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Direct to Biology:
An Approach to Streamline the DMTA Cycle in PROTAC® Discovery

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Overview

Novel degrader classes like molecular glues, and heterobifunctional degraders like proteolysis targeting chimeras (PROTACs®), have emerged as powerful strategies to eliminate disease-relevant proteins by targeted protein degradation (TPD). Many degraders have shown significant potential in oncology and immunology, including in disease models where conventional small molecule inhibitors have struggled. Some of these candidates, both PROTACs and glues, are currently undergoing clinical development. The recent Food and Drug Administration (FDA) approval of VEPPANU (vepdegestrant) in May 2026, the first-in-class PROTAC therapy for patients with ESR1-mutated, ER+/HER2- advanced breast cancer, marks a definitive turning point for the TPD field [22]. Developed through a collaboration between Pfizer and Arvinas, this milestone validates the potential of TPD to address previously undruggable targets and provides a clear blueprint for the next generation of clinical success.

The design of TPD molecules can be challenging for multiple reasons, including complex structure-property relationships, extensive reliance on cell-based assays, and time-consuming linker optimization. These issues can stretch design-make-test-analyze (DMTA) cycles to months and consume substantial synthetic and analytical resources. The direct-to-biology (D2B) approach is a practical way to address these bottlenecks. D2B couples sub-micromole scale, plate-based synthesis with the screening of crude reaction mixtures, which enables rapid exploration of linker and exit-vector space. This allows delivery of rich cell-based degradation data within days rather than weeks and months, while simultaneously reducing waste and improving sustainability.

This whitepaper outlines the principles of TPD and PROTACs, introduces the D2B concept, and explores how a D2B approach can streamline the DMTA cycle in PROTAC discovery. We explore recent literature and real-world examples to illustrate gains in speed, efficiency, and sustainability, and highlight practical considerations for scientists interested in adopting D2B in their own programs.

TPD and PROTACs

From Inhibition to Elimination

Conventional small molecule inhibitors act via an occupancy driven mechanism, meaning they block an active site or regulatory pocket in a dose-dependent manner and must remain bound to the protein of interest (POI) to maintain efficacy. Targeted protein degraders, whether they be molecular glues or bifunctional degraders like PROTACs, act through a catalytic event driven process that relies on induced proximity between the POI and the E3 ligase. Once in proximity, the POI undergoes polyubiquitination and subsequent degradation by the proteosome (Figure 1), leaving the degrader free to bind another POI molecule, allowing for lower dosing and/or less frequent dosing regimens [1], [2], [3].

