natural Sciences, Magyar tudósok krt. 2, 1117 Budapest, Hungary

Computational methods play a central role in the early stages of drug discovery and are widely used for virtual screening. Recent discoveries concerning the role of RNA in disease have sparked growing interest in using RNA as a target for novel therapies. However, the limited availability of experimentally determined 3D RNA structures, and the inaccuracy of in silico RNA structure prediction methods, creates a significant demand for ligand-based algorithms that do not require knowledge of the target structure. We have benchmarked several such methods, which were primarily designed for proteins but can also be applied to RNA by their very nature. Our results show that some of these methods can effectively build predictive models for RNA targets, while the performance of others is no better than random selection. We have also proposed a consensus method that combines the best-performing algorithms of a distinct nature. According to our studies, this approach outperforms all the other methods that were tested.

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P16 Scaling Absolute Binding Free Energy Calculations for Virtual Screening

R.H. Du[a], M. Samways[b], R. Taylor[b], J. Michel[a]

[a] EaStCHEM School of Chemistry, University of Edinburgh, David Brewster Road, Edinburgh EH9 3FJ, UK
[b] UCB, 216 Bath Road, Slough, SL1 3WE, UK

Alchemical absolute binding free energy (ABFE) calculations are accurate yet computationally expensive tools for predicting ligand–protein binding affinities. While ABFE provides high accuracy,[1] its low throughput limits its application in large-scale virtual screening. In contrast, traditional virtual screening methods using docking or machine learning offer high throughput but often suffer from limited predictive power.

To bridge this gap, we present a FastABFE protocol based on the A3FE software package[2,3] that uses ca. x10-x100 fold shorter simulation time than established ABFE protocols. We show that although the computed binding free energies deviate systematically from experimental data, reasonable qualitative rankings can be retained.

FastABFE was benchmarked on a dataset of congeneric series of 216 protein-ligand complexes for which extensive benchmarks were previously reported by Bayer.[4] We show that FastABFE rankings approach the rankings obtained by relative binding free energy methods such as PMX.

We have also evaluated the performance of FastABFE in the context of virtual screening, by using a dataset of 1162 PDE10A ligands published by Roche,[5] that we supplemented with 9574 DUD-E generated decoys. We discuss considerations such as relationship between accuracy of predicted poses and reliability of affinity rankings.

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P17 The Clock is Ticking: Residence Time as an Orthogonal Metric for Compound Prioritization

D. Dolciami, C.F. Nielsen, A. L. Baskerville, M.H. Christensen, N.K. Madsen, R.M. Ziolek

Kvantify ApS, 2100 Copenhagen, Denmark

Drug–receptor binding affinity is a primary metric used in computational drug discovery for compound prioritization, with methods such as docking, MM-GBSA, and free-energy perturbation widely applied to estimate the thermodynamic stability of target-ligand complexes. However, these approaches are equilibrium-based and do not capture the dynamic kinetics of target-ligand binding.

The target-ligand residence time, determined by the dissociation rate of the target-ligand complex, provides complementary information by describing how long a ligand remains bound to its target. In several cases, residence time has shown stronger correlation with in vivo efficacy than affinity alone and may help mitigate efficacy and ADMET liabilities. [1–3]

Historically, the high computational cost of unbinding kinetics simulations has limited their practical use in virtual screening and during early-stage compound prioritization. Here, we leverage Kvantify Koffee [4] to enable rapid prediction of target-ligand residence times across thousands of compounds within GPU-hour, with per-ligand runtimes on the order of minutes. Using representative drug discovery case studies, we evaluate the orthogonality of kinetics-based scores relative to affinity-based methods. Our results show that combining kinetics and affinity metrics improves compound ranking compared to either approach alone, supporting residence time prediction as a complementary and independent metric for computational drug discovery workflows.

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P18 De Novo Design of GALK1 Inhibitors in a Flexible Binding Pocket

A.F. Khoualdi, D.J. Cole, M. Degiacomi, W. Yue

Newcastle University, School of Natural and Environmental Sciences, Newcastle-upon-Tyne, NE1 7RU, UK
University of Edinburgh, Informatics Forum, Edinburgh , EH8 9AB, UK
Newcastle University Medical School, Newcastle-upon-Tyne, NE2 4HH, UK

Galactosemia is a rare autosomal recessive disease caused by a defect in galactose metabolism. GALK1 is a kinase enzyme involved in galactose metabolism and whose inhibition can help alleviate galactosemia [1] . By making use of the GALK1's allosteric inhibitors which are crystalized [1] , molecules with better binding properties can be designed, modified and optimized within the binding pocket using FEgrow tool [2] . Molecules can be designed interactively or automatically using substructures from databases, built and scored using FEgrow. Pocket flexibility is addressed with the conformation prediction tool Molearn [3] which uses a convolutional neural network to learn from relatively short, example MD simulation trajectories to predict the different conformations the protein will have. Designing inhibitors that fit the predicted ensemble of pocket conformations means more potent inhibitors can be generated and tested against not only a static, rigid receptor structure as is currently done in docking, for example, but against a flexible form of the receptor target. The active learning feature of FEgrow, in particular, ensures efficiency in selecting potential inhibitors from the very large chemical space.

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P19 Critical Assessment of Binding Affinity Benchmarks: Data Leakage and the Illusion of Generalization

B. Mattsson[a], W.P. Walters[b]

[a] Enlace Bio, London, EC1V 2NX, UK
[b] OpenADMET, Boston, Massachusetts, United States

Accurate prediction of protein-ligand binding affinity is a crucial goal in structure-based drug discovery, with the potential to significantly shorten development timelines. Recently, a new wave of machine learning models based on co-folding has demonstrated performance that matches or exceeds that of gold-standard physics-based methods like Free Energy Perturbation (FEP). This work provides a critical assessment of these claims, revealing that current benchmarks are heavily influenced by data leakage. We demonstrate that the commonly used 90% protein sequence similarity threshold leads to data leakage as homologous proteins with low overall similarity still can exhibit highly correlated binding profiles. Additionally, we show that a ligand-only baseline model, which lacks protein structural information, matches the performance of state-of-the-art AI models on the FEP+ 4 benchmark ($r = 0.66$). To address this issue, we propose a rigorous new benchmarking standard based on a strict ligand novelty filter (Tanimoto similarity < 0.35). On this challenging benchmark ligand-only models perform notably worse ($r = 0.12$), offering a clear baseline for evaluating genuine generalization. We argue that the field must move beyond sequence-based splits to restore confidence among medicinal chemists and to ensure that AI-driven discovery translates into successful prospective laboratory research.

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P20

Quantifying Ternary Complex Stability Through Binding Free Energy Calculations in the Geometric Route

B. Tan[a], A. Ciulli[b], J. Michel[a]

[a] EaStCHEM School of Chemistry, University of Edinburgh, David Brewster Road, Edinburgh EH9 3FJ, U.K.
[b] Division of Biological Chemistry and Drug Discovery, School of Life Sciences, University of Dundee, Dundee, Scotland, UK

Molecular glue degraders are small molecules that induce binding of target proteins to an E3 ligase, which enables ubiquitination and subsequent and subsequent proteasomal degradation of the target. This is a promising therapeutic strategy, as it enables targeting of previous "undruggable" targets and typically results in low dosing requirements and favourable drug product properties [1]. Screening of potential degrader candidates remains however a daunting task, primarily due to complicated nature of the protein-protein interface where binding occurs. We present a rigorous and precise simulation protocol that uses Molecular Dynamics (MD) simulations with Umbrella Sampling to accurately rank different ternary complexes by their relative binding free energy. The protocol adapts the geometric Collective Variable-based framework of Woo and Roux [2] with Boresch-style orientational restraints [3,4] to calculate the free energy change of the glue-bound E3 ligase binding to the target protein (or vice versa). We apply the protocol to several ternary complex systems recruiting the CRBN and DCAF16 E3 ligases to predict the relative stabilisation effect of modifying the molecular glue structure or mutating the protein interface. The protocol is successfully applied to intramolecular bivalent glues such as the BRD4 degrader IBG1 [5], a class of molecular glues that simultaneously bind two target bromodomains to achieve ternary complex formation. Overall, leveraging MD simulations with statistical mechanics based enhanced sampling techniques provides a means of accurately quantifying the stability of a ternary complex interface, aiding in the rational design of novel molecular glue degraders.

