Domainex
Driving discovery • Delivering leads

Direct-to-Biology (D2B)

Accelerating Experimental Learning in Drug Discovery



Direct to Biology

Galaxy of opportunity

The Impact of D2B

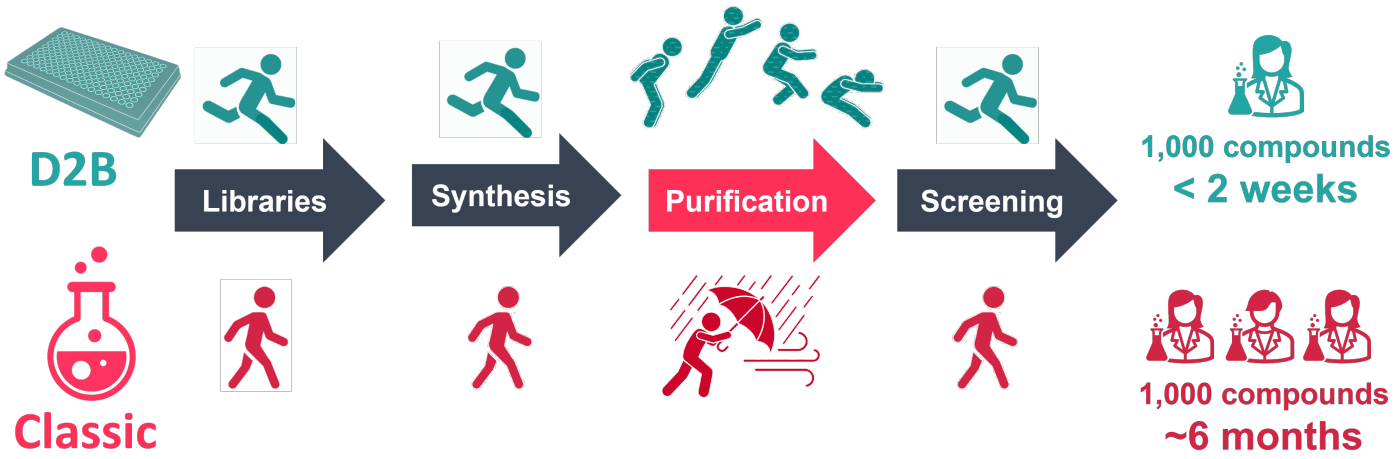
Direct-to-Biology (D2B) is an increasingly adopted drug discovery approach that combines high-throughput chemistry, rapid biological screening and integrated data analysis to accelerate Design-Make-Test-Analyse (DMTA) cycles. D2B enables hit identification, hit-to-lead optimisation and lead optimisation programmes to progress faster by generating biological and developability data directly from plate-based synthesis campaigns.

Why Direct-to-Biology?

Drug discovery increasingly demands rapid experimental validation of large numbers of design hypotheses. Although computational methods are continually improving, experimental data remains essential for driving decision making.

- **Speed:** Generate and screen hundreds to thousands of compounds within weeks.
- **Accelerated Learning:** Rapidly establish SAR and identify productive design trajectories.
- **Reduced Material Consumption:** Typical reactions require nanomole quantities of reagents, reducing material costs and environmental impact.
- **Bespoke Chemical Space:** Tailored libraries are specifically designed and created around your target, rather than relying solely on commercial screening collections.
- **Faster Decision Making:** Biological and developability data is obtained earlier, allowing focussed resources on the most promising compounds.

Output Increases by Avoiding Bottlenecks



The Domainex D2B Platform

Our integrated D2B platform brings together computational design, automated synthesis, high-throughput screening and advanced data analytics to accelerate lead discovery and optimisation.

Accelerating Design-Make-Test-Analyse (DMTA) Cycles

1. **Library Design**
   - **Structure-guided** and **computationally informed** library generation
   - Access to curated **D2B building block collections**
   - **Property-driven** compound prioritisation

2. **D2B Synthesis**
   - Plate-based synthesis using **nanomole scale** chemistry and **inline QC for plates**
   - **Single-step** and **multi-step** reaction workflows
   - **Property-driven** compound prioritisation

3. **Biological Screening**
   - **Biophysical**, **biochemical** and **cellular** assay platforms
   - **Rapid identification** of active compounds
   - Continually **increasing compatibility** with **broad range of chemical reactions**

4. **ML-Assisted Analysis**
   - Efficient analysis of **large data sets**
   - **Rapid SAR generation**
   - **Informed** progression decisions