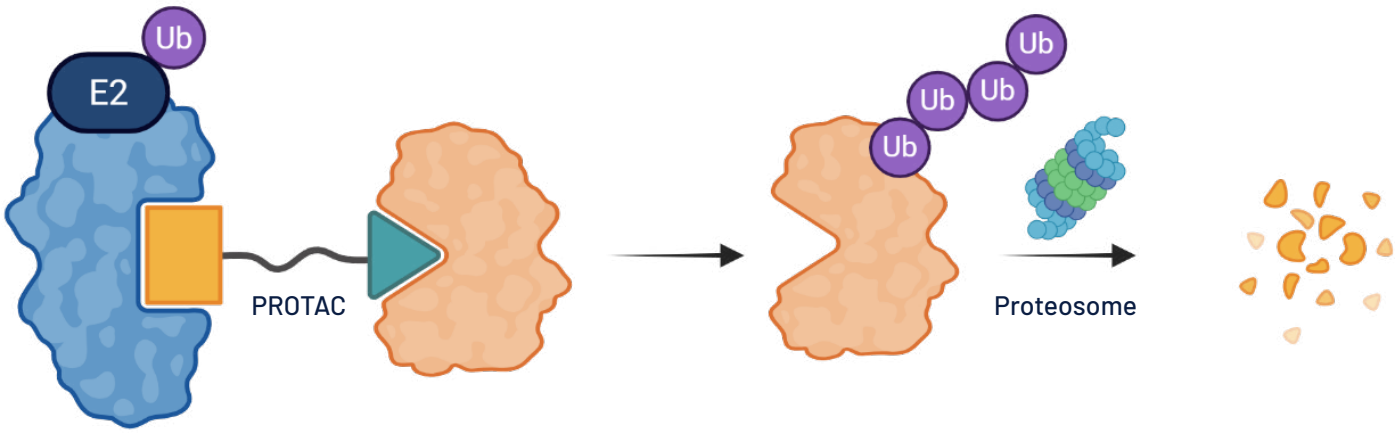

Figure 1.

Schematic representation of PROTAC-induced target degradation. Created with BioRender.com.

Many pharmacologically relevant proteins function as scaffolds or as components of extensive protein–protein interaction networks, often with shallow or featureless binding surfaces rather than classical deep pockets. As a result, they can be difficult to target using conventional small molecule inhibitors due to weak binding affinities [4]. Targeted protein degraders help to overcome this challenge by eliminating the POI rather than simply inhibiting its activity. This has broadened the range of tractable targets and contributed to idea of "drugging the undruggable" [1], [5]. In addition, targeted degraders also enable precision medicine approaches by exploiting E3 ligases with localized tissue expression patterns, to deliver improved selectivity [6], [7].

What Makes PROTAC Discovery Uniquely Challenging?

A classical PROTAC molecule consists of three key components: a ligand that binds the POI (also known as the warhead), a ligand that recruits an E3 ubiquitin ligase (e.g., Cereblon (CRBN), von Hippel-Lindau (VHL)), and a linker connecting the two (Figure 1). The PROTAC induces formation of a ternary complex between itself, the POI, and the E3 ligase, triggering polyubiquitination and proteasomal degradation of the POI [8]. Despite their advantages, PROTACs present several challenges that distinguish them from traditional small molecules:

- **Molecular properties:** PROTACs are often larger than 800 Da with high polar surface areas, hindering cell permeability and complicating optimization under classical Lipinski "rule of five" criteria [9].
- **"Linkerology":** Even subtle changes in linker length, composition, rigidity, or attachment geometry can dramatically and unpredictably alter degradation efficiency, selectivity, and off target profiles [9].
- **Ternary complex dynamics:** Degradation potency depends on cooperative ternary complex formation rather than simple binary binding affinities. As a result, improvements in binary POI:PROTAC or ligase:PROTAC binding affinities are not reliable indicators of greater POI:PROTAC:ligase ternary complex formation, and do not necessarily translate into better degradation [10], [11].
- **Assay burden:** Intracellular target degradation, not binding, is the key endpoint for degrader discovery. This means that many TPD projects rely heavily on cell-based assays to confirm degradation and to reveal mechanistic insights [3], [8], [9].

As a result, PROTAC discovery teams are required to synthesize and profile dozens to hundreds of analogues per warhead-ligase combination, whilst being unsure about what constitutes an optimal PROTAC property profile. This creates significant information-hungry and resource-intensive demands that align well with the high-throughput capabilities of D2B platforms [3], [12].

Direct-to-Biology: Concept and Workflow

What is Direct-to-Biology?

D2B is a discovery approach in which crude reaction mixtures, typically prepared at nanomole to low micromole scale in microtiter plate format, are taken directly into biological assays after minimal purification and rapid quality control. Compounds that meet predefined activity thresholds are then resynthesized, purified, and subjected to full analytical characterization and follow-up mechanistic studies [3], [13], [14]. The D2B workflow builds on established parallel chemistry, but its defining feature is the tight integration of chemistry synthesis, biology, data analysis, and automation around plate-based workflows (Figure 2). When implemented effectively, D2B can deliver three major benefits [9], [13]:

1. **Reduced timelines:** Eliminating the need to purify, weigh, and formulate every compound can reduce the cycle from design to biological data from weeks and to days (Figure 2).
2. **Higher throughput:** The use of nano- and microscale reactions, and automated liquid handlers allow for tens to hundreds of compounds to be profiled per cycle without a proportional increase in analytical burden.
3. **Improved sustainability:** Lower reaction scale without the need for preparative chromatography significantly reduces solvent use, reagent consumption, and solid waste.

