

The Drug Discovery and Delivery Core in the Translational Hearing Center at Creighton University

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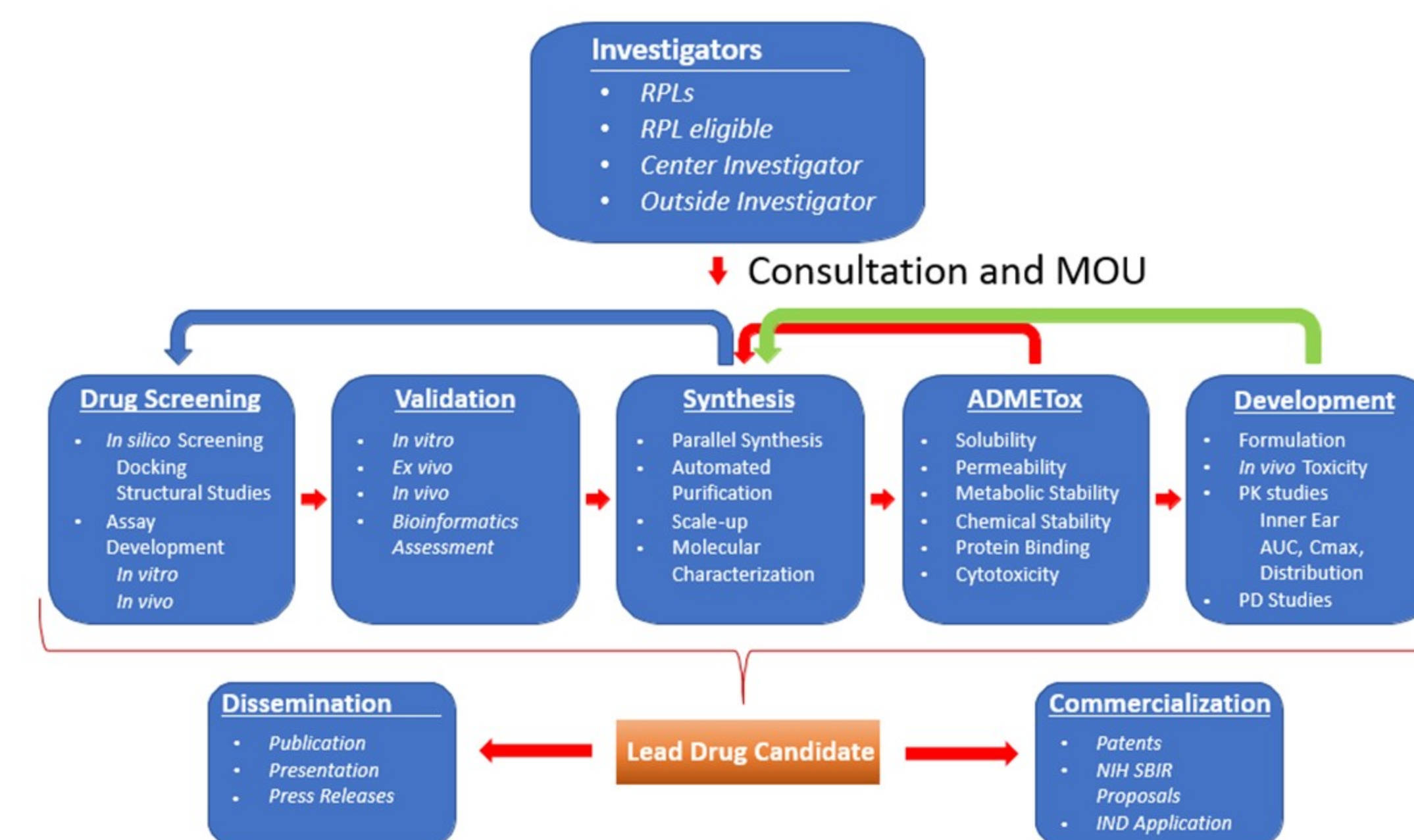
BACKGROUND

The Drug Discovery & Delivery Core (DDDC) at the Creighton Translational Hearing Center has established a state-of-the-art drug discovery and development pipeline to support research projects both within and outside the Center. This core comprises four laboratories: (i) the Drug Design, Synthesis and Validation Laboratory, (ii) the ADMETox Laboratory, (iii) the Zebrafish Laboratory, and (iv) the Cell Culture and Tissue Laboratory. With substantial support from Creighton University and neighboring institutes, the DDDC accomplished the essential equipment setup and an appropriate expertise to lead the Drug discovery projects.