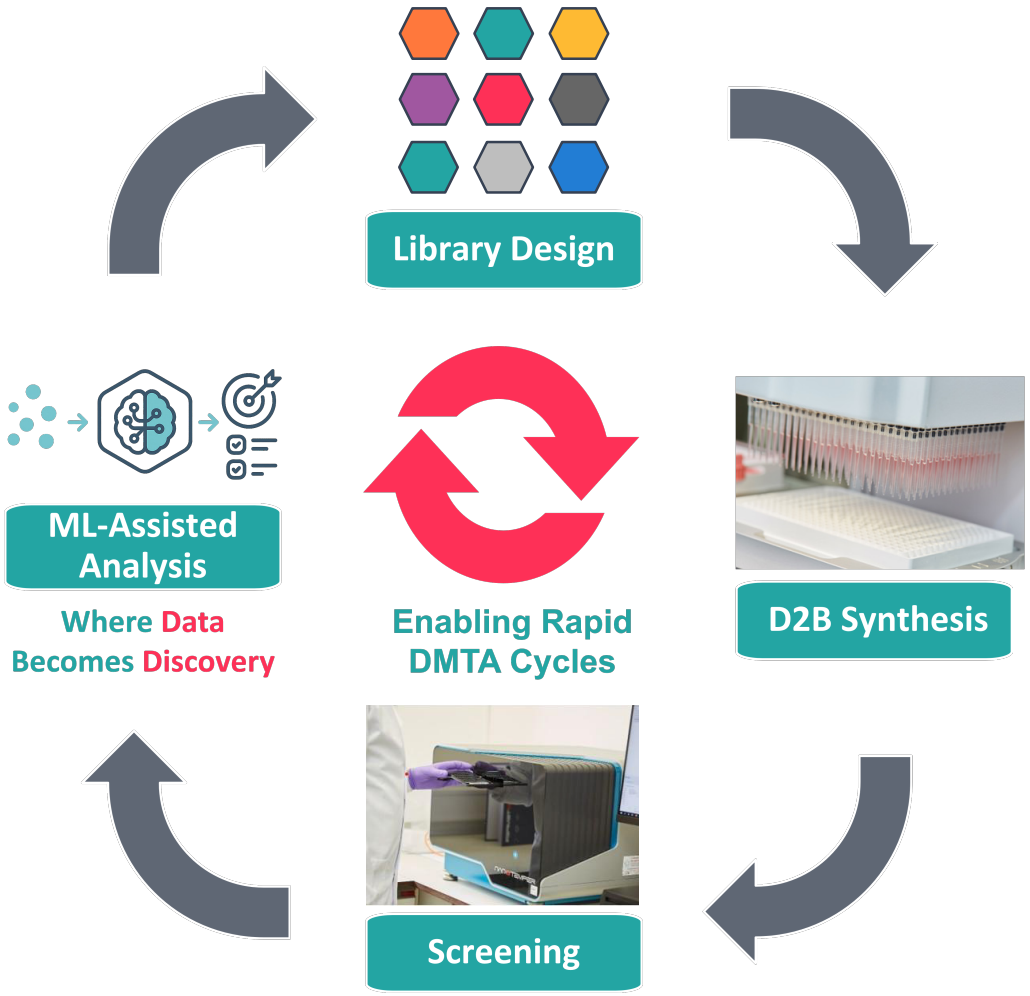
AI-Enabled Drug Discovery Requires Rapid Experimental Validation

Artificial Intelligence (AI) and Machine Learning (ML) are transforming compound design by enabling the rapid generation of thousands of chemical hypotheses. The challenge is no longer generating ideas but rapidly determining which ideas warrant further investment.

Domainex's Direct-to-Biology platform provides the experimental engine required to validate AI-generated hypotheses, enabling rapid DMTA cycles that transform predictions into actionable biological data.

By combining computational design, D2B synthesis, biological screening and machine learning-assisted analysis, we help clients identify promising chemical series promptly and focus resources on the most productive areas of chemical space.

The Domainex DMTA Cycle



Wide Bioassay and Chemistry Capabilities

Domainex has developed a broad D2B reaction toolkit capable of supporting diverse drug discovery programmes:

Bioassay	Compatibility with Reaction Type							
	Amide Coupling	Suzuki Coupling	Reductive Amination	Buchwald-Hartwig	S_N2/ SNAr	CuAAC	Photoredox Coupling	Amide Suzuki de-boc
GCI/SPR	✓	✓	✓	✓	NT	NT	NT	NT
Spectral Shift	✓	✓	✓	✓	NT	NT	NT	NT
HiBiT	✓	✓	✓	✓	✓	✓	✓	✓
Intact Mass Spec*	✓	NT	NT	NT	NT	NT	NT	NT
Flow Cytometry	✓	NT	NT	NT	NT	NT	NT	NT
CellTiter-Glo	✓	✓	✓	✓	✓	✓	✓	✓
HTRF/FRET	✓	✓	NT	NT	NT	NT	NT	NT
Microsomal Clearance	✓	✓	NT	NT	NT	NT	NT	NT