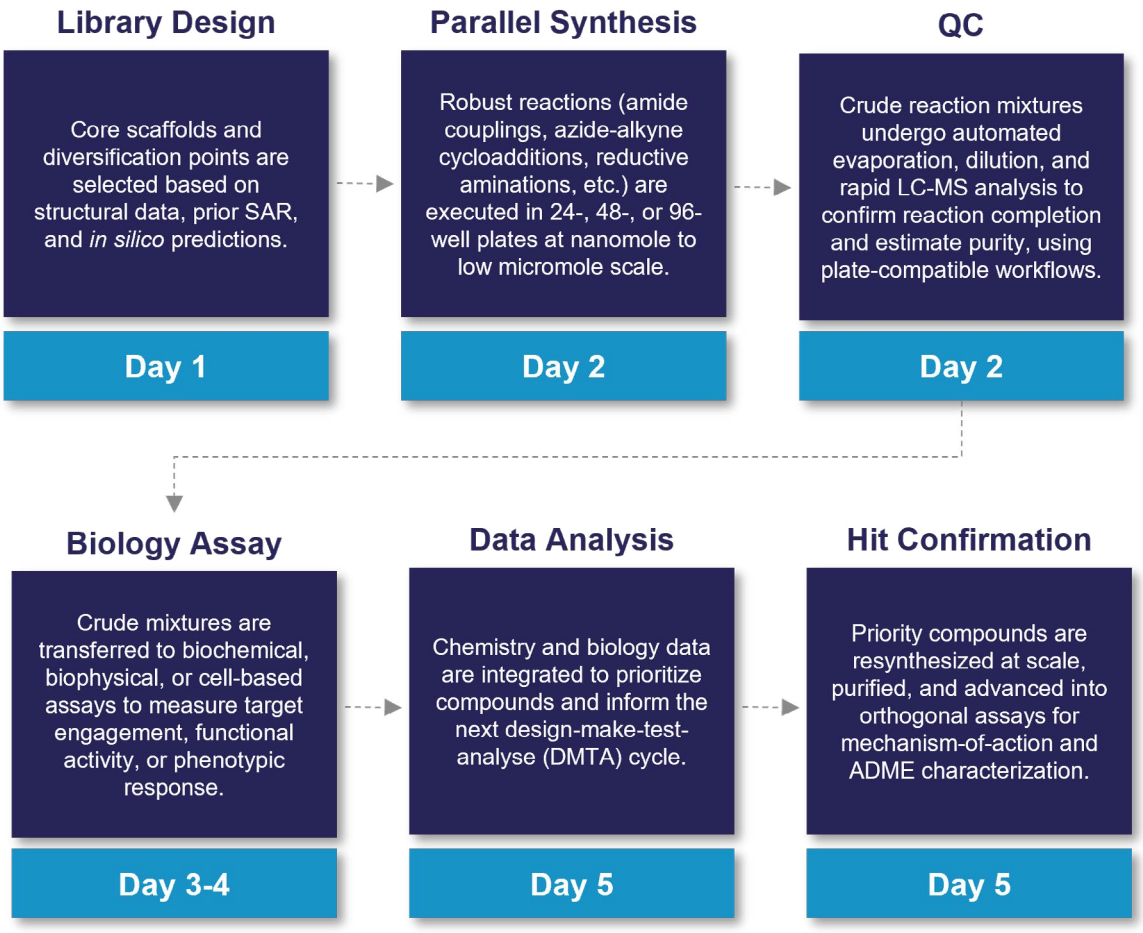

Figure 2.

