Implementing fully automated kinase inhibitor characterization using a robotic system

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Executive summary

The family of Janus kinases (JAK) play an important role in several disease areas, including oncology, immunology/ inflammation and longevity, and have also been identified as potential therapeutic targets for COVID-19. Arctoris deployed its automated drug discovery platform, Ulysses, to generate a comprehensive dataset on 24 small molecules against all four members of the JAK family. In under 100 h, the platform completed an extensive experimental program resulting in a large, structured dataset revealing a diverse set of pharmacologically distinct profiles.

Background

About 50 kinase inhibitors have been approved by the FDA so far. High resolution molecular profiling can enable better data-driven decision earlier in the drug discovery process, saving time & resources, and leading to superior molecular design. However, many commonly used biochemical assay formats tend to be quenched or stopped to maximise throughput & efficiency – at the cost of depth & detail.

Achievement

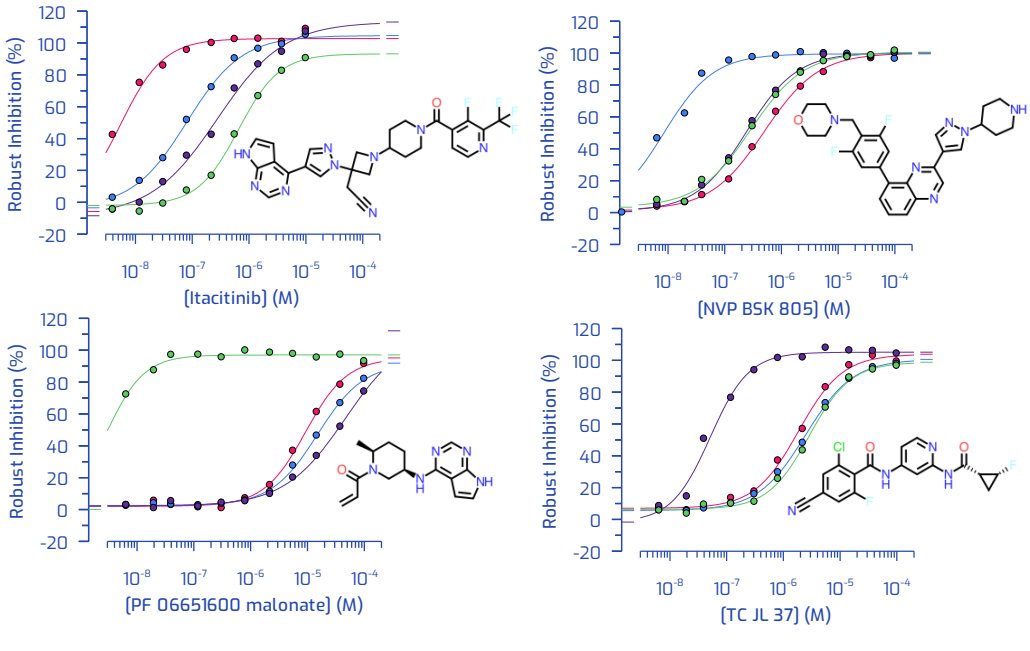
We developed a robotics-enabled process for fully automated kinase inhibitor characterisation, providing an unparalleled depth of data capture, going beyond the current state-of-the-art of biochemical assay setup. We validated our technology platform establishing assays against four members of the Janus Kinase family (JAK1, JAK2, JAK3, TYK2).

Fig. 1: Expedited assay setup & dataset generation <100h

Methods

Reagent validation, assay development, calibration, and optimisation were expedited through systematic multifactorial experimental design, high density assay plate formats & versatile automated liquid handling. The Arctoris platform affords 9 orders of magnitude range in liquid handling with picolitre precision & contact-free digital dispensing. Fully automated protocols were optimised, validated, versioned, and explicitly encoded. The analytical pipelines apply robust statistical modelling to provide an impartial assessment of performance, outlier identification/ exclusion, and data validation, ensuring analytical fidelity.