The DDDC at Creighton employs contemporary, innovative chemical synthesis to modify chemical structures systematically to design and develop novel pharmacophore(s), optimizing the efficacy and bioavailability of candidate othotherapeutic drugs while minimizing toxicity. At the DDDC we provide efficient and accurate analytical services, ensuring confidence in the structural integrity, purity, and stability of molecular syntheses. Additionally, lead compounds can undergo pre-formulation studies for enhanced characterization, paving the way for further preclinical and clinical testing.

Addressing the global challenge of identifying researchers capable of supporting significant research investments, the DDDC aims to ensure its pipeline of graduate trainees, understands the research challenges in both academia and industry, fostering opportunities for academic and industry-academic collaborations. With a proven track record in advancing drug discovery, synthesis and initiating research projects on time and within budget, we continue to broaden our expertise and invest in a knowledge-based drug discovery core at a dedicated academic medical center.

SERVICES



Cell Culture and Tissue Lab^a



- **Biosafety Cabinets:** Four Labconco Axiom type C1, NUAIRE Laminar Flow
- **CO₂ Incubators:** Four PHCbi Cell-iQ series incubator in the cell culture room, Heracell VIOS 160i and Forma Steri-cycle incubators in the tissue culture room
- **Countess 3 FL Automated Cell counter** with Brightfield, DAPI, GFP and RFP filters
- **Microscopes:** Leica DMI1 inverted phase contrast microscope, Leica S9D stereo microscope
- **Centrifuges:** Sorvall ST8R, Sorvall Legend X1R refrigerated centrifuges
- **Other equipment:** Thermo Scientific Precision GP15D dry baths, microcentrifuges, refrigerator for media storage.

