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Direct-to-Discovery: Extending Direct-to-Biology Paradigms to Accelerate Drug Discovery

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Introduction

Eroom's Law highlights a key challenge in pharmaceutical R&D: despite technological advances, drug discovery is becoming slower and more expensive.[1] In 2024, the average cost to bring a drug to market reached $2.23 billion, yet the rate of compounds progressing to the clinic has remained largely unchanged.[2,3] This widening gap underscores the urgent need for more efficient approaches that maintain scientific rigour.

Direct-to-Biology (D2B) reduces DMTA cycle times by synthesising compounds in parallel and screening crude reaction mixtures (CRMs). However, it is typically limited to measuring affinity or efficacy.

We present an integrated platform that expands D2B through Direct-to-Crystal (D2C) and Direct-to-DMPK (D2DMPK), enabling simultaneous generation of structural, biological, and developability data from CRMs to improve decision making and efficiency in early drug discovery.

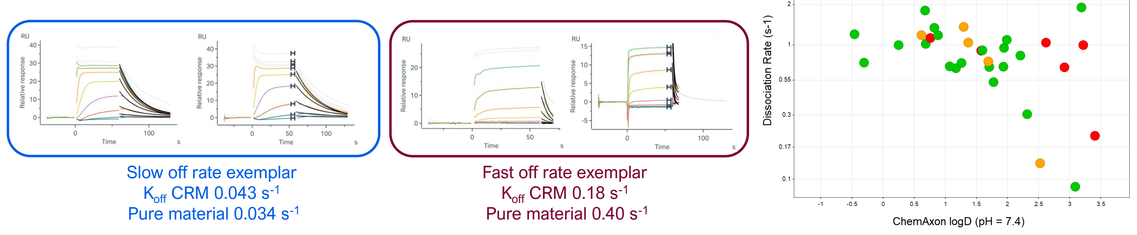
1 High-Throughput Chemistry

Our D2B platform builds on over a decade of High-Throughput Chemistry and Experimentation (HTC and HTE) expertise. By leveraging these capabilities, we can rapidly identify and validate assay-compatible conditions across diverse reaction classes. Coupled with rigorously curated monomer libraries, this enables efficient exploration of broad chemical space and the generation of rich, biologically relevant data.

Figure 1: Our HTC workflow. Computational approaches and Generative AI influence and inform library designs, which are rapidly transformed into physical samples using robust and reproducible synthetic methods. Where necessary solvent switching or semi-purification are integrated into the automation platform.

2 Direct-to-Biology – Biophysics and Beyond

A survey of the literature indicates a range of assay modalities have been used in D2B.[3] We have found that the measurement of off-rate screening (ORS)[4] by SPR is a powerful method to rank compounds as this technique is independent of reaction conversion (**Figure 2**).



Slow off rate exemplar
K_{off} CRM 0.043 s^{-1}
Pure material 0.034 s^{-1}

Fast off rate exemplar
K_{off} CRM 0.18 s^{-1}
Pure material 0.40 s^{-1}

Figure 2: Comparative off-rate screening of CRMs and pure materials (left, centre). CRMs with ~20% product conversion and above can be identified with measurable SPR dissociation rates (right). Note: Points coloured by reaction conversion: green = conversion ≥ 70%; amber = 70%>conversion≥40%; red = conversion <40%

Whilst SPR confirms target binding, it does not offer insight into functional activity. We have successfully extended D2B to incorporate functional readouts in both biochemical and cellular assays. A critical component of assay selection is the early evaluation of reaction intermediates, reagents, and solvents to ensure compatibility and suitability for specific chemical transformations. These assays have utility in early Hit-to-Lead (H2L) campaigns, for both small molecule inhibitors and for the rapid identification of heterobifunctional degraders.

3 Direct-to-Crystal (D2C)

Crystallography is a powerful tool in drug discovery, traditionally relying on soaking or co crystallisation with purified compounds. The use of CRMs is less established, but pioneering work by Scanlon[5] and von Delft[6] has shown its value in fragment-based drug discovery (FBDD). We extend this approach beyond FBDD to confirm target engagement and enable rapid progression into structure guided optimisation, accelerating timelines and improving early decision making.