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P21 Rapid Generation of Ligand Conformations from Overlapping Fragments

A. Henry[a], A. Ajamian[b], L. Zondagh[b], P. Labute[b]

[a] Chemical Computing Group, St Johns Innovation Centre, Cowley Road, Cambridge CB4 0WS, UK
[b] Chemical Computing Group, 1010 Sherbrooke St., W., Suite 910, Montreal QC H3A 2R7, Canada

Conformation Import generates rapidly calculated low-energy conformations of molecules from SD files, SMILES and MOE molecular databases. The imported molecules are split into overlapping fragments, conformations of the fragments are created using forcefield minimization, and then reassembled to give the conformation of the whole molecule. The fragmentation rules now create fewer fragments with a better chemical context, using the Amber:EHT forcefield. Penalty functions are used to filter unwanted conformations, such as cis-amides and boat saturated rings, unless there are no conformations with trans-amides and chair saturated rings. To validate the method the generated conformations were compared to ligand conformations derived from crystallographic receptor-ligand complexes. Conformations were generated for 10,000 ligands from 25 protein families and the RMS deviation was measured between the conformations and the crystallographic bound ligand conformation. Changes to the protocol for setting the ligand protonation state and refinement of the conformations were investigated.

P22

An ABMD-Based Protocol for Estimating Rankings of Ligand Residence Times in Pharmacologically Relevant Targets

A. Coricello[a], M. Musgaard[b], B.G. Tehan[c], G. Bottegoni[a,d]

[a] Università degli Studi di Urbino "Carlo Bo", Urbino, 61029, Italy
[b] Independent Researcher, Oxford, UK
[c] OMass Therapeutics Ltd, Oxford OX4 2GX, UK
[d] University of Birmingham, Birmingham, B15 2TT, UK

Understanding ligand dissociation kinetics is a key aspect of modern drug discovery, as residence time is closely linked to both drug efficacy and safety. Computational approaches, particularly those based on molecular dynamics (MD) simulations, offer a valuable means to investigate unbinding processes. However, capturing such rare events efficiently across multiple systems remains a significant challenge (1).

In this work, we describe a workflow based on Adiabatic Bias Molecular Dynamics (ABMD) simulations for the estimation of relative ligand unbinding times across congeneric series (2,3). ABMD employs a harmonic bias potential that selectively acts when the system moves away from a predefined reaction coordinate endpoint, thereby promoting progression toward ligand dissociation while preserving the natural dynamics of the system.

Starting from equilibrated protein–ligand complexes, our protocol uses the distance between the centers of mass of the ligand and the binding site as the collective variable to guide unbinding. The workflow integrates all stages of the simulation pipeline, including system setup, equilibration, production MD, and ABMD runs, followed by automated trajectory analysis. For each system, multiple independent replicas are performed, and simulations are continued until ligand dissociation occurs or a predefined maximum simulation time is reached. The approach has been implemented using the PLUMED plugin on both AMBER and GROMACS simulation packages.

The method has been validated on pharmacologically relevant targets, including thrombin, the A2A receptor, HSP90, and CDK8. Across these systems, the computed average unbinding times showed encouraging agreement with experimentally determined kinetic data, supporting the reliability of the protocol in ranking ligand residence times.

Overall, this ABMD-based workflow provides a practical and scalable strategy for investigating ligand unbinding kinetics and may represent a useful addition to computational pipelines in drug discovery.

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P23 A Problem-Solving Molecular Design Tool for Removing hERG Channel Binding Liability

S. Kaempf[a], A.G. Leach[a], S. Freeman[a], L. Venetucci[b]

[a] University of Manchester, Oxford Road, Manchester, M13 9PL
[b] University of Manchester, Division of Cardiovascular Sciences, Grafton Street, Manchester, M13 9NT

Matched molecular pair analysis (MMPA) is a widely used approach for investigating structure–activity relationships by comparing compounds that differ by well-defined chemical transformations [1]. By directly linking structural changes to experimental activity differences, MMPA is a useful tool to guide medicinal chemists. In this work our computational "theoceptor" model that predicts ligand binding geometries and relative binding affinities is applied to a set of MMPs for the cardiac potassium channel, hERG, using a range of cryo-EM structures [2]. This enables structural transformations to be rationalised and provides chemists with a chemically reasonable estimate of the binding pose. This approach allows chemists to identify chemically intuitive modifications in compounds to reduce hERG binding liability.

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P24

KinSPEC: Kinase Sequence-based Prior-guided Explainable Compound–protein Interaction Framework

H. Wang, D.R. Houston

Institute of Quantitative Biology, Biochemistry and Biotechnology, School of Biological Science, University of Edinburgh, U.K.

In early-stage drug discovery, a key challenge is to identify which small molecules are likely to interact with specific proteins. Computational ("in silico") virtual screening provides a fast and cost-effective way to prioritise compound-target interactions (CPI) before experimental testing. Traditional approaches often rely on detailed experimental 3D protein structures or previously known active molecules, which are not always available. This has motivated the development of sequence-based methods that rely solely on protein sequences. Most existing sequence-based models are designed to work across multiple protein families. While these general models are widely applicable, they may struggle to capture subtle differences within specific families. This is particularly important for kinases, a large family of structurally similar proteins whose selectivity is typically determined by a few variable residues.

Here, we present KinSPEC, a kinase-specific sequence-based framework, integrating prior knowledge from structurally aligned sequences of kinase binding pockets (KLIFS) with molecular fingerprints, to predict kinase-compound interactions. KinSPEC applies linear sparse autoencoders to learn compact and reversible embedding features of molecules and kinases. A downstream XGBoost classifier predicts interaction with traceable feature attribution. By combining decoder-based inversion with TreeSHAP, the model maps the predictive signals back to the original molecular substructures and kinase residues.

KinSPEC shows superior early enrichment performance compared to other sequence-based baselines across a compound-similarity spectrum designed based on the VSDS-vd TrueDecoy dataset, with generalisation further evaluated on the external KIBA benchmark. Finally, interpretability analysis suggests that KinSPEC captures statistically discriminative features within the kinase family, rather than directly inferring physical interaction sites. In conclusion, KinSPEC provides an interpretable framework for kinase-specific virtual screening and target selectivity analysis.

P25 Prospective Applications of Machine Learning and Generative AI for ERAP1 Inhibitor Design

M. Ballarotto[a], M.À. Galmés Ordinas[a,b], A. Kalusa[a], M. Palomba[a], T. McHardy[a], A. McClarron[a,c], E. Dixon[a], J. Nkrumah[a], A. Hayes[a], R. Ruddle[a], D. Hinchen[a,d], O. Pierrat[a], Y.-V. Le Bihan[a], R. van Montfort[a], A. Scarpino[a], G. Newton[a]

[a] Centre for Cancer Drug Discovery, The Institute of Cancer Research, 15 Cotswold Road, Sutton SM2 5NG, U.K.
[b] Department of Biocatalysis, Institute of Catalysis, CSIC, Marie Curie 2, 28049, Madrid, Spain
[c] Insmed, Babraham Research Campus, Cambridge, CB22 3FH, U.K.
[d] Molekulare u Strukturelle Biologie, ETH Zürich, Otto-Stern-Weg 5, 8093 Zürich, Switzerland

Endoplasmic Reticulum Aminopeptidase 1 (ERAP1) is an aminopeptidase that plays a key role in the antigen presentation pathway. Inhibition of ERAP1 activity is an attractive therapeutic strategy in immuno-oncology as it can drive the activation of adaptive immune responses from the patient's immune system.[1]

To aid the medicinal chemistry efforts to target ERAP1 we have applied cutting-edge Machine Learning (ML) and Generative AI (GenAI) to two in-house chemical series, tailoring the approach according to the available experimental data for each series. These techniques have been proven to be able to accelerate the drug discovery process, assisting compound selection by predicting compound properties[2] or supporting compound design,[3] respectively.