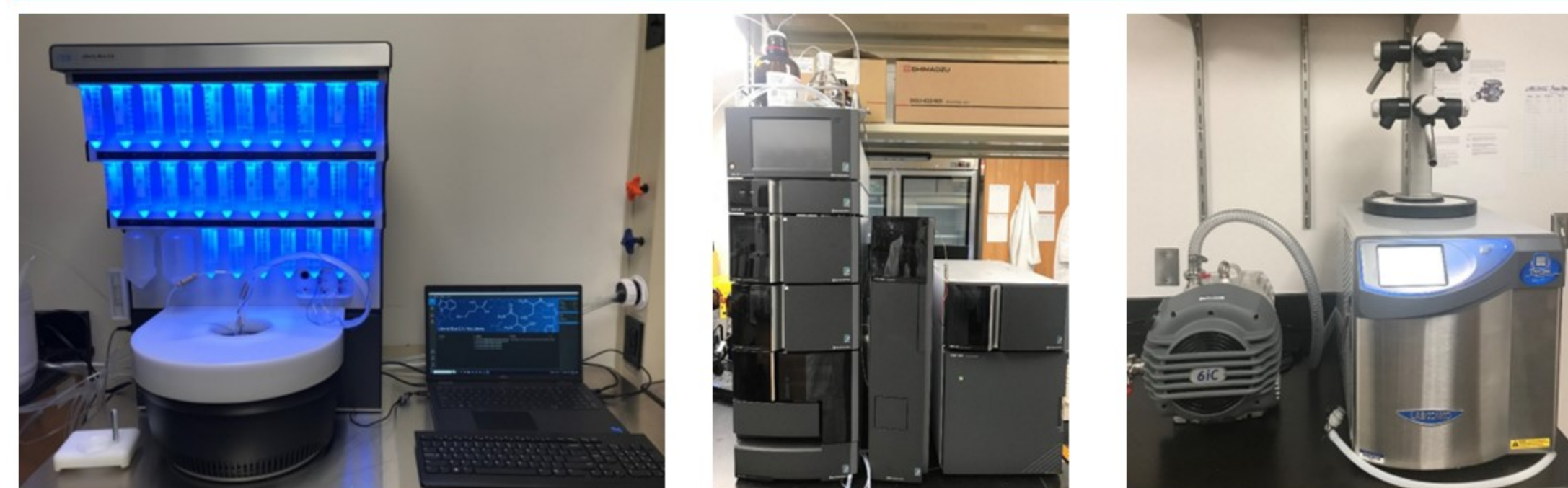
Zebrafish Lab^a



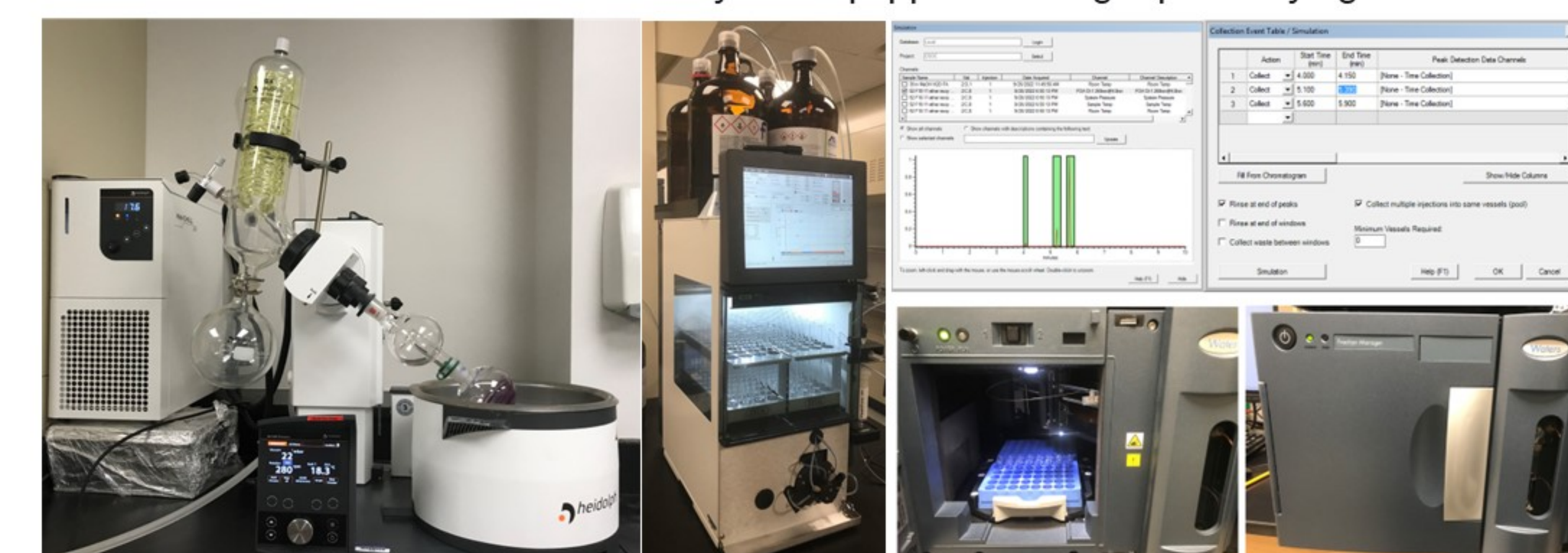
The Zebrafish services of the Drug Discovery and Delivery core provide support for behavioral, developmental, and neurobiological studies. Researchers have access to fish housing, breeding, and use of several instruments specific for using zebrafish as a model organism. We can support researchers and facility users through any of the following services. Additional project-specific support for users can be arranged as needed.