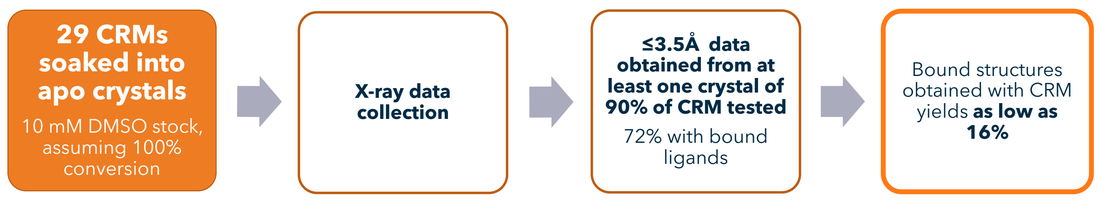


Figure 3: Workflow for Direct-to-Crystal (D2C). In this example 29 CRM were directly soaked into apo crystals, with useable data obtained from wells with as low as 16% conversion observed

Importantly, even low conversion reactions can yield structural insight, as the protein binding site selectively enriches active species from CRMs. This phenomenon, termed binding site purification of actives (B-SPA), is consistently observed and highlights the robustness of the approach.

References

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4 Direct-to-Physicochemistry and DMPK (D2DMPK)

Robust potency and target engagement data are essential for compound prioritisation, but assessing DMPK risk is equally critical for identifying viable development candidates.

We show that chromatographic methods such as ChromLogD and ePSA can generate decision-making data directly from CRMs, supporting compound selection for in vivo studies. These methods are applicable to both small molecules and bRo5 derivatives (**Figure 4**) and, being concentration-independent, deliver strong correlations.

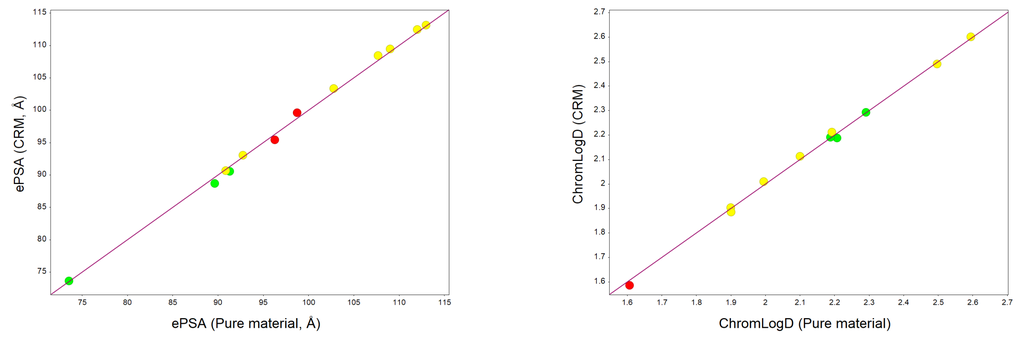

Figure 4: Determination of ePSA (left) and ChromLogD (right) for matched crude and pure samples. Colours indicate overall reaction conversion for the CRMs (0-25%, 25-75%, 75-100%).

Following work published by Krska,[7] we have also demonstrated that CRMs can be robustly evaluated in microsomal stability models, with most compounds demonstrating a good correlation between CRM and pure material (**Figure 5**). Taken together, these assays support the rapid and direct prioritisation of unpurified compounds from high-throughput experimentation into initial in vivo PK experiments

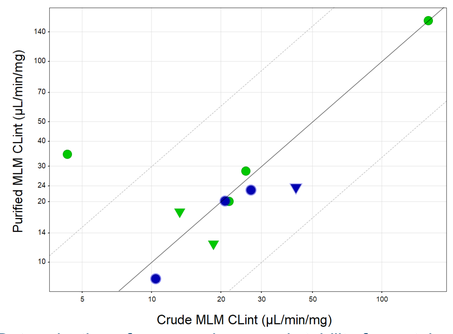

Figure 5: Determination of mouse microsomal stability for matched crude and pure samples. Colours indicate reaction conversion for the CRM (**>90%, 80-90%**)

5 Machine-Learning Models

Direct-to-Discovery workflows rapidly generate rich datasets across a range of parameters. Building machine learning (ML) models using affinity/efficacy, physicochemical and/or metabolic stability data, completes the DMTA cycle and powers AI-driven design, enabling faster, more informed decisions and accelerating drug discovery.