Given the larger amount of available experimental data in Series 1, we followed a ligand-based approach by combining a Free-Wilson analysis of Series 1 compounds with the training of local ML models to predict key compound properties. This allowed the enumeration and scoring of a large virtual combinatorial library, with the goal of identifying compounds with the most balanced property profile.

On the other hand, we followed a structure-based approach together with the application of GenAI to assist the development of Series 2. A docking-based Reinforcement Learning (RL) workflow, using the publicly available REINVENT4[4] model, was used to decorate a central core with the aim of producing novel design ideas to interact with an underexplored subpocket.

Continuous integration with medicinal chemists in the project, from the design of the RL workflow to the evaluation of the generated molecules, was a key component for the collaboration success. Multiple iterative rounds of compound assessment allowed for the selection of a set of promising molecules for each approach, which are currently being put through our internal assay cascade.

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P26 Cheminformatics-driven Docking, Machine Learning and Generative AI for the Development of Covalent Modulators and Degraders based on Cereblon

H. Lan

Frontier CADD, Royston, Hertfordshire, United Kingdom

This poster will demonstrate a comprehensive computational drug discovery project focused on developing covalent modulators for the Cereblon (CRBN) and Targeted Protein Degradation (TPD). The workflow integrates cheminformatic data curation from public, patent and enamine's commercial databases with the generation of synthetic chemical libraries to fill existing gaps in covalent modality research. Assisted with available CRBN-based ternary complex structures (IKZF2, WIZ), the study further utilises pharmacophore shape and distance constrained docking to prioritise degrader candidates in physically reasonable space. Such space was ultimately refined with QSAR modelling (classic ML, GNNs) and reinforced with generative AI platforms (smilesRNN, REINVENT4) to identify some reactive 'sweet' molecules that meet specific drug-likeness criteria - desired solubility, lipophilicity and TPSA etc., which are indicative for synthetic trial and potential development in DMPK/ADME.

[1] Some 'Learning' in Cheminformatics, QSAR and Generative AI (https://haolan-compchem.github.io/posts/2026-03-16/)

P27 Expanding the Alchemy Toolbox: Multi-Method Alchemical Networks with OpenFE

J.T. Horton[a], H. M. Baumann[a], I. Alibay[a], A. Travitz[a], J. RB. Eastwood[a], M. M. Henry[a,b], D. Mobley[a,c]

[a] Open Free Energy, Open Molecular Software Foundation, Davis, California 95616, United States
[b] Chodera Lab, Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[c] Department of Pharmaceutical Sciences, University of California, Irvine

Relative binding free energy (RBFE) methods are established as an efficient and reliable approach for prioritising compounds in drug discovery. Through a large-scale collaborative public benchmarking initiative, the Open Free Energy project has shown that its open source hybrid topology implementation delivers robust performance across a diverse range of targets and transformation types on public benchmarks and private industry datasets [1].
However, certain classes of transformations remain challenging within the hybrid topology framework. In particular, scaffold hopping and transformations involving substantial topological changes, as well as the correct treatment of dummy atoms to ensure well-behaved and factorisable free energy contributions[2] are nontrivial. These cases can violate key assumptions underpinning hybrid approaches, leading to reduced accuracy or convergence issues.
To address these limitations, we explore the use of mixed alchemical networks that integrate both hybrid topology and separated topology[3,4] methodologies within a unified framework. This multi-method strategy aims to retain the efficiency and robustness of hybrid approaches where applicable, while enabling accurate treatment of more complex transformations via separated topologies.
Here, we investigate how such heterogeneous networks can be systematically constructed to improve accuracy on challenging edges while maintaining overall computational efficiency. We further examine heuristic rules for automatically selecting the appropriate alchemical method on a per-transformation basis, to enable scalable, automated network design in prospective applications.

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P28 Learning the Role of Dynamics of Kinase Activation Loops

M. Mattia[a], M.T. Egiacomi[a], A.S.J.S. Mey[a], E. Rosta[b]

[a] EaStCHEM School of Chemistry, University of Edinburgh, Joseph Black Building, David Brewster Road, EH9 3FJ, Edinburgh, UK
[b] Department of Physics and Astronomy, University College London, Gower Street, WC1E 6BT, London, UK

Kinases are a class of proteins often found overexpressed in cancer cells, making them a candidate for drug design [1]. Several thousand kinase structures have been solved, revealing conserved structure motives that include an IDR called the “activation loop” (A-loop). Kinase function is regulated through a conformational switch between an inactive and an active state. The goal of this work is to characterise how A-loop rearrangements may be linked to kinase activation [2].

We have assembled a dataset comprising of 2523 kinase structures to identify structural patterns that correlate A-loop conformations with kinase activation state. By looking at A-loop conformational states, we can classify kinases into active and inactive states and elucidate their correlation with structural changes across all kinase catalytic domains. We show that classifying kinase conformations based on A-loop geometry yields an 82% accuracy in predicting kinase activation state. Furthermore, a specific distance between the phosphate-binding loop (P-loop) and the terminal region of the C-lobe accounts for the shift in A-loop conformation in 90% of cases. Knowledge gained from this analysis will aid in defining reaction coordinates to effectively sample kinase activation through enhanced-sampling molecular dynamics simulations.

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P29 QSAR-Enabled Predictive Modelling for Safety

R.L. Marchese Robinson[a], L. Southgate[a], N.K. Geitner[b]

[a] Jealott's Hill International Research Centre, Syngenta Crop Protection, Product Safety Department, Bracknell, Berkshire RG42 6EY, U.K
[b] Syngenta Crop Protection, Product Safety Department, 410 Swing Road Greensboro, NC 27409, USA

Syngenta is committed to innovative digital modelling in support of the accelerated delivery of safe and sustainable novel plant protection product active ingredients to the market. The Product Safety QSAR-Enabled Predictive Modelling Team works alongside other QSAR modellers at Syngenta to develop and deploy new models to support candidate selection and design. We drive innovation by implementing the state of the art in-house and via collaboration with academics and other thought leaders. Our poster will discuss the following: (i) how we deploy models internally to most effectively support candidate selection and design, including generative chemistry; (ii) examples of Product Safety models we have developed for these purposes, or are currently working on; (iii) examples of recently completed and ongoing academic collaborations we have funded to drive innovation and contribute to the wider scientific community.

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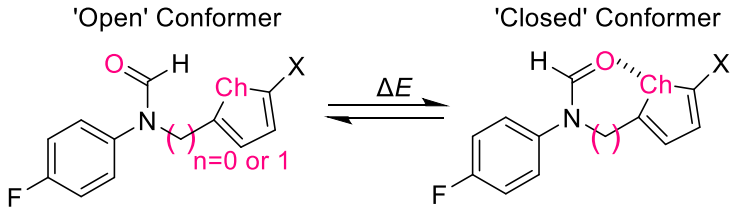
P30 Switching off Electron Delocalisation in Chalcogen-Bonding Balances

B. Raynor, S.L. Cockroft

EaStCHEM School of Chemistry, University of Edinburgh, Joseph Black Building, David Brewster Rd, Edinburgh EH9 3FJ

The physiochemical origins of chalcogen bonding interactions are heavily debated due to the difficulty in dissecting electrostatic and electron-delocalisation contributions.[1] Here we dissect the nature of chalcogen bonding interactions using synthetic molecular balances, density functional theory calculations, and natural bond orbital analysis. Molecular balances are excellent tools for quantifying molecular interactions, since their ability to form two conformers arises from the presence or absence of specific intermolecular forces (Figure 1).[2] Previous research indicated the importance of n→σ* orbital delocalisation as the fundamental nature of chalcogen-bonding interactions.[3] Our present work finds that adding a methyl linker between the chalcogen bond donor and acceptor sites enabled n→σ* orbital delocalisation to be switched off, thereby enabling dissection of the orbital delocalisation and electrostatic components to the total interaction energy.



