Flexible and Integrated Collaborative Tool to Aid, Coordinate, and Inspire Small Molecule Discovery - Application to Kinase Inhibitors

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Introduction

Modern drug discovery draws on a vast array of information sources and resources to progress through the classic Design-Make-Test-Analyze (DMTA) cycle (Figure 1). This makes the coordination of information and relevant tasks a challenging process.

We present Torx™, a new web-based application that joins molecule design and analysis to the tracking of synthesis and testing into a single portal to coordinate all chemistry.

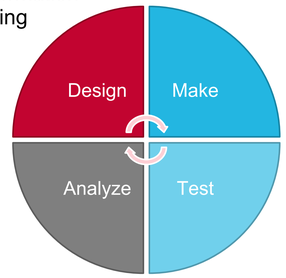


Figure 1: The molecule discovery cycle.

Torx

Within Torx,[1] a new platform for small molecule discovery chemistry, a new molecule can be tracked from the initial idea, to the design process in a mixed 2D/3D environment, to the planning of resources for synthesis, and then to the analysis of the results from biological testing.

Torx is a collaborative tool developed by Cresset[2] and Elixir[3]. It combines cutting edge 3D molecular design and review with detailed synthesis tracking and a data analysis module.

Accessible 3D design

The design module within Torx combines collaborative 2D and 3D design by automatically converting molecules from a 2D chemical sketcher application to a 3D model inside the protein active site. Changes to the 2D structure are propagated 'live' to the 3D window enabling real-time 3D design.

Collaborative platform

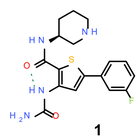
Collaboration and teamwork are vital to all stages of the molecule discovery cycle. Molecule designers can choose to 'share' their session with other users enabling live collaboration on the selected design, while a review module allows teams to jointly decide which ideas are worthy of being progressed to synthesis.

Analysis

The analysis module provides a simple but powerful interface to navigate the biological data obtained within the project and relate this back to a 3D context where possible. The analysis workflow can be collaboratively shared across users in a similar fashion to the design module.

Customizable

To satisfy the demands of modern drug discovery teams, all aspects of the Torx workflow can be augmented, extended and customized as required. This is achieved within a plugin framework that allows company-specific information sources or analysis methods to be quickly added to the web application.



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CHK1 IC_{50} = 5 nM

Figure 2: Structure and CHK1 inhibitory activity of compound **1**.

Application to kinase inhibitors

Starting from compound **1**, a checkpoint kinase 1 (CHK1) inhibitor (Figure 2), Yang *et al.* recently developed new 5,6-bicyclic scaffolds as novel CHK1 inhibitors using X-ray structure-based drug design.[4] We use the X-ray structure of compound **1** in complex with CHK1 (PDB ID 2YDJ) as starting point for model building in Torx.

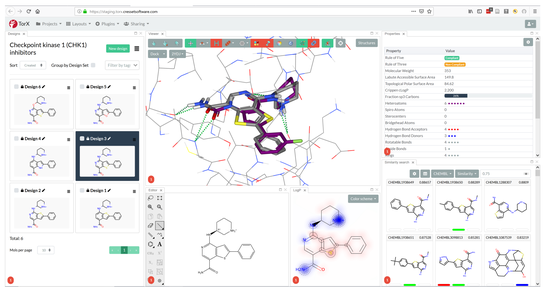

Figure 3: Assessing Designs 1-6 in the context of the binding site while monitoring physico-chemical properties and 2D similarity to existing compounds.

Each new 5,6-bicyclic scaffold (Designs 1 to 6 in Figure 3), was drawn in the 2D editor of Torx and automatically converted 'live' into a 3D model. New designs can be either aligned to reference compound **1** (Figure 4, left) or docked into the protein active site (Figure 4, right), enabling immediate assessment of each design by comparison to a reference ligand and/or by its potential interactions with the target protein.

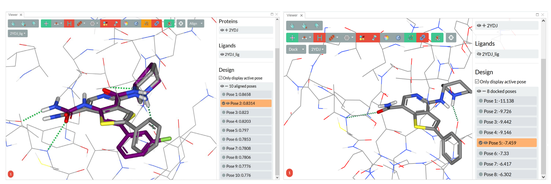

Figure 4: Design 3 (grey; IC_{50} = 7 nM) mimics the bioactive conformation of compound **1** (purple) both when aligned to the co-crystallized reference (left) and when docked into CHK1 (right).

The associated electrostatic potential (ESP), field points, and molecular surfaces can also be visualized to further inform molecular design (Figure 5).

