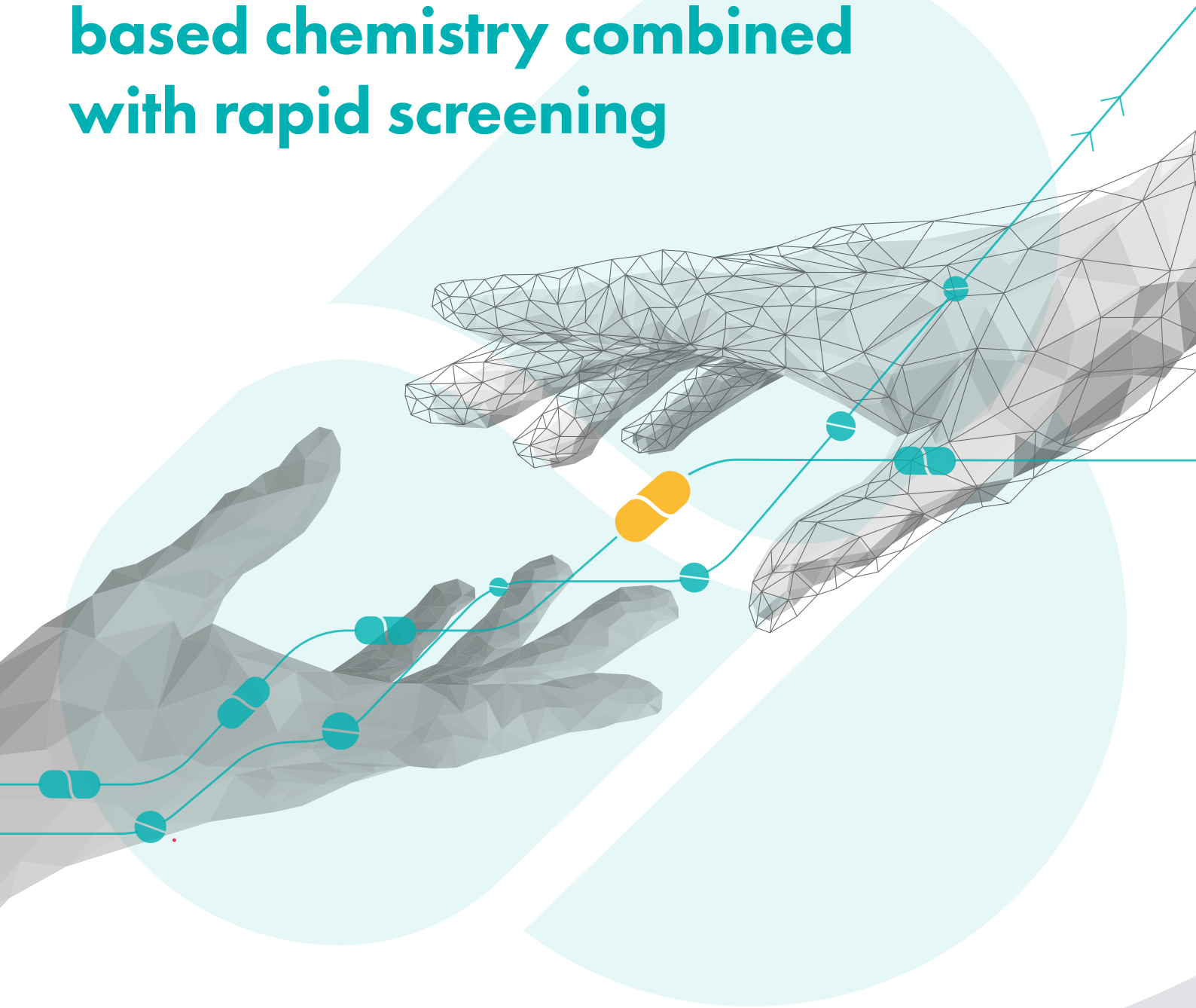




**Direct to Biology**  
Galaxy of opportunity

# Revolutionising Drug Discovery - Unleashing the power of plate- based chemistry combined with rapid screening



Unleash the full potential of our D2B expertise on your drug discovery project. Whether it's to enable your [Targeted Protein Degradator \(TPD\)](#) project or supercharge your [hit-to-lead \(H2L\)](#) or [lead optimisation \(LO\)](#) programmes, Direct-to-Biology will open up a galaxy of opportunity for you! So, partner with Domainex and revolutionise your drug discovery process today.