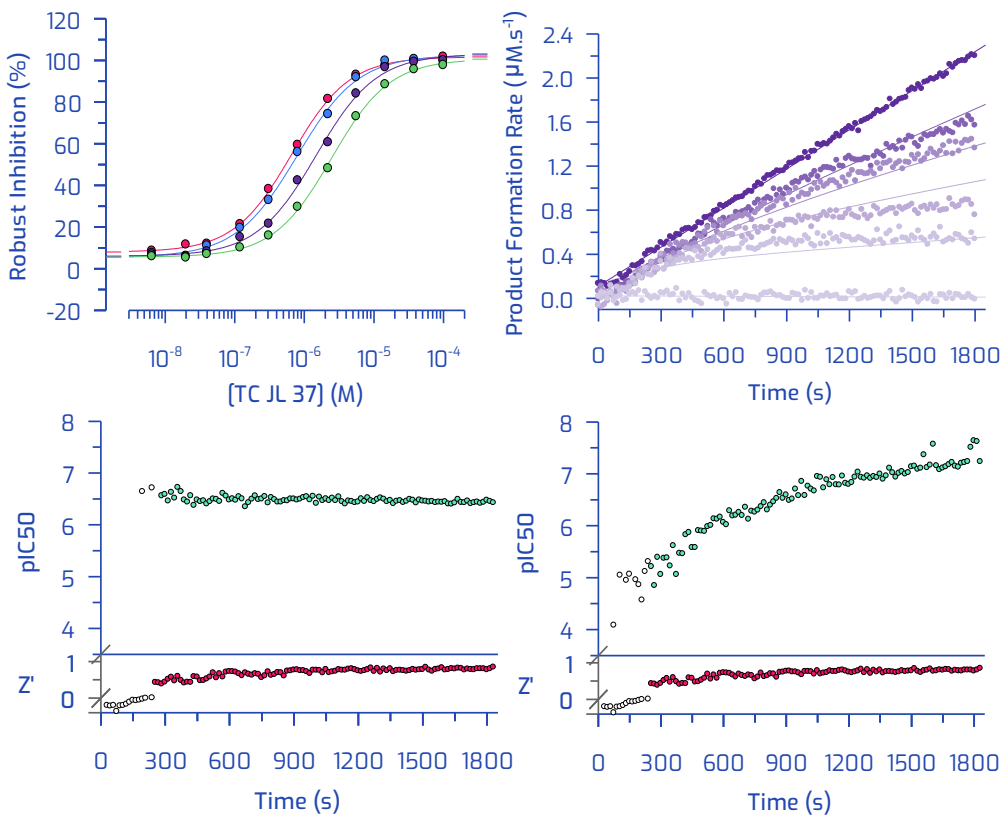
Fig. 2: Exemplar JAK inhibitor selectivity profiles



Results

Robust potency measurements of all inhibitors were established against each of the JAK targets. Our unique platform, assay design, and deep expertise enabled the identification of molecules within the JAK inhibitor set that exhibit a range of kinetic properties. Our mechanistic analyses can help to elucidate mode of inhibition (competitive, allosteric, synergistic etc.) as well as provide information pertaining to the kinetic selectivity, enabling fine tuning of pharmacology and the avoidance of unwanted off-target toxicity.

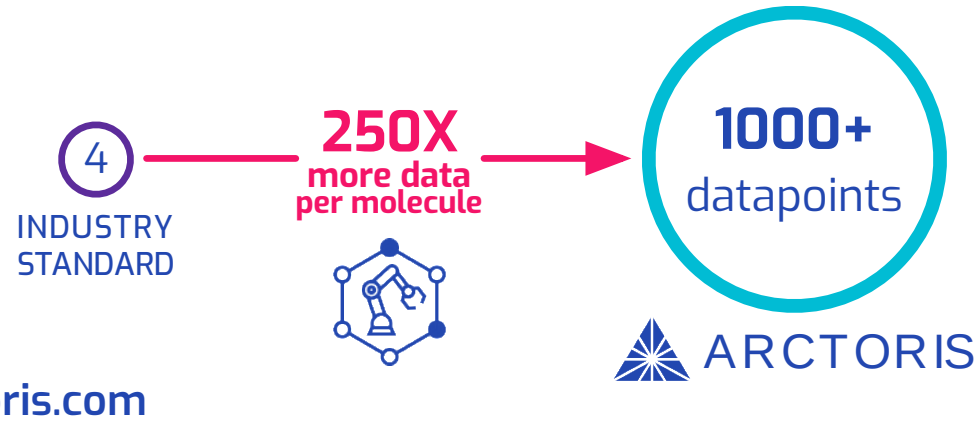
Fig. 3: Mode of action/active site competition & inhibition onset rates (top) and comparative quick equilibration & moderate potency vs. slow equilibration & high potency inhibitors (bottom)



Relevance

Combining the power of precise end-to-end automation of experimental processes and intelligent analytical pipelines generates deeper, richer, fully structured, datasets, thereby enabling better and faster decision-making. These powerful platform technologies will play a crucial role in the future of drug discovery as the industry seeks faster and more cost-effective solutions - a need also highlighted by the COVID-19 pandemic.

Fig. 4: Robotic discovery for dataset generation



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