- Behavioral Analysis
- Drug Screening
- Genetic Manipulation
- Zebrafish Imaging

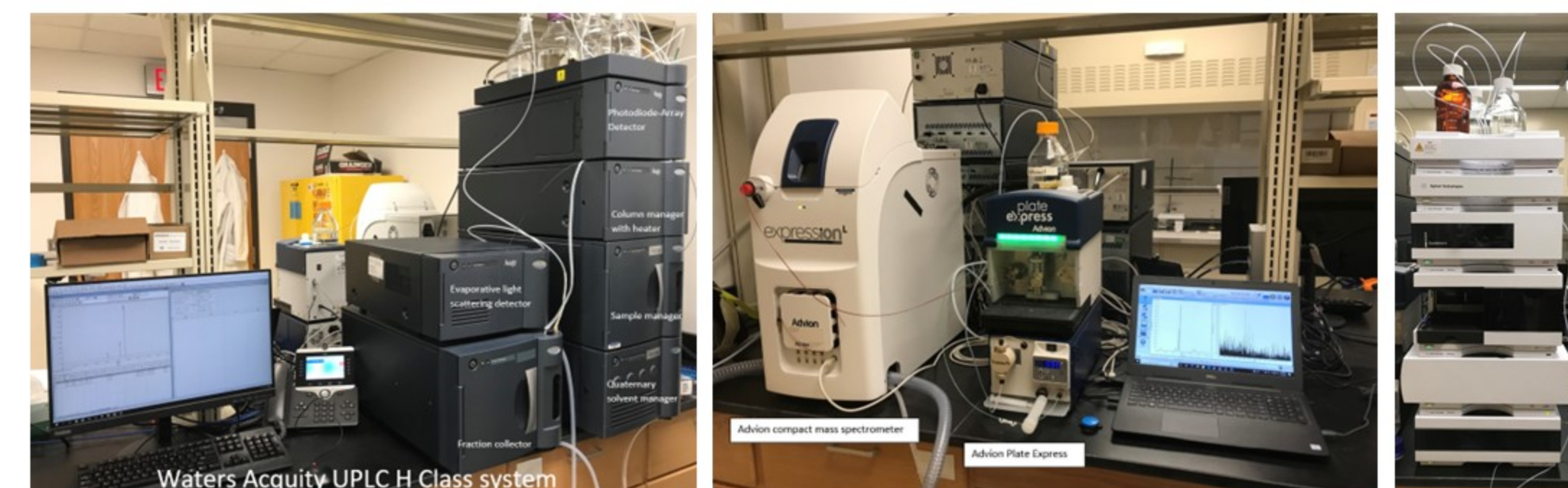
Drug Design, Synthesis and Validation Lab



- CEM Liberty 2.0 peptide synthesizer is equipped with a microwave reactor, 27 amino acid positions, and an integrated reaction vessel camera.
- Shimadzu Nexera HPLC is equipped with a system controller, degassing unit, fraction collector, UV-VIS detector, column oven, autosampler, and solvent delivery module.
- LABCONCO 2.5L Freezezone freeze dryer is equipped with eight ports drying manifold.



- The Waters Fraction Manager is designed for the collection of narrow and closely eluting compounds found in UPLC separations, specifically for microgram-scale samples.
- Buchi Pure C-810 Flash Chromatography System comes with a UV-Vis detector and fraction collector.
- The Rotary evaporator can be used for evaporation, distillation, and solvent recovery.



- Waters ACQUITY H PLUS Ultra-performance liquid chromatography is equipped with a photo diode array detector, column manager, FTN autosampler, quaternary solvent pump, and an analytical fraction collector.
- Advion Expression¹ Compact mass spectrometer is equipped with a single quadrupole analyzer with a mass range up to m/z 2,000, an Electrospray Ionization (ESI) ion source, and the Plate Express for direct analysis of TLC plates and spots.
- Agilent 1100 Series HPLC is equipped with a degasser, quaternary pump, autosampler, and diode array detector.