Note: NT - Not Tested

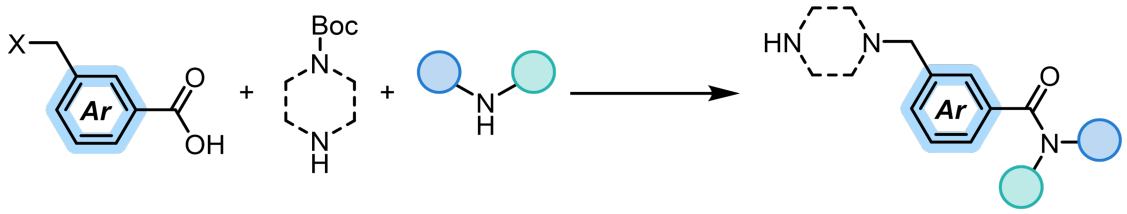
* D2B has been used with MS to generate various molecules with covalent warheads for covalent drug discovery

Multi-step D2B Chemistry

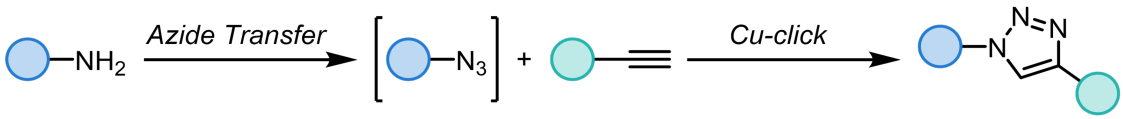
A key advancement in modern D2B workflows is the ability to undertake multi-step reaction sequences directly within a plate-based format. This allows the rapid generation of significantly more complex molecules than traditional first-generation D2B approaches and expands the applicability of the technology across multiple modalities. The D2B platform has been successfully applied to targeted protein degraders (PROTAC®), molecular glues, covalent inhibitors, fragment-based drug discovery and traditional small molecules.

Examples Include:

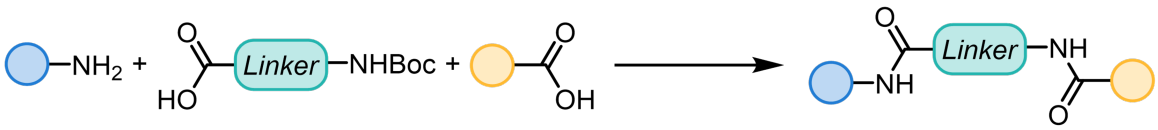
S_N2 → Amide Coupling → Deprotection



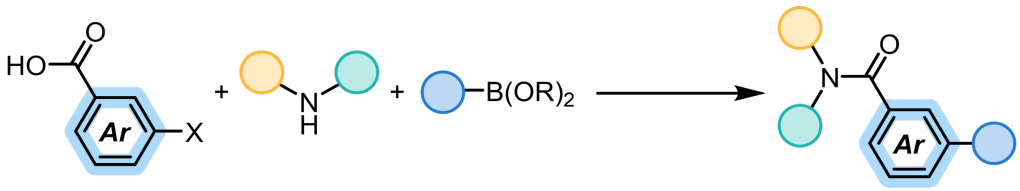
One-Pot Azide Formation → CuAAC Click Reaction



Amide Coupling → Deprotection → Amide Coupling



Amide Coupling → Suzuki Coupling → Deprotection



(PROTAC® is a registered trademark of Arvinas Operations, Inc., and is used under license)

D2ADME: Early ADME Profiling from Direct-to-Biology Campaigns

Domainex's D2ADME platform extends the value of D2B campaigns by allowing the collection of key drug property data directly from screening samples.

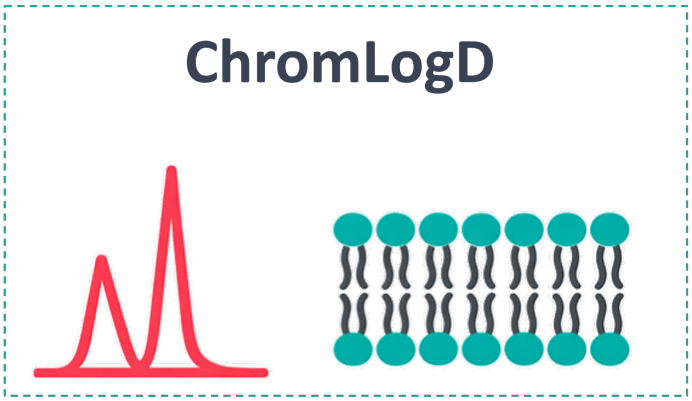
Available D2ADME Readouts

- **ChromLogD**
- **Experimental Polar Surface Area (EPSA)**
- **Microsomal stability, Cl_{Int}**

