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User Group Meeting

User Group Meeting Presentation Abstracts

Tuesday 18th June

Session 1: 09:10

Cresset offering in the Design – Make – Test – Analyze (DMTA) application space for small molecule drug discovery.
Tim Cheeseright, Cresset

Session 2: 09:30

Picolinamide Complex III Inhibitors: Discovery, Synthesis and Structure- Activity Relationship of novel benzothiazoles for disease control.
Victoria Jackson, Globachem

Phytopathogenic fungi can cause plant diseases that reduce crop yield and quality. Mitochondrial complex III is one of the most promising targets for a number of pharmaceuticals and fungicides. Due to the wide-spread use of complex III-inhibiting fungicides (e.g. the strobulurins), a considerable increase in resistance has occurred worldwide. Therefore, inhibitors with novel scaffolds, different mechanisms of action, and potent activity against complex III are still in great demand. Quinone inside inhibitors bind within the fungicidal binding site of the cytochrome bc_1 complex demonstrating broad spectrum fungicide disease control, and are not cross resistant with quinone outside inhibitors.[1]

An inventive new sub-class of fungicides has been discovered and highlights the use of the Cresset tools; Cresset XedeX™, Cresset Flare™ and Spark™ in the discovery process. The structure-activity relationship along with a summary of the biological activity of benzothiazole picolinamides will be presented. [2]

REFERENCES
[1] Young, D. H.; Wang, N..; Meyer, S. T.; Avila-Adame, C. Characterization of the mechanism of action of the fungicide fenpicoxamid and its metabolite UK-2A, Pest. Manag. Sci., 2018; 74 (2): 489–498.
[2] Jackson, Victoria ; Jordan, Linda; Burgin, Ryan N.; McGaw, Oliver J. S.; Muir, Calum W.; Ceban, Victor. Application of Molecular-Modeling, Scaffold-Hopping, and Bioisosteric Approaches to the Discovery of New Heterocyclic Picolinamides, J. Agric. Food Chem, 2022; 70 (36): 11031-11041

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Session 3: 10:00

What's in the lab. *Mark Mackey, Cresset*

Session 4: 11:10

What's new in Cresset desktop products: exciting new science and features for ligand-based and structure-based design.
Giovanna Tedesco, Cresset. Sofia Bariami, Cresset

In this talk we will give you an overview of the cutting-edge science and the latest features in Cresset desktop applications. Among others, these include;

- The Molecular Mechanics/ Generalized Born Surface Area (MM/GBSA) method, for very fast predictions of binding affinity for small molecules
- Charge perturbations for Flare FEP, greatly extending the domain of applicability of Free Energy Perturbation (FEP) calculations in Flare
- 3D protein structure prediction with Homology modelling
- Seamless integration of Spark, Cresset scaffold hopping and R-Group replacement application, into Flare
- The new Flare Python Extension manager.

Session 5: 12:10

Calculating binding free energies for G protein-coupled receptors (GPCRs): accurately capturing lipid/membrane exposed binding interactions in P2Y1. *Cresset*

G protein-coupled receptors (GPCRs) are a large family of cell surface receptors that play a crucial role in mediating the effects of various signaling molecules and are thus an important class of drug targets. For modeling with good accuracy, GPCRs are a difficult case study as the protein has many atoms, ligands, membrane lipids and solvent to account for. Faster and more accurate computational solutions are required for these challenging systems. Here, we discuss a workflow using computational chemistry methods that are available within Cresset's software, Flare™ to arrive at accurate binding free energies for three GPCR datasets, mainly focusing on P2Y1 which has ligands bound to a lipid-exposed binding site.

The methods used are:

1. Molecular Dynamics (MD)

2. Water analysis solving the Ornstein-Zernike equation (3D-RISM)
3. Alignment of ligands for FEP (Conf Hunt & Align)
4. Relative binding free-energy (RBFE) perturbation theory (Flare FEP).

We show that using the methods stated can result in reliable predictions for GPCR protein-ligand binding affinities, even in the P2Y1 case where the ligand is at the lipid-protein interface. Until recently the computational cost of such a large system (93,255 atoms) would be prohibitively large. Implementing methods that ensure a stable and appropriately hydrated binding site (a suitable snapshot of *in vivo* binding action) as input for RBFE calculations, results in an efficient process with accurate results. The efficiency of the RBFE calculation itself is improved by the implementation of adaptive Lambda (λ) schedules and automated intermediate generation. The results to be presented for the predicted binding free energies of 30 ligands of the P2Y1 system, match the measured experimental affinities closely (MUE is 1.17 kcal/mol). Benchmark statistics obtained for two other GPCR systems investigated (OX2 and A2A) are similarly promising. Such difficult computational problems posed by GPCR systems can now be solved relatively quickly with good accuracy by using these methods, demonstrated by the workflow we present.