Variable-linker molecular balances used to quantify chalcogen bonding interactions.

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P31 Development of Shape Searching of the Synthon Representation of Large Libraries to Include Disconnected Fragment Shape Searching

D.A. Cosgrove[a], E.J. Griffen[b,c], F. Imrie[d]

[a] Cozchemix Ltd
[b] MedChemica Consultancy Ltd, The Motorworks, Chestergate ,Macclesfield. SK11 6DU
[c] Openbind consortium
[d] Department of Statistics, University of Oxford. 24-29 St Giles', Oxford OX1 3LB

Shape searching remains a highly attractive approach to hit finding and analogue searching. The advent of ultra large databases of synthesisable molecules makes the searching of these databases with a shape query highly desirable. Although substructure searching via searching the synthon representation of databases is now possible, the searching of shapes within the synthon representation adds additional complexities.
Within the Openbind consortium we are interested in the large scale application of fragment based lead generation. Of the three strategies for increasing fragment potency: growing, merging and linking, fragment linking is highly attractive but remains technically challenging. By searching for "shape analogues" of fragments that are part of linked molecules contained within large virtual databases we hope to accelerate the process of fragment based lead generation by moving directly from fragments to linked accessible molecules.
Here we report initial results from our studies.

P32 Supporting Prospective TIES Calculations with Stereochemistry-Aware Superimposition, Rule-Based RBFE Network Generation, and FEgrow Docking

M. Bieniek[a,b], S. Wan[b], A. Bhati[b], K. Liu[b], D. Green[b], M. Todd[b], H. Löeffler[c], M. Klähn[c], P. Coveney[b]

[a] University of Edinburgh, Data Intelligence Hub, Edinburgh
[b] University College London, Centre for Computational Science, Chemistry Departments, London
[c] AstraZeneca

Prospective application of **TIES relative binding free energy (RBFE)** calculations depends strongly on robust setup of ligand perturbation networks, atom mappings, and starting protein-ligand complexes. In this work, we developed a practical workflow to support TIES in lead optimisation, with particular focus on reducing manual intervention in system preparation.

A **rule-based graph traversal strategy** was used to construct chemically sensible RBFE networks, selecting tractable perturbations across ligand series while avoiding problematic transformations. To improve alchemical mappings and starting geometries, we implemented **stereochemistry-aware ligand superimposition**, which is particularly important for chiral compounds and closely related analogues. For structure preparation, ligands were docked using **FEgrow** either into available crystal structures or into alternative receptor conformations selected on the basis of promising experimental observations, providing suitable starting complexes for TIES calculations.

Together, these tools enabled a more systematic and reproducible setup of prospective RBFE calculations. Applied within the wider optimisation workflow for **WDR91**, the resulting TIES-supported prioritisation contributed to compound selection for synthesis and experimental testing, ultimately leading to **an experimentally confirmed chiral binder with KD 320-384 nM**.

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P33 Molecular Inpainting for Elaborating Fragments into Hit-like Molecules

A.V. Patnaik[a], V. Gopalkrishnan[a], N.T. Runcie[b], D. Michieletto[a], A.S.J.S. Mey[c]

[a] School of Physics and Astronomy, University of Edinburgh, Peter Guthrie Tait Road, Edinburgh EH9 3FD, United Kingdom
[b] School of Chemistry, University of Edinburgh, Edinburgh, United Kingdom
[c] EASTCHEM School of Chemistry, University of Edinburgh, Edinburgh, United Kingdom

Fragment-based drug discovery often requires linking or merging multiple fragment hits to form complete, drug-like molecules. Existing methods handle these tasks separately: rule-based tools merge overlapping fragments using geometric heuristics [1], while generative models design linkers based on idealized artificially generated fragments [2]. We present a unified refinement framework that operates directly on fragments using a pre-trained small-molecule diffusion model. Our approach iteratively denoises fragment inputs to generate continuous molecules, resolving overlaps and discontinuities in 3D space without relying on explicit pocket information, predefined linker templates, or hard geometric rules. This single diffusion-based process dynamically handles both linking and merging. Benchmarking against state-of-the-art tools demonstrates improved chemical validity and strong potential for high-throughput fragment elaboration.

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P34 Multi-Partner Foundation Models for Molecular Embeddings Improve Early ADMET and Potency Prediction in Drug Discovery

D. Crusius, J. Menke, R. Greenhalgh

deepmirror, Victoria House, London, UK

Generalisable molecular representations remain a core challenge in early drug discovery, where the scarcity of program-specific data limits the utility of locally trained models. We present a foundation model approach to molecular embeddings, trained on large-scale curated datasets aggregated across multiple industry partners, and evaluate its impact on ADMET and potency prediction across diverse drug discovery programs. By harmonising data from multiple sources, the model learns transferable embeddings that serve as a strong prior for downstream finetuning via an AutoML framework. We evaluate across three regimes: (a) low-data program specific models, (b) a global LogD model benchmarked against held-out in-series data as pretraining scale increases, and (c) out-of-series generalisation to chemical space beyond the training distribution. Results across ADMET and potency endpoints consistently favour the foundation model approach over both program-specific baselines and public global models. Critically, LogD predictive performance improves monotonically with the number of contributing pretraining partners, directly isolating the value of multi-partner data aggregation for embedding quality. Participation in the OpenADMET Expansion Therapeutics blind challenge provides additional external validation. These findings establish that foundation models pretrained on curated multi-partner molecular data produce embeddings of sufficient quality for downstream modelling.

P35

Large-Scale Collaborative Assessment of Binding Free Energy Calculations for Drug Discovery Using OpenFE

I. Alibay[a], V. H. Baumann[a], J. Horton[a], A. Travitz[a], J. R. B. Eastwood[a], M. M. Henry[a,b], D. Mobley[a,c]

[a] Open Free Energy, Open Molecular Software Foundation, Davis, California 95616, United States
[b] Chodera Lab, Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[c] Department of Pharmaceutical Sciences, University of California, Irvine

Accurately measuring binding affinity changes is key to driving the pharmaceutical development process. Rigorous physics-based in silico approaches, particularly alchemical free energy methods, have become a popular tool for ranking compound affinity. Here we present the results of a large-scale precompetitive collaborative assessment of relative binding free energy (RBFE) calculations involving participants from 15 pharmaceutical companies.[1] In this assessment, we evaluated the use of the Open Free Energy (OpenFE) RBFE Protocol on both public and blinded private in-house datasets. For the public datasets, 60 systems (>800 ligands) provided by Ross et al.[2] were chosen while the private inhouse datasets were selected by each participating pharmaceutical company. Results from this benchmark, one of the largest of its kind, offer unique insights into the current reliability of opensource alchemical tools, focusing on those offered by OpenFE, and their suitability for use in active drug discovery projects.