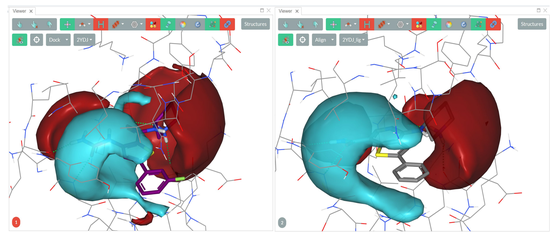

Figure 5: Comparison of ESP maps between compound **1** (left) and Design 3 (right).

Specific and key information about designs are updated live in all plugins, whether they are similarity searches, physico-chemical properties or LogP predictions (Figure 6), thus allowing users to make informed decisions to improve or select designs to move forward in the synthesis process.

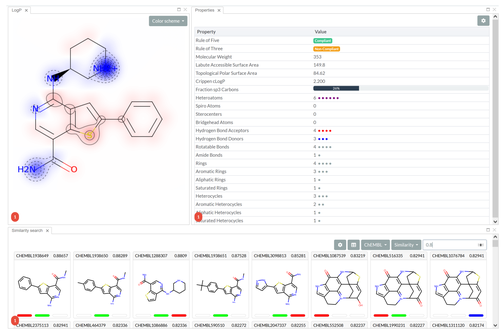

Figure 6: Design 3 LogP with per-atom partitioning based on the Crippen-Wildman scheme (top left), predicted physico-chemical properties (top right), and results of a fingerprint-based similarity search against the ChEMBL database (bottom).

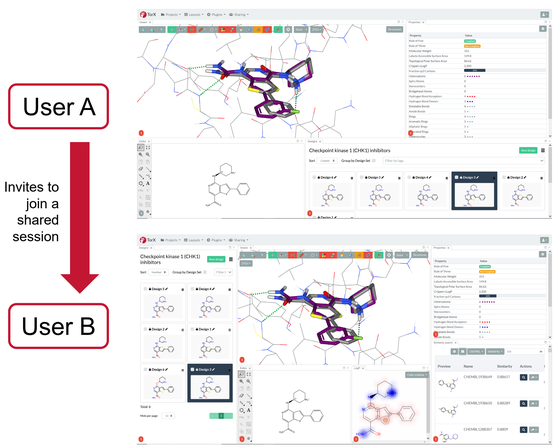

Figure 7: User A invites user B into a collaborative session where they share the design they are working on. Both 2D sketch and 3D view are synced for the two users, while the other plugins maintain their user-specific layout.

The design and analysis processes can effectively be achieved in collaboration with team members, both internally and externally (Figure 7).

Users may join a shared session where they actively participate in editing designs live, updating the 3D pose and analyzing chemical properties as the molecule evolves, facilitating communication and collective decision making.

Tracking compounds

Cresset has partnered with Elixir, provider of real-time workflow tracking applications, to obtain immediate feedback on the status of every molecule in the DMTA cycle.

Tracking of successful designs through synthesis and testing, whether in-house or through an external partner, can be achieved using chemTraX™, a dedicated *kanban* style tracking board with customizable workflow and business rules, detailed privacy and security settings, and clear visual feedback on the status of any single or set of compounds.

Detailed labelling, alerting and priority settings enable users to gain exactly the information that they need whilst not compromising corporate security: from the bench chemist seeing their 'to-do' list for the week to the project manager's overview of which compounds are in the pipeline, who is making them and where (Figure 8).

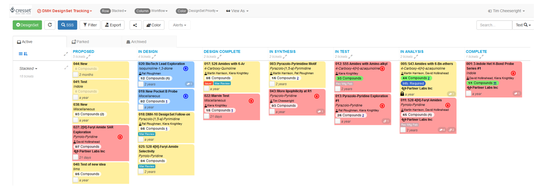

Figure 8: Progression of ideas through the synthesis pipeline can be effectively monitored through the chemTraX *kanban* boards.

Conclusion

Torx is a new platform for small molecule drug discovery. It provides customizable 2D/3D design and analysis modules combined with molecule tracking throughout the DMTA cycle. It increases the efficiency of project teams by facilitating interactive communication and collaboration across internal and external partners.

Torx is due for release in September 2019.

References

1. https://www.torx-platform.com/
2. https://www.cresset-group.com/
3. https://www.elixirsoftware.co.uk/
4. Yang, B. *et al.*, J. Med. Chem. 2018, 61, 1061−1073