### Benefits of Direct-to-Biology (D2B) in Drug Discovery

Drug discovery is a complex and time-consuming process that requires the seamless integration of multiple disciplines and technologies. D2B has revolutionised the field by combining 'plate-based chemistry' with rapid biological screening.

The key benefits of employing Domainex's D2B expertise in your integrated drug discovery project include:

### Compound Library Design

Our expert computational chemists will design compound libraries tailored to your project's requirements. Using known Structure Activity Relationships (SAR), literature compound information, and/or structure-based drug design (SBDD), our team will perform modelling experiments to ensure that every compound is relevant, even within a large plate-based chemistry library. *In silico* property predictions will be performed to allow pre-filtering of targets to fit your required property space. Our experienced medicinal chemists will provide a recommendation on the suitability of scaffolds and reaction types for plate-based chemistry.



## Plate-Based Chemistry

**1 Accelerated compound synthesis:** Plate-based chemistry allows for the simultaneous synthesis of multiple compounds using automated compound handling, drastically reducing the time required to generate diverse analogue libraries.

For your **TPD project**:

- o Our chemistry teams will prepare libraries of degrader compounds comprising of the protein of interest (POI) binder, coupled to a variety of linkers and E3 ligase binding motifs (e.g. VLH-1, CRBN etc.).
- o We have an in-house 'toolbox' of partial PROTACs ready for immediate reaction with POI binders in plate-based format.

For your **H2L and LO programmes**,

- o Our team will synthesise analogues in plate-based format to reduce 'Design-Make-Test-Analyse' (DMTA) cycles and expedite the generation of SAR.

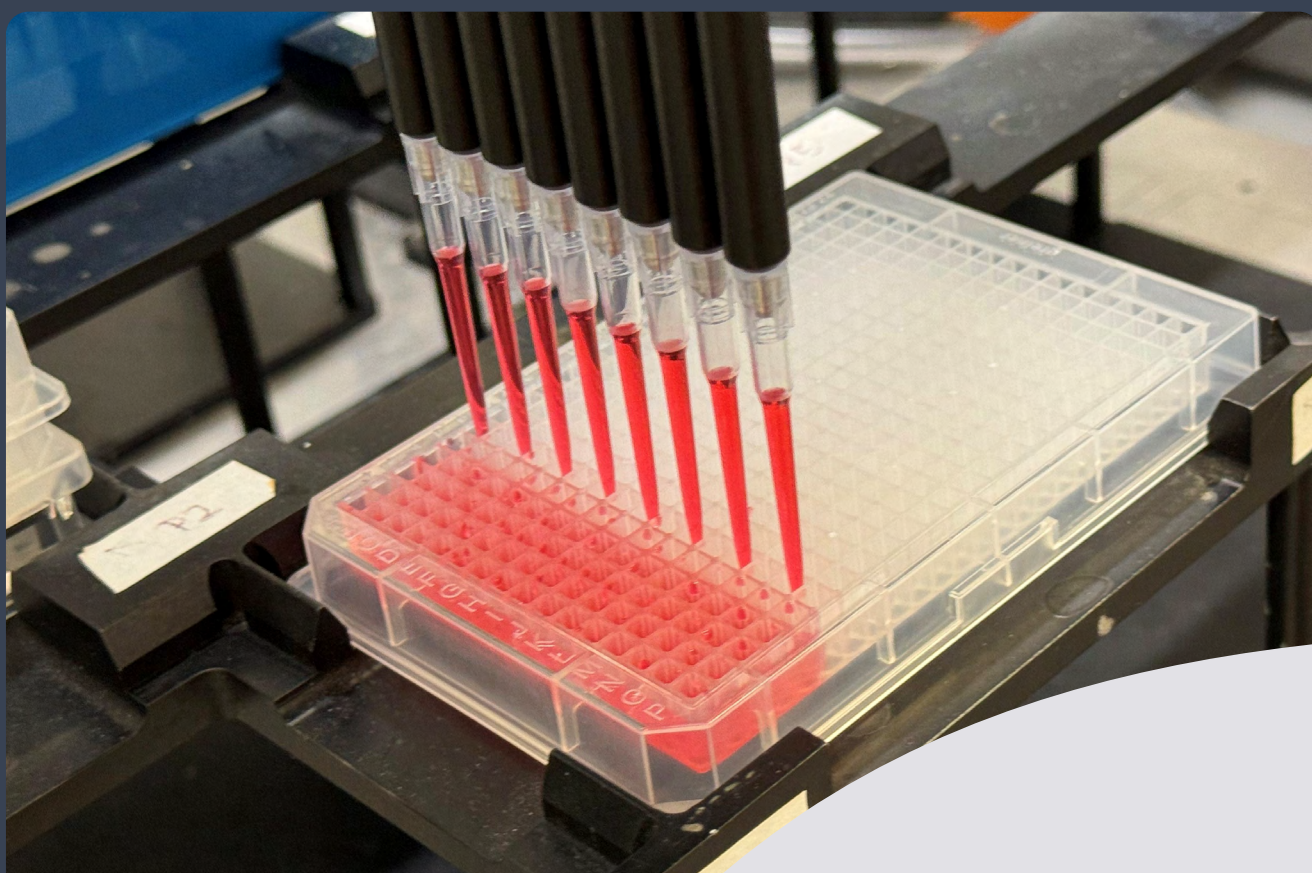
**2 Expanded chemical diversity:** By creating diverse compound libraries, plate-based chemistry broadens the scope of compound properties that can be explored in each cycle. This increased chemical diversity enhances the likelihood of discovering novel, potent, selective, and efficacious drug candidates.