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P36 AI-Driven Design of GLP-1R PAMs: A Synergy of Generative Models, Active Learning, and Molecular Dynamics

J. Clark-Nicolas[a,b], A. Morrison[c], M. Watkins[a], A. Pugliese[c]

[a] School of Engineering and Physical Sciences, University of Lincoln, Brayford Pool, Lincoln, England
[b] Dept. Pure & Applied Chemistry, University of Strathclyde, Glasgow, Scotland
[c] BioAscent Discovery Ltd, Bo'Ness Rd., Newhouse, Scotland

The vastness of theoretical drug-like chemical space presents a fundamental challenge for modern drug discovery[1]. Here, we present a generative workflow that addresses this issue through the integration of reinforcement learning-driven molecular generation, adaptive distribution-driven filtering, and transfer learning. The workflow leverages the REINVENT framework[2] and employs adaptive selection criteria based on iteration-specific histogram peaks to avoid reliance on fixed thresholds. Structure-based evaluation is performed using ensemble docking[3] into multiple receptor conformations derived from molecular dynamics simulations, combined with protein-ligand contact surface area (CSA) calculations. As a test case, we applied this approach to the design of novel positive allosteric modulators (PAMs) of the glucagon-like peptide-1 receptor (GLP-1R), which act via a "molecular glue" mechanism to stabilize the endogenous agonist-receptor interface[4]. Across iterations, the workflow yielded consistent enrichment in predicted binding affinity, drug-likeness, and synthetic accessibility. Notably, the top-ranking candidates significantly outperformed the reference compound in docking scores and drug-likeness while successfully recapitulating the glue-like interaction profile. These results demonstrate the ability of the proposed closed-loop framework to steer generative models toward target-relevant regions of chemical space and generate diverse, high-quality candidate molecules.

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P37 Smarter Compound Selection: Active Learning-Driven FEP for Faster High-Affinity Ranking

V. Marinova, D. McMahon, V.K. Ramaswamy, M. Habgood, M.D. Mackey

Cresset, New Cambridge House, Bassingbourn Road, Litlington SG8 0SS, Cambridgeshire, United Kingdom

As compound libraries continue to grow, there is an increasing need for cost effective methods that can accurately predict biological activity at scale for accelerating drug development.
Active learning (AL), based on models built on binding potency predictions from free energy perturbation calculations (FEP), is a powerful tool for lead optimization. A robust AL-FEP protocol enables screening large molecular libraries, saving time and computational costs.
In this work, we present an AL-FEP approach which helps identify promising active compounds using much less data than traditional methods 1.
Our method demonstrates good selection of high activity compounds when compared to higher cost activity prediction calculations (Flare™ FEP, Boltz-2) on three different systems. Overall, this provides a fast, affordable way to screen large collections of compounds and focus effort on the most promising candidates.

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[3] Flare™ https://cresset-group.com/software/flare/

P38 SureChEMBL2.0: Evolving a Database for Annotated Patents

I.Ismail, N. Bosc, T. Kiziloren, E. Felix, C. Moreno, R. Arcila, A.R. Leach, B. Zdrazil, N.M. O'Boyle

European Molecular Biology Laboratory-European Bioinformatics Institute (EMBL-EBI), Chemical Biology Services, Hinxton, Cambridge CB10 1SD, UK

Patents describe and protect innovation, representing indirectly a rich source of information for drug development. First occurrences of compound and compound-target interaction often happen in the patent literature [1]. Despite the documents being freely accessible, data access remains challenging, and annotations are required for large-scale analysis. SureChEMBL [2] is a freely available resource that delivers extra value from patents, historically extracting chemical structures from text and images, but also more recently annotating the biomedical lexicon.

In 2025 we delivered SureChEMBL2.0, a major milestone offering a more robust pipeline for an improved data delivery. Relying on our improved system architecture, we are next going to offer improved annotation using newly implemented tools.

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P39 Development of Small-Molecule Inhibitors for TWIK-2 via Fragment-Based Virtual Screening and MD Simulations

N. von Engelhardt, A. Ketzel, S. Ghysbrecht, B. Tuerkaydin, P. Zhou, H. Sun

Research Unit of Structural Chemistry & Computational Biophysics,
Leibniz-Forschungsinstitut für Molekulare Pharmakologie, Berlin 13125, Germany.
Institut für Chemie, Strukturelle Chemische Biologie und Cheminformatik,
Technische Universität Berlin, Berlin 10623, Germany
NMPA Key Laboratory for Research and Evaluation of Drug Metabolism, Guangdong Provincial Key Laboratory of New Drug Screening and Guangdong-Hong Kong-Macao Joint Laboratory for New Drug Screening, School of Pharmaceutical Sciences, Southern Medical University, Guangzhou 510515, China.

Ion channels are among the most successful classes of drug targets; however, the two-pore-domain potassium (K2P) channels remain relatively underexplored for therapeutic development. K2P channels are widely expressed across human tissues and play critical roles in physiological processes including pain modulation, neuroprotection, and cardiac action potential repolarization.1-4 Electrophysiological (EP) studies have identified an FDA-approved small-molecule drug, as an inhibitor of the K2P channels TWIK-2 and TREK-1. In this study, binding poses and inhibitory mechanisms were investigated using molecular docking and molecular dynamics (MD) simulations. Binding poses identified were consistent with interactions observed for the known K2P channel modulator ML335. The poses and mechanisms were subsequently leveraged in a fragment-based virtual screening using ChemSpaceDocking of the WuXi GalaXi chemical space to identify novel inhibitors of the TWIK-2 channel. From an initial set of candidates, 20 compounds were selected for experimental validation. EP testing identified three active hits, including one compound exhibiting strong inhibition of TWIK-2, approaching the efficacy of the FDA drug.

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P40 Rational Thermostability Engineering of PL28 Ulvan Lyase Using AI-Based Protein Embeddings, Molecular Dynamics, and Alchemical Free Energy Calculations

A. Tilewale[a,b], C.Zhang[b], J. Michel[b], D. Patel[a]

[a] Gujarat Biotechnology University, Department of Industrial Biotechnology, Gandhinagar, 382355, India
[b] University of Edinburgh, School of Chemistry, Edinburgh, EH9 3FJ, UK

Ulvan lyases are attractive biocatalysts for the depolymerisation and valorisation of ulvan, a sulfated marine polysaccharide with increasing biotechnological potential. However, their industrial deployment is frequently limited by poor thermal stability. To address this, we developed an AI-assisted framework for thermostability engineering of a PL28 ulvan lyase that combines mutation-space definition, protein embedding-based screening, physics-based refinement, and MD-based validation.

Candidate positions were first defined through structural analysis, conserved-residue mapping, functional-site annotation, and MD-derived flexibility profiling, allowing catalytically critical and structurally sensitive residues to be excluded by mutation masking. This yielded an accessible sequence space of 5,757 variants. These were screened using zero-shot fitness scores from a protein language model together with a graph neural network trained for thermal stability prediction. From this, 1,385 embedding-positive and 793 stability-positive variants were identified, including 231 common candidates. Application of the mutation mask further narrowed this set to 21 shortlisted variants.

Shortlisted variants were prioritised using empirical force-field-based ΔΔG calculations and examined through high-temperature MD simulations. Comparative ΔRMSD and ΔRMSF analyses enabled identification of mutants with improved dynamic behaviour relative to the wild-type enzyme. Current work extends this framework through alchemical free-energy calculations to quantify mutational effects on protein stability and ligand binding. Collectively, this study demonstrates a practical and scalable strategy for AI-guided enzyme thermostability engineering and provides a strong foundation for experimental validation of improved ulvan lyase variants.

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P41 Data Analysis and Modelling of Toxicity End Points for Seizure Risk

J.L. McDonagh[a,b], L.A. Zolkiewski[a], K.L. Rockley[a], R.A. Roberts[a], H.G. Jennings[a], M.A. Maizières[a], K. Jones[a], K. Newman[a], E.J. Griffen[b], J.E. Stacey[b], M.J. Morton[a]

[a] ApconiX, Alderley Park, Mereside, Macclesfield SK10 4TG
[b] MedChemica Consultancy Ltd, Motorworks, Macclesfield, Cheshire. SK11 6DU, UK

Data modelling methods, such as, machine learning and deep learning models can be used for the classification and prediction of toxicity end points. CNS liability is a major risk in drug discovery and development, leading to delays and failures yet it remains a consideration typically at later stages of the discovery process. Here, we outline the use of statistical analysis and machine learning to build insights into structural liabilities associated with CNS ion channels $K_V2.1$, $Na_V1.2$, the $\alpha_1\beta_2\gamma_2$ GABAA and $\alpha_4\beta_2$ nicotinic receptors.