D2B workflows and direct screening of crude reactions compresses traditional DMTA cycles from weeks to days.

These advantages make D2B particularly attractive for projects that require a rapid exploration of structure activity relationships (SARs) and significant cell-based screening, as is the case for complex modalities like PROTACs. The modular nature of PROTAC architecture also naturally suits 24-, 96- or 384-well plate-based array chemistry and allows for systematic sampling of a broad physicochemical space by combining a set of warheads with diverse linkers [3]. Importantly, D2B is also applicable to different modalities including fragments [14], covalent inhibitors [15], and molecular glues [16], [17], each of which are associated with their own specific challenges

Impact on the DMTA Cycle and Sustainability

Traditional PROTAC discovery projects can take 4–12 weeks from computational/medicinal chemistry design to generation of cell-based target degradation data when including synthesis, purification, analytical characterization, and biology data. The D2B approach compresses this timeline down to days (Table 1), with published case studies against BRD4 [9] and Aurora Kinase A [12] demonstrating success within a week. D2B analysis cycles also allow for more systematic sampling of linker length, rigidity, and exit vector combinations. Multiplexed biology readouts for target engagement, degradation, permeability, and toxicity enable early derisking and deselection before time and resources are further invested in resynthesis. These gains in improved efficiency and data quality increase confidence in potential identification of developable candidates within allocated budget and time constraints. The advantages that D2B offers in speed also directly translate to compelling benefits in terms of sustainability for PROTAC development [3], [13]. These include:

- Reducing solvent use by >90% compared to traditional milligram scale synthesis.
- Reducing consumption of expensive POI warheads and, in some cases, proprietary E3 ligase ligands.
- Reducing energy footprint as there is less of a reliance on purification workflows that sometimes require multiple evaporation cycles.

Parameter	Conventional Workflow	D2B Workflow
Scale	20 µmol	2 µmol
POI-Ls	1 – 1.3 g	60–80 mg
80 x E3-L-Linker Intermediates	1.3 g	80 mg
Solvent	DMF (300 µL per vial)	DMSO (100 µL per vial)
Purification	40 L of MeCN	-
Time	4–12 weeks	5 days

Table 1.

Comparison of conventional synthesis workflow (purified) and D2B (non- purified) workflow for a theoretical 80 PROTAC library.

Evidence for Acceleration and Richer SAR

Multiple groups, both in academia and industry have developed D2B platforms that have led to the successful identification of promising candidates. The Janssen Research & Development group synthesized 91 diverse linker analogs using nanomole scale amide coupling and profiled crude reaction mixtures across four cell-based assays measuring E3 ligase engagement, target degradation, permeability, and cytotoxicity. The resulting data revealed non-intuitive "linkerology" trends, suggesting an optimal linker length of 8–12 atoms and unexpected polarity effects [9]. Gaining insights into these trends via traditional methods would have been impractical, given the D2B Workflow milligram amounts of PROTACs.

Our own D2B workflow delivered BRD4-HiBiT degradation data using crude reaction mixtures from an 80-member PROTAC library with enriched linker diversity. The entire workflow (Figure 3; Table 1), including design, synthesis and initial cellular SAR could be completed in five days, representing a significant change from traditional timelines.