**3 Efficient resource allocation:** By identifying compounds with desirable biological activity early on, you can focus your resources and budget on those compounds which have the highest chances of successful progression.

**4 Miniaturisation of reactions:** Plate-based chemistry enables the miniaturisation of reactions, reducing the quantity of reagents and compounds required. This not only conserves valuable resources and reduces the environmental impact of drug discovery, but also allows for the screening of a larger number of compounds in a shorter timeframe.

**5 High throughput purification:** Plate-based chemistry can be combined with mass-directed reverse phase preparative chromatography to rapidly produce compounds with high-purity.

**6 Access to Domainex's highly skilled team of [synthetic chemists](#)**



## Rapid Screening:

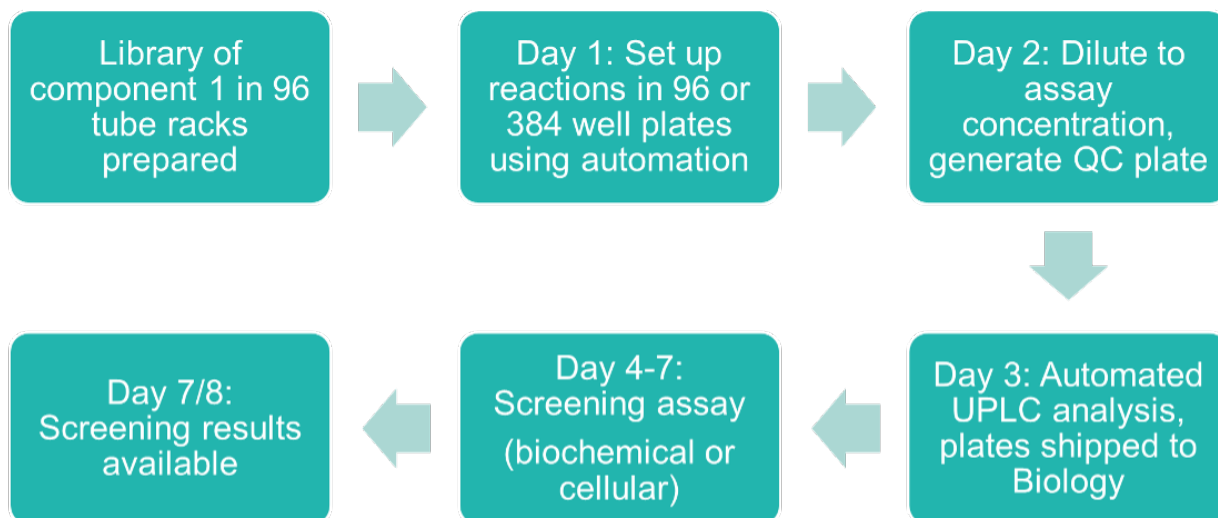
- 1 Customised assay development:** Our highly skilled assay biologists work closely with your team to design assays tailored to your specific targets and therapeutic areas. Our expert biologists employ their vast experience and knowledge to ensure the assays are optimised for success.
- 2 Efficient hit validation:** D2B approaches quickly assess the biological activity of compounds, enabling the rapid validation of hits identified during High-Throughput Screening (HTS), Virtual Screening or TPD analogue evaluation. This expedites the selection of the most promising compounds for further design or development.
- 3 Early mechanism of action insights:** Understanding the mechanism of action of compounds at an early stage helps researchers make informed decisions during lead optimisation. Direct-to-biology approaches aid in elucidating compound interactions with target proteins and pathways.
- 4 De-risking development:** By gaining insights into a compound's biological activity and mechanism of action early on, D2B reduces the risk of progressing with compounds that might have unforeseen toxicities or lack efficacy.
- 5 Rapid SAR profiling:** The generation of a multitude of structurally related compounds through plate-based chemistry, coupled with D2B screening, facilitates rapid SAR profiling in expedited DMTA cycles. The understanding of the relationship between chemical structure and biological activity is crucial for H2L and LO.
  - o For your TPD project, our team will investigate POI binding, ternary complex formation and the level of cellular protein degradation (e.g. by Nano-Glo® and automated Western blotting)
  - o ChromLogD and experimental polar surface area (EPSA) measurements can be obtained from crude reaction mixtures to assist design and accelerate DMTA cycles. This information on polarity and lipophilicity can be generated within days of obtaining assay data.
- 6 Data-driven decision making:** Data obtained from D2B experiments provides quantitative and qualitative information, empowering data-driven decision-making throughout the drug discovery process.
- 7 Optimisation of ADME properties:** Early knowledge of a compound's Absorption, Distribution, Metabolism, and Excretion (ADME) properties can guide lead optimisation efforts, increasing the likelihood of developing compounds with favourable pharmacokinetic profiles.