Session 6: 13:50

Covalent Docking in Flare™: Ensemble Covalent Docking.
Nathan Kidley, Cresset

Throughout this presentation, we will demonstrate covalent docking in Flare™. Docking in Flare™ is one of the platform's most popular functions, providing its users with detailed feedback on new molecule designs, high enrichment in virtual screening, and excellent pose prediction. Until recently, the docking experiments that were available were 'Normal', 'Covalent', and 'Ensemble'. Normal docking is the standard docking feature: a ligand docked to a protein within a specified spatial energy grid. Covalent docking adds the formation of a covalent bond between a nucleophilic residue of the protein and a reactive warhead in the ligand. Finally, Ensemble docking allows the user to apply Normal docking to several protein conformations at once.

A more recently added feature is 'Ensemble Covalent' docking, the option that combines Covalent and Ensemble: this new feature allows the user to apply covalent docking to several proteins at once.

Session 7: 14:20

Probing the design of PI-2620 with Cresset molecular modelling tools in the field of Tau PET tracer, intended for use as a diagnostic for Alzheimer's Disease and other tauopathies.

Andreia Serra, AC Immune

Positron Emission tomography (PET) tracers are specifically developed small molecules used in the identification and characterization of many neurodegenerative diseases and where precision medicine is fundamental for the selection of an effective treatment.

PI-2620 is a potential best-in-class PET tracer currently in a phase 3 trial in Alzheimer's disease (AD). PI-2620 binds specifically to pathological Tau aggregates in AD, has suitable physicochemical properties to enter the brain, and is selective over other protein aggregates. Furthermore, PI-2620 has the ability to bind to 4-repeat Tau isoforms like Corticobasal degeneration (CBD) and Progressive Supranuclear Palsy (PSP) and extending to additional tauopathies such as Pick's disease patients (3-repeat Tau isoforms).

Based around the tricyclic core of PI-2620 and using the Cresset Forge software version 10.6.0, a quantitative structure activity relationship (QSAR) was developed for 57 selected compounds with a range of binding affinities for Tau measured at IC50 (nM). Additionally, shape and electrostatic surfaces analysis between PI-2620 and harmine, monoamine oxidase-A (MAO-A) inhibitor, were

executed using the Activity Atlas tool from Cresset1. These analyses rationalize the key role of the nitrogen atom in the tricyclic core upon the binding affinity to Tau and off-target selectivity to MAO-A.

Additional modelling was performed in order to obtain a more detailed understanding of PI-2620 potential binding poses to Tau on brain sections from AD, CBD, PSP and Pick's disease patients. In here silico investigations were performed including conformation hunting, predicted enthalpies and docking of PI-2620 to cryo-EM structure of Tau aggregates derived from AD brain and a few binding sites were identified using the Cresset Flare software version 1.02.

In summary, Cresset tools have been very valuable to generate QSAR models and to simulate probable binding sites. Together, these data provide a better understanding on how PI-2620 Tau PET tracer is distinctly specific and selective.

References:

1. Kroth H et al, Bioorg. Med. Chem., 2021
2. Kroth H et al, J. Med. Chem., 2021

Session 8: 14:50

Streamlining the design of PROTACs® and PROTAC linkers.
Jessica Plescia, Cresset

A high percentage of pharmaceutical targets are 'undruggable' by small molecules. To address this issue, researchers have recently turned to Proteolysis Targeting Chimeras (PROTACs®). PROTACs are bifunctional molecules that aim to mark a protein of interest for protein degradation, wherein a target-binding ligand and a ligase-binding ligand are connected via a linker. This system allows the target protein to be tagged for protein degradation by a proteosome complex. However, the design of PROTACs can be quite challenging, including the search for novel linkers, the optimization of linker properties, and the prediction of how the PROTAC will bind to the protein complex.

Throughout this presentation, we will explore PROTACs and demonstrate how software solutions Spark™ and Flare™ can help overcome some of these challenges and streamline the design of PROTACs and PROTAC linkers.

Session 9: 16:00

The Open Force Field Consortium: An update on its progress and plans.
David Mobley, Open ForceField

In this talk, I give an overview of the Open Force Field (OpenFF) Consortium and project. The talk will place an emphasis on the OpenFF approach to force fields and key scientific innovations and insights employed in and resulting from the project. OpenFF so far appears to have developed into the most accurate public small molecule force field, so this talk will include innovations leading to that, results from benchmarking, and an update on near-term plans for further work, as well as highlights from OpenFF-enabled work from collaborators and outside researchers. Much more work is still needed in this space, and we look forward to working with the community to further progress molecular modeling.

Session 10: 16:30

With our head in the Cloud: what's new in Cresset web-based development.
Giovanna Tedesco, Cresset. Angeles Pulido, Cresset

In the highly competitive new molecule discovery landscape, it is vital for companies to constantly improve the efficiency of their processes. The digital transformation of the discovery pipelines has been of paramount importance for cost reduction and optimization of workflow effectiveness, unprecedently empowered by cloud technology.