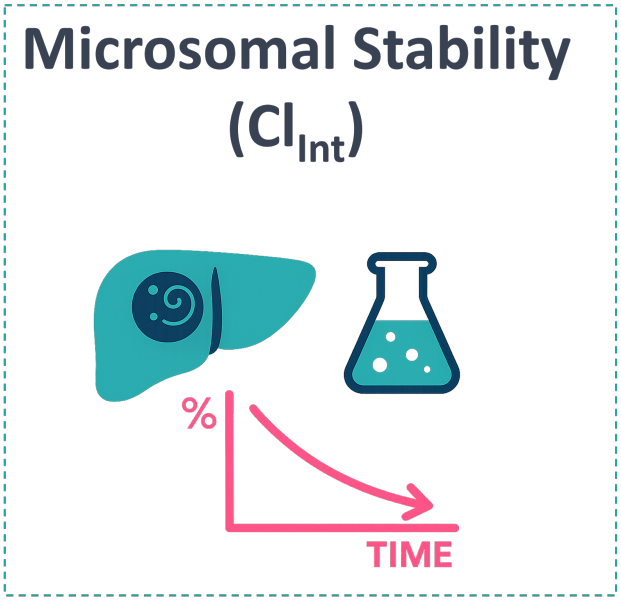
Early insight into compound developability is provided, while helping teams prioritise molecules with the best balance of potency and drug-like properties.

Benefits

- **No purification required**
- **Compatible with multiple reaction classes**
- **Additional value from existing screening samples**
- **Supports faster project progression and more efficient resource allocations**









Quality Built into Every D2B Campaign

Our D2B Workflow Includes:

1. D2B compatibility and reaction optimisation	2. Plate-based synthesis and automated UPLC-MS analysis	3. Compound quality heat map generation	4. Data-driven progression criteria	5. Hit confirmation via resynthesis and purification
Output: This rigorous approach ensures confidence in the biological data generated throughout a D2B campaign				

Start Your Direct-to-Biology Project with Domainex

Domainex provides a fully integrated Direct-to-Biology (D2B) platform that combined medicinal chemistry, biological screening, and ADME profiling to provide a data-driven service that accelerates drug discovery.

- ✓ Extensive single and multi-step D2B chemistry
- ✓ Integrated biology, biophysics, and screening expertise
- ✓ Dedicated D2ADME capabilities
- ✓ Proprietary D2B building block collections
- ✓ Computationally-guided library design
- ✓ Machine learning-assisted data analysis
- ✓ Expertise accross PROTACs®, molecular glues, fragments, covalent inhibitors, and small molecules
- ✓ Flexible project design tailored to your programme

Across chemistry, biology and data science, our scientists work to ensure every D2B campaign delivers meaningful insights that accelerate drug discovery programmes.

Direct-to-Biology: Accelerating Experimental Learning in Drug Discovery

Contact Domainex to discuss how Direct-to-Biology (D2B) and our integrated discovery expertise can support your drug discovery campaign.

www.domainex.co.uk **enquiries@domainex.co.uk**

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About Domainex

Domainex is a fully integrated drug discovery services company based in Cambridge, UK, supporting pharmaceutical, biotechnology, academic, and patient foundation partners worldwide. With more than 80 scientists and ambitious growth plans, Domainex provides end-to-end expertise spanning the entire drug discovery journey, from disease target selection through to candidate drug nomination.

Renowned for scientific excellence, innovative thinking, and the generation of high-value intellectual property, Domainex combines rigorous experimental science with a collaborative approach. By building strong, long-term partnerships, we deliver tailored solutions that help our clients accelerate discovery and achieve their research objectives.

How Can Domainex Help Your Drug Discovery Project?

Our multidisciplinary team includes molecular biologists, protein biochemists, assay biologists, structural biologists, medicinal, computational and bioanalytical chemists, in vitro pharmacologists, and ADME scientists. Together, they provide the expertise required to advance drug discovery programmes efficiently and effectively towards development.

Drawing on more than 25 years of experience across a diverse range of therapeutic areas and target classes, we design tailored programmes that address your specific needs at every stage of the preclinical drug discovery process.

Located within Cambridge, Europe's leading bioscience hub, Domainex benefits from privileged access to world-class scientific expertise, innovative collaborations, and cutting-edge technologies. This unique environment enables us to help clients overcome complex discovery challenges, de-risk programmes, and accelerate the path to successful candidate selection.

Contact us

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

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