## Summary

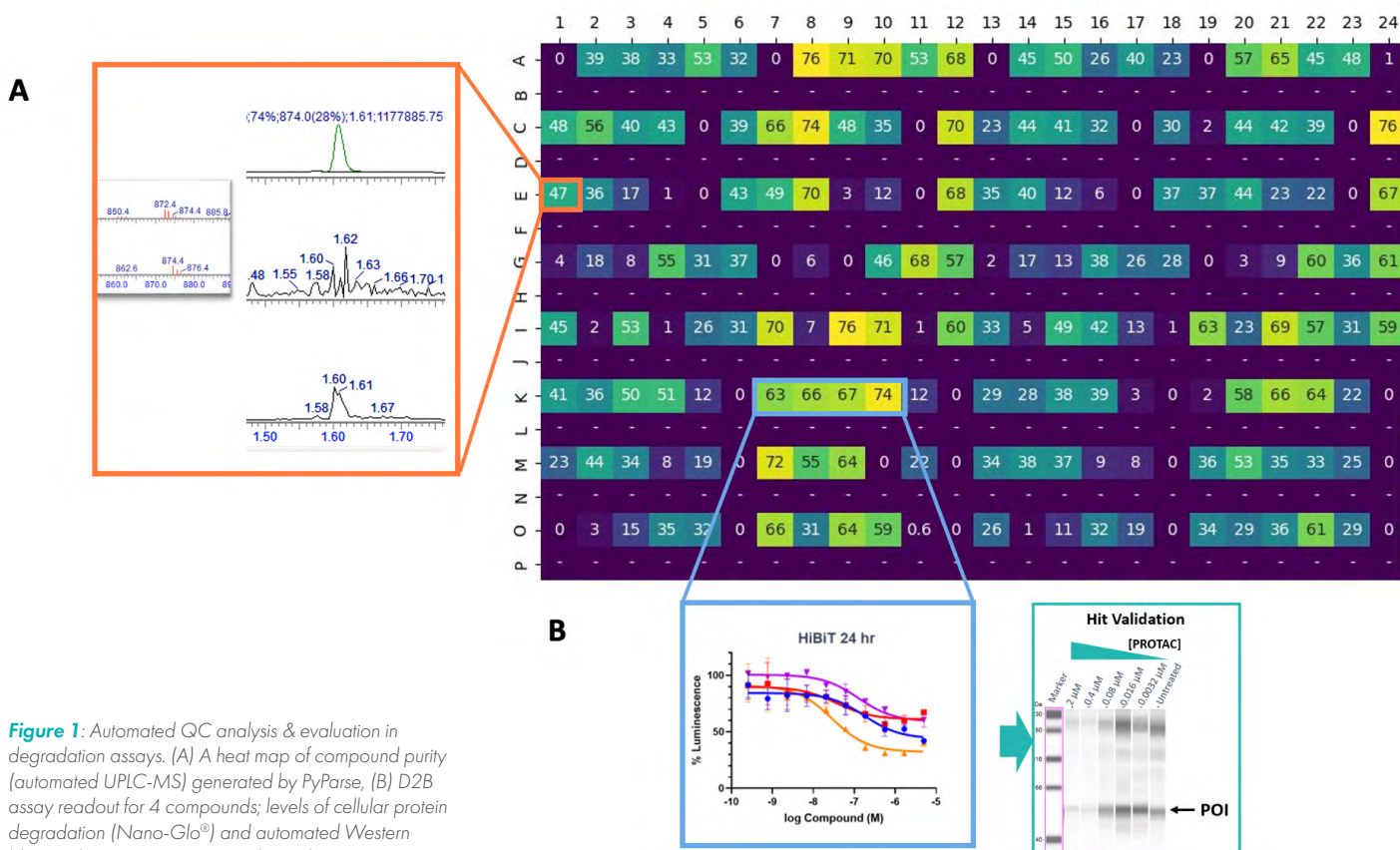
D2B combines plate-based chemistry with rapid screening, synergistically enhancing the efficiency and success of drug discovery. These methods allow researchers to explore rapidly chemical space, identify hits, validate their biological activity, gain early insights into mechanism of action and assess the ADME properties, ultimately streamlining the development of novel and effective therapeutics. By embracing these cutting-edge techniques, Domainex will accelerate your drug discovery programmes and help you to bring life-changing medicines to patients more efficiently and effectively.