We have developed a small bespoke in-house data set comprised of molecular structures selected from the Enamine REAL database based upon structural reference compounds of known activity. Using an electrophysiology assay the dose-response and IC50 values were determined. We present an initial data analysis and preliminary modelling based on this data set, highlighting key early scientific findings from this approach.

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P42 Structural Dynamics Analysis of Nitrite Reductase AniA

A. Azar

University of Edinburgh, School of Chemistry, Edinburgh, UK

Metalloenzymes are essential to many biological processes, yet the coupling between metal binding, structural dynamics, and oligomerisation remains poorly understood. Here, we investigate a copper-dependent enzyme that exists as a monomer in its apo form and assembles into a trimer upon metal loading. The enzyme contains two distinct copper sites: a buried Type 1 copper site within each monomer and a Type 2 copper site located at the interface between adjacent subunits, which forms the catalytic centre (Sikora et al.,2017). A central unresolved question is whether copper binding drives trimerisation or whether trimer formation is required for copper incorporation, particularly given that both processes are slow and effectively irreversible in vitro.

Using molecular dynamics simulations combined with quantum-mechanical parameterisation, we characterised the structural and thermodynamic behaviour of the enzyme across apo and holo states. Type 1 copper binding lowers the free energy of association, promoting trimer formation, while simultaneously inducing conformational shifts at the Type 2 site that favour metal coordination, indicating long-range allosteric coupling. These effects are accompanied by pronounced rearrangements in a C-terminal region, which is flexible in the apo state and remains disordered in the holo monomer but becomes stabilised in the holo trimer. Together, these results show that copper binding alone is insufficient for stabilisation; instead, Type 1 loading drives both oligomerisation and pre-organisation of the catalytic site, revealing a cooperative mechanism linking metal binding, structural ordering, and trimer assembly.

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P43 Molecular Dynamics Insights into Ion Conduction and Gating Mechanisms of PKD2

C. Zhang, J. Michel

University of Edinburgh, EaStChem School of Chemistry, Edinburgh, EH9 3FJ, UK

Polycystin-2 (PKD2) is a member of the Transient Receptor Potential Polycystin (TRPP) channel family whose dysfunction is associated with autosomal dominant polycystic kidney disease (ADPKD), a common inherited kidney disorder. The detailed gating mechanisms remain unclear, with two possible hypotheses: a π-to-α helix transition that leads to pore opening1, or the π-bulge acting as a hinge2.

In this work, we combine molecular dynamics simulations with enhanced sampling to evaluate these hypotheses and characterise ion permeation. Two structural models corresponding to the proposed mechanisms were constructed and their conductance systematically assessed under K^+, Na^+, and Ca^{2+} conditions respectively. Under the CHARMM36m force field with CHARMM TIP3P water, the α-helix open state exhibits dewetting and remains non-conductive, whereas the π-bulge model achieves physiologically reasonable conductance when electronic continuum correction (ECC) is applied. Using AMBER19SB with OPC water and 12-6-4 ion parameters, both models become conductive. However, the α-helix state still underestimates conductance relative to experimental data. Further analysis reveals distinct ion permeation behaviours across species. Together, our findings support the π- bulge mechanism as the more plausible gating model and provide a framework linking gating, permeation, and modulation in PKD2 channels.

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P44 Beautiful Visualisations with Molecular Nodes

B. Johnston

The University of Western Australia, Perth, 6009, Australia

Programs such as PyMOL, ChimeraX and VMD excel at scientific analysis of structural data, but lack the visual rendering capabilities of a dedicated 3D modelling and animation program such as Blender. Access to realistic lighting and complex animation techniques make Blender well suited for visualising scientific topics such as structural biology. In this work I present Molecular Nodes, a plugin for Blender that enables import of molecular structural formats such as .pdb, .pdbx/.cif, .mmcif, direct download from the wwPDB via a 4-character PDB ID, and import of molecular dynamics trajectories from software such as GROMACS, CHARMM, and LAMMPS.

Previously, importing a static model to a 3D program required exporting generated geometry from PyMOL or ChimeraX before importing to Blender — a computationally intensive process that breaks the link between the 3D model and the data that generated it. Molecular Nodes shifts this paradigm by leveraging Blender's procedural modelling system, Geometry Nodes, which handles and manipulates tabular numeric data and generates new geometry from it. Structural data from .pdb files is imported directly into Blender, where a suite of functions enables manipulation of atomic data and generation of 3D geometry. This allows rapid import and geometry generation, including molecular dynamics trajectories with the ability to regenerate geometry for each frame. With access to underlying atomic data, novel animations can be created — such as binding and unbinding of protein chains or movement of amino acid side chains — driven by bonds and B-factors present in the structure. Molecular Nodes gives researchers easy access to complex, beautiful animations of molecular data, helping them communicate more effectively with peers and the public.

S01 The Virtual Screening for Potential Allosteric Inhibitors Targeting PIF-Pocket of MAST Protein Kinases

A.O. Steshenko, S.P. Ozheredov, S.I. Spivak, Ya.B. Blume, P.A. Karpov

Institute of Food Biotechnology and Genomics of the National Academy of Sciences of Ukraine,
Baidy-Vyshnevetskoho str., 2A, Kyiv, 04123, Ukraine

Contact: karpov@nas.gov.ua

[Link to poster]

Microtubule-associated serine/threonine kinases (MAST) are linked to a broad spectrum of diseases, including cancer, neurological disorders, inflammatory bowel disease, and type 2 diabetes; however, no selective inhibitors of MAST family members have been identified to date. The MAST family comprises five members — MAST1–4 and MASTL (GWL) — and represents a promising but underexplored therapeutic target. Most kinase inhibitors target the ATP-binding pocket, which is highly conserved throughout the kinome, making selectivity difficult to achieve. Prior work revealed that the ATP-binding site is fully conserved among MAST subfamily members, offering no basis for selective targeting. The PIF pocket, an allosteric site shared by AGC kinases but with markedly greater amino acid variability, presents a more promising alternative. Its effectors have shown strong selectivity across the AGC superfamily, with established inhibition protocols already validated for PDK1, PKC, and S6K. This study focuses on virtual screening for MAST-selective PIF pocket inhibitors, with subsequent analysis of isotype-binding variability across MAST1–4 and MASTL.

Primary pharmacophore screening identified 23 hits from virtual screening. All selected compounds showed preferential binding to the PIF pocket among MAST family members, regardless of additional affinity for the ATP or K pockets. Predicted affinity for MASTL was consistently lower than for other family members. Among the Enamine compounds, Z15749680 demonstrated the best overall binding parameters and serves as the primary reference for combinatorial optimization and in vitro testing, while Z279671592 was identified as the most promising candidate for isotype-neutral inhibition. SBF1 showed strong affinity for the PIF and K sites of MAST1/3/4 — peaking at the MAST4 PIF site — but minimal interaction with the MASTL PIF site and the MAST2 ATP pocket. Control compound PS423 displayed the highest affinity for the PIF sites of MAST1–3, while Z87739851 was selective for MAST4, and Z19748016 showed elevated affinity for MAST2 and MAST4. Z318373636 and Z56794203 were most active at the MAST1/3 and MAST1–3 PIF sites, respectively, and Z18477561 showed no predicted interaction with the MAST3 ATP-binding site.