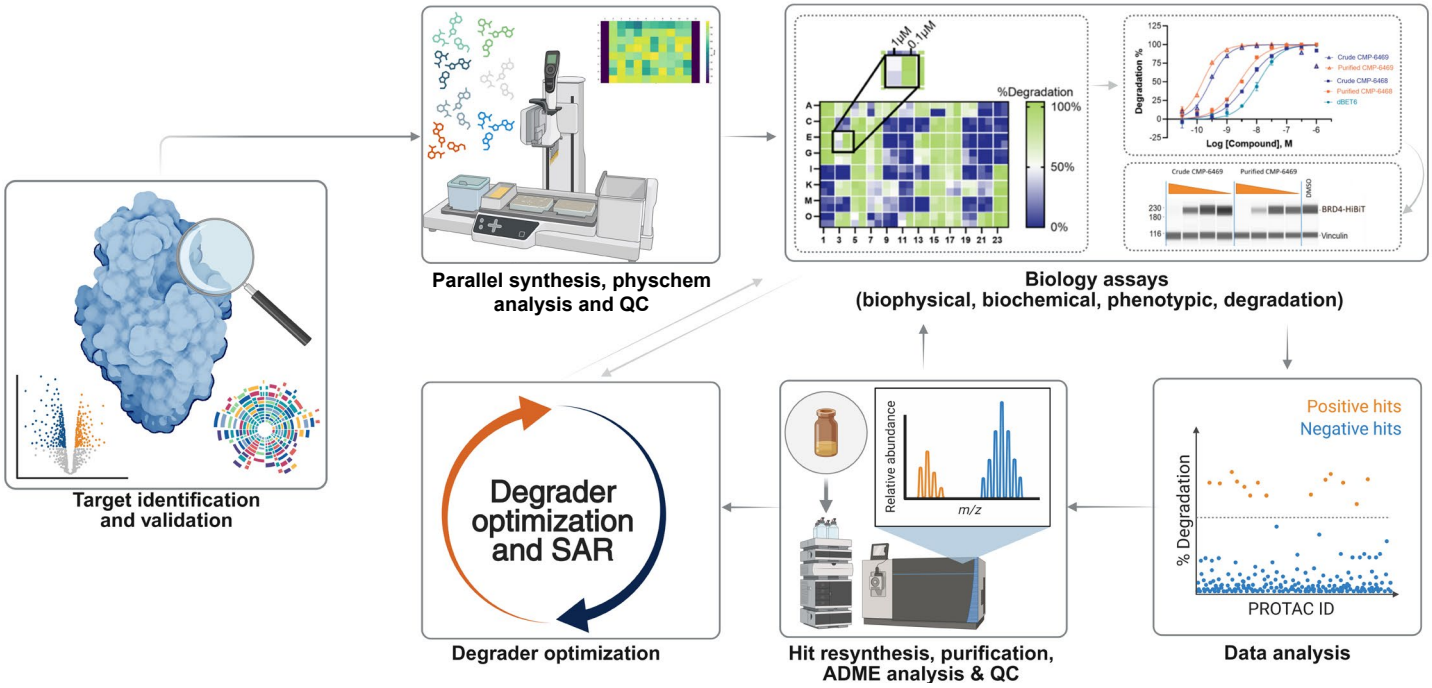

Figure 3.

Example BRD4 D2B workflow for hit degrader identification and optimization at Concept Life Sciences. Created with BioRender.com.

Complementary approaches have also exploited modular photoclick chemistry to assemble PROTAC libraries in microtiter plates at nanomole scale, followed by direct testing in cell-based screening assays [18], [19]. This strategy further expands throughput and chemical diversity, making it especially useful for exploring new warhead-ligase combinations and other underexplored degrader design spaces.

The complete value of D2B is revealed when integrated into broader discovery ecosystems. Structural biology and computational modelling help to rationalize observed SAR through ternary complex geometry, while proteomics and transcriptomics characterize on- and off-target degradation to guide selectivity optimization. In addition, current machine learning models that have been trained on D2B datasets can predict degradation outcomes from structure and physicochemical properties [20], [21].

In these examples and countless others, the main theme that emerges is that dense, systematically generated datasets can reveal degradation-specific SAR and linker-dependent effects more efficiently than lower throughput workflows. This accelerates project timelines while providing richer, more reliable data to inform iterative DMTA cycles and identify optimal lead candidates. For CROs, academic, and industry discovery teams, integrating high-throughput D2B chemistry with comprehensive biological profiling and data analysis represents a hallmark of advanced TPD capabilities.