## Domainex's D2B Workflow

Up to **380 compounds** can be generated in a single plate and screened using the workflow below:



- Plate-based reaction optimisation is undertaken prior to D2B to ensure workflow efficiency and to minimise reagent usage
- Utilising this process, 1,000s of compounds can be synthesised and screened in less than 1 month
- Automated QC and analysis, using UPLC MS, is conducted to allow a heat-map overview to be produced to assess the quality of each plate (see Figure 1)
- Hits can be observed even when a relatively low sample purity is observed.



**Figure 1:** Automated QC analysis & evaluation in degradation assays. (A) A heat map of compound purity (automated UPLC-MS) generated by PyParse, (B) D2B assay readout for 4 compounds; levels of cellular protein degradation (Nano-Glo®) and automated Western blotting showing concentration dependent TPD.

# About Domainex

Domainex is a fully integrated drug discovery service company based at Cambridge, UK. We serve pharmaceutical, biotechnology, academic organisations and patient foundations globally. We have ambitious growth plans and currently have over 100 scientists. We provide integrated services, from disease target selection to candidate drug nomination. We have a very strong reputation for contributing innovative ideas, undertaking high-quality experiments and for generating intellectual property on behalf of our clients. We strive to build strong, dynamic relationships. In 2022, we served over 90 clients from the UK, Europe, the United States, Japan and Australia and had a project renewal rate of over 80%.

## How Can Domainex Help Your Drug Discovery Project?

Our highly experienced, multi-disciplined scientists – molecular biologists, protein biochemists, assay biologists, structural biologists, medicinal, computational and bio/analytical chemists, *in vitro* pharmacologists and ADME scientists – will support you to advance your drug discovery projects towards drug development effectively and efficiently. We provide customised programmes to address your specific needs at each stage of drug discovery. We draw from a wealth of expertise built up over the last 20 years across a wide range of drug targets and therapeutic areas. From our sites within Europe's leading bioscience hub at Cambridge, UK and with access to the very latest cutting-edge technologies, we are able to help you realise your goals and enrich your discovery pipeline.

## Contacts

If you would like to know more about Domainex's discovery services, or speak to us regarding your own drug discovery needs, please contact us at: [enquiries@domainex.co.uk](mailto:enquiries@domainex.co.uk)

Alternatively we can be contacted directly as follows:

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