No PIF-effectors have been reported for MAST family kinases, despite this pocket being one of the most experimentally validated sites of allosteric inhibition in the AGC family. Initial characterization of the MAST PIF pocket used reference ligand 78W (from PDK1 structure 5LVO), identifying 13 residues within 6 Å across all family members. Sequence variations detected at these positions (K/LI/I/[AV]5F/R/SF[ED]10/LCM) suggest potential isotype-specific differences in ligand binding. As no experimental MAST kinase structures exist, complexes of MAST1–4 and GWL with 78W were reconstructed using the AlphaFold3-based Protenix server. A generalized pharmacophore was derived and used for a Pharmit server virtual screening of the Enamine Ltd. library (60.5 million conformers for 4.1 million compounds). Pharmacophore screening with steric constraints and standard filters (MaxScore=0; Max mRMSD=1; Single conformer=ON) yielded 23 hits. Subsequent AI-assisted complex reconstruction identified three binding sites within the MAST catalytic domain: the allosteric

PIF pocket, the ATP-binding site, and the K-pocket. The selected hits were validated by molecular docking in CCDC GOLD (ChemPLP/ASP fitness functions; Genetic Algorithm, Search Efficiency=200%). Crystallographically confirmed AGC kinase inhibitors were used as positive control. Up to 10 hypotheses for each compound were ranked based on ChemPLP score.

It was concluded that PIF pocket represents a viable site for selective inhibition of MAST family members, and it was confirmed by isotype-specific differences in ligand binding profiles. Virtual screening of the Enamine Ltd. library combined with AI-assisted structural reconstruction and CCDC GOLD docking identified Z15749680 as the lead compound, and Z279671592 as the most promising isotype-neutral candidate. The consistently lower predicted affinity for MASTL across all compounds suggests structural features of the MASTL PIF pocket that distinguish it from other family members, and it may be base for future isoform-selective design. These findings establish a foundation for experimental validation and structure-based optimization of MAST-selective PIF pocket inhibitors.

S02 Investigation of the Interactions of Dinitroaniline-Series Compounds with α-Tubulins from Different Species and Ecotypes of the Plasmodium spp

A.M. Rachkovska, S.P. Ozheredov, Ya.B. Blume, P.A. Karpov

Institute of Food Biotechnology and Genomics of the National Academy of Sciences of Ukraine,
Baidy-Vyshnevetskoho str., 2A, Kyiv, 04123, Ukraine

Contact: karpov@nas.gov.ua

[Link to poster]

Microtubules (MT) are major components of the eukaryotic cytoskeleton, found in all eukaryotic cells and involved in mitosis, cell motility, intracellular transport, and the maintenance of cell shape. MTs are composed of α- and β-tubulin subunits assembled into linear protofilaments. By targeting plant α-tubulin, derivatives of 2,6-dinitroanilines (e.g., trifluralin, ethalfluralin, pendimethalin, oryzalin, etc.) disrupt microtubule assembly, inhibiting cell division and growth.

In addition to their use as herbicides, dinitroanilines show promise as antiprotozoal agents for treating parasites such as Toxoplasma gondii, Trypanosoma cruzi, Leishmania major and Plasmodium falciparum. Since these compounds do not bind to vertebrate tubulin, they exhibit low toxicity to humans, paving the way for the development of safe and effective next-generation antimalarial drugs. In light of new data on the mechanism of ligand binding in T. gondii, the objective of this work is a comprehensive in silico study of dinitroaniline compound binding with Plasmodium α-tubulins across different species and ecotypes.

Several models for dinitroaniline binding to tubulin have been proposed over the last decades. However, none of these models adequately explained all known resistance mutations. A new ligand-induced dinitroaniline binding model, similar to that of pironetin (PDB: 5FNV and 5LA6), was recently proposed for T. gondii by Aguayo-Ortiz and Dominguez (2022) and reasonably explains the basis of the main dinitroaniline resistance mutations (https:// tubulinmutations.bio.uci.edu/).

The interaction with Apicomplexan α-tubulin and its absence in vertebrates render dinitroanilines promising antiprotozoal candidates. Consequently, the challenge of this work was to study their binding to Plasmodium α-tubulins across different species and ecotypes.

Based on data from UniProtKB and the RCSB Protein Data Bank, 101 full-length α-tubulin amino acid sequences of Plasmodium spp. were selected. The key amino acid residues of the binding site “pocket” were identified based on structural modelling, multiple alignment of sequences and structures. The clustering of selected α-tubulins resulted in 37 unique sequences, while the analysis of the binding site revealed three variations in the ligand-binding pocket. These variations in site determinate three types of tubulin variants that were selected for structural modeling and protein–ligand binding analysis. Using AlphaFold3-based Protenix service, the complexes of three Plasmodium α-tubulin variants with dinitroanilines (trifluralin, orizalin, pendimethalin, etalfluralin) and amyprophos-methyl were predicted.

The Protenix / AlphaFold3 predictions confirmed ligand poses similar to previous model proposed for T. gondii by Aguayo-Ortiz and Dominguez (2022). Also, structural superposition of AI-predicted complexes, revealed nearly identical ligands orientations for both types of ligand-binding pocket. The high conservatism of the binding site and the stability of the complexes mark dinitroaniline derivatives as promising candidates for antimalarial drugs

that affect the parasite's microtubules with minimal impact on human. The results of molecular dynamics simulations (210 ns) proved the stability of all studied dinitroaniline complexes (APM - amyprophos-methyl, ORY - oryzalin, TFL - trifluralin, PEN - pendimethalin, ETH ethylfluralin) with α-tubulin isotypes known at the time of the study for Plasmodium sp. Research has demonstrated that dinitroaniline derivatives bind to α-tubulin in Plasmodium species through a ligand-induced mechanism similar to that observed in Toxoplasma gondii. An examination of available α-tubulin sequences identified two variations in the amino acid composition of the dinitroaniline binding pockets within the genus. Nevertheless, all known α-tubulin isoforms in Plasmodium species exhibit an equal capacity to interact with these compounds, as corroborated by molecular docking, molecular dynamics, and molecular complex reconstruction using artificial intelligence tools (AlphaFold3 / Protenix + Gromacs).

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S03

Identification of Novel SGLT2 Inhibitors via Virtual Screening and Structural Analysis

A.P. Karpova, L.M. Shmagai, P.A. Karpov

Institute of Food Biotechnology and Genomics of the National Academy of Sciences of Ukraine,
Baidy-Vyshnevetskoho str., 2A, Kyiv, 04123, Ukraine

Contact: karpov@nas.gov.ua

[Link to poster]

Blood glucose control remains one of the most critical factors in diabetes therapy [1]. Major progress in the development of antihyperglycemic agents was marked by the discovery of gliflozins — selective inhibitors of sodium-glucose cotransporter 2 (SGLT2), encoded by the SLC5A2 gene. By inhibiting SGLT2, these agents promote urinary glucose excretion and have proven effective for the management of type 2 diabetes mellitus (T2DM) [2]. In 2022, the deposition of human SGLT2 structures in the RCSB Protein Data Bank opened new avenues for rational structure-based design and virtual screening of renal glucose reabsorption inhibitors [3].

The objective of the current study was the structural biological analysis and virtual screening of potential SGLT2 inhibitors. Based on the sequence analysis of 12 SLC5 cotransporter isotypes and chemogenomic clustering of target binding sites, the feasibility of developing specific SGLT2 inhibitors was demonstrated. The occurrence of induced-fit binding during the formation of SGLT2-inhibitor complexes was confirmed, and a virtual screening protocol based on pharmacophore searching and molecular docking was developed. From the Enamine Ltd. library, containing 4,117,328 unique compounds, 36 potential SGLT2 inhibitors were selected. Ranking based on scoring functions and ligand-protein interaction energies allowed for the identification of five lead compounds. A database revision of the selected leads was performed using PubChem, DrugBank, and the U.S. Food & Drug Administration (FDA) records.

Enamine Ltd. compound Z2235801995 was identified as the active ingredient of the gliflozin drug INVOKAMET (Johnson & Johnson, FDA Reference ID: 4129180). Compound Z2417819595 was excluded following structural expertise. Among the three remaining compounds, two (Z2195993226 and Z2195993230) are reported as potential gliflozins for the first time. Another compound, Z1494829516, was identified as the hydroxyisoflavone Puerarin (or Kakonein), a known autophagy inducer positioned as a cardioprotective, antioxidant, anti-inflammatory, antipyretic agent, and ferroptosis inhibitor. However, its interaction with human SGLT2 and its glucose-lowering activity are predicted here for the first time.