Practical Considerations for Adopting a D2B PROTAC Project

Unlike screening with traditional purified compounds, working with crude mixtures in D2B workflows places specific demands on assay design, data interpretation, and validation strategies [9], [12]. For example:

- D2B requires biochemical cell-based and assays to tolerate residual solvents, reagents, and by-products that may have been carried over from plate-based synthesis.
- Following plate-based synthesis, compound concentration is based on assumed conversion. Therefore, normalization using internal standards or LC-MS response factors can improve well-to-well comparisons and help with generating accurate dose response curves in screening assays.
- Hits emerging from crude D2B screens should always be confirmed with purified material in orthogonal assays that separate binding (e.g., FRET, FP), ternary complex formation (e.g., SPR, ITC), and degradation (e.g. HiBiT assays, SimpleWestern blot, quantitative proteomics, high content imaging).

Working with Concept Life Sciences

At Concept Life Sciences, we combine deep scientific expertise with integrated capabilities to accelerate your D2B degrader discovery programs. By leveraging our robust assay cascades, we ensure that the speed of your D2B workflow does not come at the cost of data quality. We partner with you to deliver:

- **Computational chemistry & CADD:** Predictive molecular modeling and computer-aided drug design to accelerate hit-to-lead optimization.
- **Chemistry & ADME:** Integrated medicinal chemistry and ADME support to optimize the PK/PD properties of your lead molecules.
- **Protein production:** Expert production of high-quality proteins optimized for downstream biochemical and biophysical applications.
- **Biophysical characterization:** Advanced insights into binary and ternary complex formation, including affinity, kinetics, stoichiometry, and cooperativity.
- **Assay development & screening:** Comprehensive assay design and orthogonal screening cascades to minimize false hits.
- **Structural biology:** High-resolution structural insights with Cryo-EM analysis of heterobifunctional and molecular glue degraders.

Outlook: From Concept Through to Clinic

The recent Food and Drug Administration (FDA) approval of VEPPANU (vepdegestrant) in May 2026, the first-in-class PROTAC therapy for patients with ESR1-mutated, ER+/HER2- advanced breast cancer, marks a definitive turning point for the TPD field [22]. This milestone validates the potential of TPD to address previously undruggable targets and provides a clear blueprint for the next generation of clinical success.

As the industry pivots toward more rational molecular glue discovery and advanced induced-proximity modalities, the need for precision and speed has never been greater. The D2B approach is a versatile, modular platform that provides the depth and robustness required to navigate this expanding landscape. By integrating reliable plate-based workflows with high-throughput biological screening, our D2B platform enables you to explore wider chemical space with reduced timelines and a lower environmental footprint.

For scientists focused on the next wave of degrader discovery, Concept Life Sciences offers a practical route to condense DMTA cycles, generate richer SAR data, and align your research with modern sustainability goals. This is an exceptionally exciting time for the field, and with the right integrated service partner, the path from the initial concept to the clinic has never been more attainable.

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[1a]PROTAC® is a registered trademark of Arvinas.

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About Concept Life Sciences

Concept Life Sciences is a leading contract research organisation (CRO) serving the global life sciences industry. For over 25 years, the company, and its heritage companies, have provided consultative and collaborative drug discovery and development services. Our approach, supported by passionate scientists and world-leading capabilities, enables clients to overcome complex scientific challenges across a broad range of therapeutic areas, improving program success rates. The company has successfully helped 29 candidates advance to the clinic.

The company offers sophisticated translational biology services coupled with exceptional end-to-end chemistry capabilities across all modalities including small molecules, biologics, peptides and cell & gene therapies, with the ability to seamlessly integrate capabilities and provide bespoke solutions to address client needs.

Collectively, the company's high-quality services and commitment to customer service across the drug development pathway enhances efficiency in drug discovery, helping clients advance their drugs to clinic in as little as 32 months, well ahead of the industry average of 60 months.

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