6 Case Study – Novel Oncology Target

Our HitSynergy platform was applied to a novel oncology target, identifying a lead-like hit from HTS (pIC_{50} 4.4; LLE 3.8; LE 0.35). Following SAR-by-catalogue, D2B accelerated optimisation.

A diversity-oriented nanoscale array (4 × 96-well plates) achieved a 60% success rate. All CRMs, including low-conversion analogues, were screened in a functional biochemical assay and prioritised by potency, conversion, and LLE (**Figure 6**). Of 29 compounds progressed to D2C, 21 bound the same allosteric site as the initial hit (**Figures 3, 7**).

Resynthesis of 14 key analogues validated this approach, delivering sub-micromolar compounds and ~100-fold potency improvement within weeks (**Figure 8**). For strategic reasons, CRMs were not advanced to D2DMPK

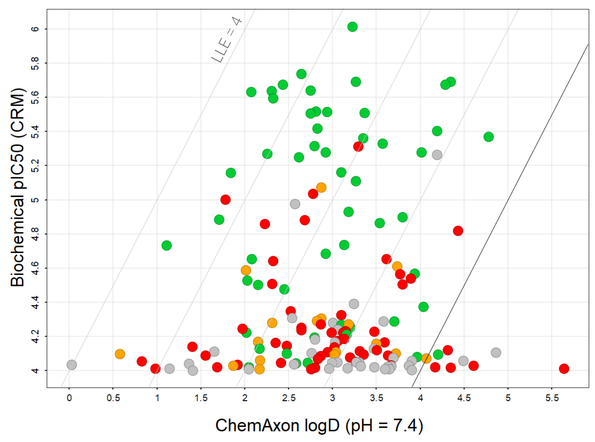

Figure 6: LLE plot of CRM . Size and colours indicate reaction conversion for the CRM (**>60%, 40-60%, <40%**)

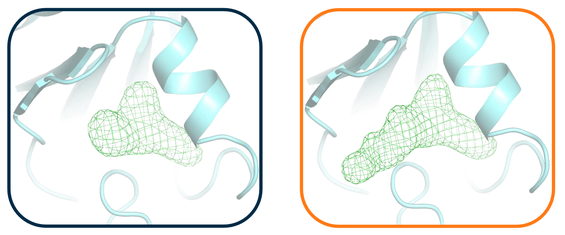

Figure 7: Omit maps contoured at 3 σ of bound HTS hit and elaborated CRM derivative, prepared at 35% conversion, soaked into apo crystal

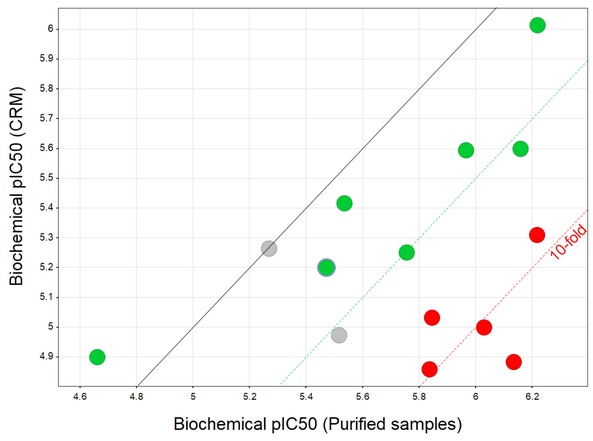

Figure 8: Comparison of biochemical data for CRM and purified samples. Colours indicate reaction conversion for the CRM (**>60%, <40%**)

7 Summary

Extending Direct-to-Biology into an integrated **Direct-to-Discovery** framework unlocks the full value of high-throughput chemistry. By combining rapid synthesis with biological, structural, physicochemical, and DMPK readouts, we enable informed decision-making directly from CRMs. Approaches such as D2C, and D2DMPK provide robust, complementary insights that accelerate SAR development while maintaining data quality. When coupled with machine-learning-driven design, this paradigm represents a transformative step toward faster, data-rich, and more efficient drug discovery.