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S04 Identification of Small Molecules Targeting the Interdomain Cleft (IDC) of Bacterial FtsZ

D.S. Ozheredov, S.P. Ozheredov, O.M. Demchuk, S.I. Spivak, Ya.B. Blume, P.A. Karpov

Institute of Food Biotechnology and Genomics of the National Academy of Sciences of Ukraine, Baidy-Vyshnevetskoho str., 2A, Kyiv, 04123, Ukraine

Contact: karpov@nas.gov.ua

[Link to poster]

The bacterial binary fission apparatus comprises a complex protein ensemble known as the divisome. Among its components, Filamenting temperature-sensitive mutant Z (FtsZ) is critical for Z-ring formation and the recruitment of downstream proteins [1]. This makes FtsZ a promising molecular target for inhibiting bacterial cell division [2, 3].

Based on RCSB PDB and ChEMBL data, a library of 379 FtsZ effectors was compiled. Nine 2,6-difluorobenzamide derivatives from RCSB Protein Data Bank served as positive controls, while six compounds targeting alternative sites were used as negative controls. Point-cloud models of the inter-domain cleft (IDC) pockets were constructed based on 11 S. aureus FtsZ structures in complex with 2,6-difluorobenzamides (including ligands OLQ, 9PC, OM8, OMW, ZI1, ZI6, ZI7, and ZI9). Our analysis confirmed significant variability in IDC pocket volume and shape resulting from induced fit a. Four distinct conformational states were identified, indicating that docking ligands into a single static 3D model of FtsZ is inadequate. Consequently, virtual screening efficiency were significantly improved by using an ensemble of targets that accounts for this conformational plasticity.

To identify IDC-specific effectors, the library (with pre-generated conformers) was uploaded to Pharmit. Pharmacophore screening strategy relied on 11 individual sessions - one for each PDB complex - to account for induced-fit variations. Pharmacophores were defined by analyzing h-bonds, hydrophobicity, electrostatics, and interaction maps using BIOVIA Discovery Studio. To minimize false positives, shape constraints were applied to the target pocket. Following these sessions, 89 unique compounds were selected based on scoring and redundancy filtration. The binding potential of the selected compounds was further evaluated via molecular docking using CCDC GOLD and iGEMDOCK. An ensemble of targets (PDB: 3VOB, 5XDT, 6YD1, and 5XDU) was employed to account for the previously identified flexibility of the IDC pocket. Visual assessment in PyMOL and scoring via the ChemPLP and ASP functions in GOLD confirmed plausible binding poses for all selected compounds. Final evaluation in iGEMDOCK enabled quantification of binding energies (Total Energy/Fitness), accounting for hydrogen bonds (H-Bonds), electrostatics (Elec), van der Waals (VDW) forces, and the steric potential of ligand-protein adaptation (AverConPair).

Thus, by combining pharmacophore screening and molecular docking of 379 known bacterial FtsZ effectors, we identified 88 potential inhibitors associated with the IDC site, along with one curcumin-based lead. These compounds will undergo further biochemical validation and serve as templates for the combinatorial design of novel inhibitors of bacterial cell division.

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S05

Identification of Effectors Bacterial FtsZ Targeting the Sites of Coumarin Binding

D.S. Ozheredov, S.P. Ozheredov, O.M. Demchuk, S.I. Spivak, Ya.B. Blume, P.A. Karpov

Institute of Food Biotechnology and Genomics of the National Academy of Sciences of Ukraine, Baidy-Vyshnevetskoho str., 2A, Kyiv, 04123, Ukraine

Contact: karpov@nas.gov.ua

[Link to poster]

In the face of rising bacterial resistance, a bacterial FtsZ remains a critical target for the inhibition of binary fission. To avoid the toxicity problems associated with GTP-competitive inhibitors targeting the NBS site, current studies have pivoted toward ligands with alternative mechanisms of action. Recently it was shown that fungal metabolite 4-hydroxycoumarin (4HC) interacts with FtsZ at two distinct pockets, BP1 and BP2 (PDB: 6Y1V, 6Y1U) [1]. Unlike benzamide effectors of the interdomain cleft (IDC), 4HC binds FtsZ exclusively in the nucleotide-free state. This interaction is governed by the conformational flexibility of the H7 helix, where 4HC induces allosteric shifts and a "deformational break" disrupting the NBS pocket, preventing proper protofilament assembly. Notably, the BP2 site of 4HC fits the Taxol-binding site in β-tubulin, reinforcing the evolutionary homology of these proteins. Given that the binding sites for the majority of known FtsZ effectors (379 in the ChEMBL db) remain unknown.

Using RCSB Protein Data Bank structures, we compared 4HC interactions with BP1 and BP2 sites. Our data confirm Almani et al. (2021) data that 4HC has lower affinity for BP2 than BP1, and binds exclusively to GTP-free FtsZ [1, 4]. The presence of ligands in the BP1 and BP2 pockets caused internal displacements and this mobility predetermine the strategy of subsequent screening protocols. CavitOmiX analysis showed that both sites remain open in the apo-state. MD simulations confirmed that transient ligand binding in BP2 is the condition for correct formation of a stable 4HC complex with the BP1 site [1, 4].

It was selected ten compounds with proven FtsZ interaction based on PDB and literature data [1, 3]. SOM and UMAP analyses of the joint group of control and 379 ChEMBL effectors identified a isolated Coumarin cluster. Similar compounds were identified within shared 'valleys' and isolated from other clusters by chemical landscape 'ridges' and structural distance. PDB-structures 6Y1U.B and 6Y1V.B were used for pharmacophore construction. Subsequent Pharmit screening and flexible docking with CCDC GOLD yielded 13 hits, leading to a final selection of 47 compounds: 10 from the control group and 37 from chemoinformatic analysis. Flexible docking in CCDC GOLD showed that 41 of the 47 selected compounds demonstrated correct poses in the BP1 pocket. For the BP2 pocket, docking predicted complexes for 45 ligands, with the compound CID: 103961572 being the only exception. Notably, five ligands that did not fit the BP1 pocket showed reliable docking poses in BP2. Subsequent AI reconstruction of the complexes using the Protenix Server (https://protenix-server.com) reduced the number of candidates to 40.

To estimate the potential binding energy of the selected compounds to BP1 and BP2, we performed redocking using iGEMDOCK to quantitatively assess the total energy of ligand–protein interactions, taking into account the contributions of hydrogen bonds (H-bonds), van der Waals forces (vdW), and electrostatics (Elec) [2; 5]. Further ranking was performed based on the 'Total Energy' values calculated for BP1, as this site is associated with the inhibitory effect of 4HC [1]. All compounds of the control group demonstrate relatively similar binding

energy values with BP1 and BP2 with a slight advantage in favor of BP1. Also, since BP2 is significantly larger than BP1 and yields more favorable binding energies, we suggest it may overlap with the IDC pocket. Also, some compounds showed superior 'Total Energy' for the BP2 pocket, and we suggest that it may share the space with the IDC pocket. Essentially, these two sites represent opposite ends of a single 'super-pocket'. CavitOmiX catalophoric casts for M. tuberculosis FtsZ (in complex with 4HC, PDB: 6Y1U.B) and S. aureus FtsZ (in complex with PC190723) showed significant mutual overlap. This suggests the existence of a combined BP2/IDC super-pocket, and consequently, the potential for specific BP2 effectors. However, despite possessing a Coumarin scaffold, certain structural features—particularly molecular size—may hinder interaction of this compounds with the BP1 pocket. According with results of current research, the selected effectors can be categorized into two subgroups: (1) 'true' 4HC-like compounds primarily targeting the BP1 pocket, and (2) BP2/IDC super-pocket effectors. The latter include bulky derivatives unable to bind BP1. Since their binding is centered on the BP2 site, their mechanism likely involves allosteric shifts distinct from those of canonical IDC effectors.

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