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In this presentation we will show the evolution of Cresset's CADD workbench to provide flexible and diverse cloud-based solutions, tailored to the needs of your organization. We will discuss how highly scalable computing, secure access to worldwide results and user-friendly tools enable you to accelerate your discovery programs.

Wednesday 19th June

Session 1: 09:10

Use of Torx to support medchem discussions, decision making and design-make-test cycle time measurements.
Udo Lange, AbbVie

Session 2: 09:40

Torx Product Development Updates.
Simon Dawson, Torx

In this session we will introduce you to the latest Torx features and provide insights into planned enhancements for 2024 and beyond.

Session 3: 10:50

Making better design decisions through collaboration in Torx Design-Analyze.
Mari Goldsmith, Torx. Simon Dawson, Torx

Efficient molecule design requires input from multiple disciplines, and collaborators in geographically diverse locations and organizations. Traditional methods of communication and delays in conveying results to the wider team can result in siloed ways of working, significantly hindering innovation and leading to missed opportunities or unnecessary re-work. In addition to time lost due to inefficient communication, considerable effort is often spent preparing single-use and non-chemically aware documents such as reports and slide-decks or searching corporate systems for relevant information.

Torx was designed from the ground up as a collaborative molecule design application and hence incorporates multiple methods to enhance cross-team collaboration, avoid unnecessary work and reduce design cycle time. In this session we will demonstrate how Torx Design-Analyze can drive efficiencies in the design process by enabling users to collaborate through real-time data instead of 2D screenshots and static text, eliminate non-value-add tasks such as preparing single-use slide

decks, and make informed design decisions through seamless connection to corporate data sources and third-party tools.

Session 4: 11:20

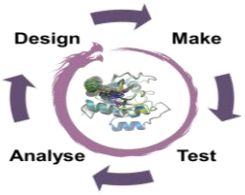
The Alchemists' Charm: Accelerating Drug Design with Crafted Molecular Platforms
Seb Degorce, Charm Therapeutics

DragonFold is CHARM's flagship deep-learning model that can predict the 3D protein-ligand crystal structure of a protein-ligand pair, using only the amino acid sequence of a protein and the 2D structure of a small molecule ligand as input.

The ability to integrate CHARM proprietary model data, including the output from DragonFold, into a customised TorX suite has enabled CHARM design teams to develop a platform that enables all aspects of molecular design.

We will present how using TorX fits within our Design-Make-Test-Analyse workflows and contributes to efficient DMTA cycles through enhanced collaboration between scientists, both internally and externally.

CHARM THERAPEUTICS



SCAN ME

Session 5: 12:00

Streamlining work management and communication with external providers in Torx Make and Test.
Mari Goldsmith, Torx. Huw Jones, Elixir

Partnering with external providers such as CROs on discovery projects has enormous benefits, enabling rapid access to expert knowledge and streamlined workflows without the initial overhead of building a new, specialized team internally. However, clear, effective, and secure communication between organizations working in multiple time zones can often be challenging, impacting both productivity and data security. Furthermore, without an efficient way to visualize the workload across both internal and external team members, resourcing decisions can become uninformed, exacerbating existing bottlenecks rather than resolving them.

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In this session we will show how using Torx Make ensures chemists are up to date with the latest status information from both internal and external collaborators, enabling them to delegate resources efficiently, track and adjust compound priorities in real time, and ensure everyone in the project is always working on the most important targets. Once compounds have been synthesized, we show how Torx Test offers a centralized and automated system for submission of test requests across multiple organizations, enabling test providers to manage their services more effectively, and ensuring chemists can leverage results as soon as they are ready.

Session 6: 13:40

Dynamic compound prioritisation using Torx Make to accelerate pre-clinical small molecule discovery.
Alfie Brennan, Evariste

Evariste's principal goal is to establish a machine-learning first platform for all stages of preclinical drug discovery, with a particular focus on novel target discovery and small molecule optimisation. As part of this effort, we have built a suite of proprietary machine learning algorithms and compound designers, which individual chemists can use to manage compound discovery across multiple projects.

Dynamic reprioritisation of synthetic targets in response to new data for existing compounds is an administrative hurdle which takes up the time of highly skilled scientists. Utilising the Torx API and our CDD/Torx integration, we have vastly reduced chemist input required for compound reprioritisation and novel design ideation. As soon as new data is added to our CDD database, our modelling platform will automatically perform a series of steps:

- Retrieve and rescore all molecules in TorxMake according to a pre-defined TPP
- Alert project scientists to discrepancies between compound scores and synthesis priorities
- Design and score 10,000 – 100,000 novel compounds
- Provide a list of high scoring designs to chemists for consideration and addition to TorxMake
- Update a modelling dashboard highlighting project progression

This workflow requires minimal chemistry input and maximises the time spent by chemists on discovery challenges not suited to automation. We will present examples of this workflow using Evariste's lead project, a series of best-in-class PKMYT1 inhibitors.