ADMETox Lab

A Absorption

- Aqueous solubility
- Permeability

D Distribution

- Aqueous solubility
- Permeability
- Human Plasma Protein Binding

M Metabolism

- Metabolic stability

E Excretion

- Clearance

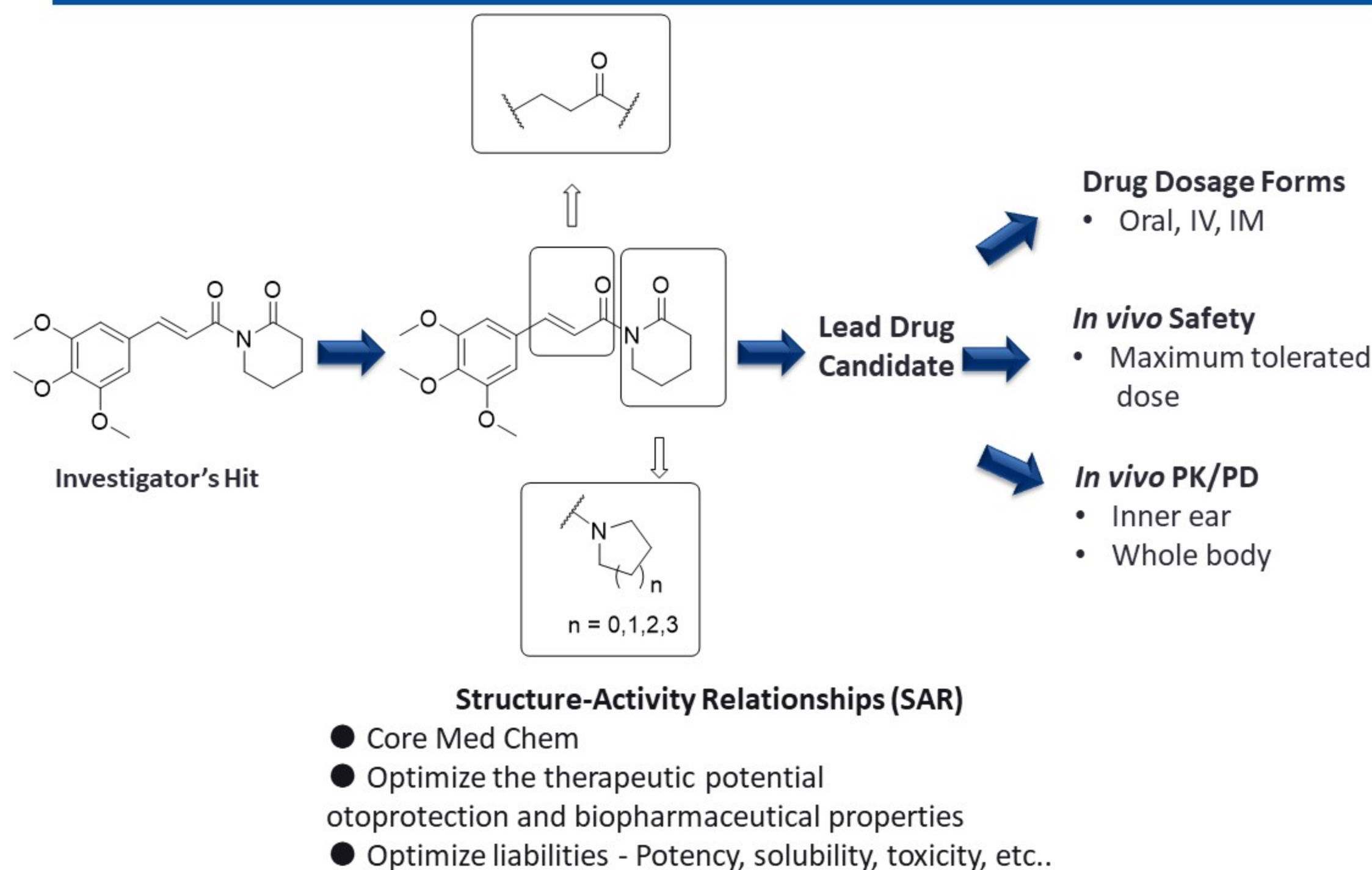
Tox Toxicity

- Safety
- Cytotoxicity
- Ames test

96-well plate-based *in vitro* assays to rapidly determine:

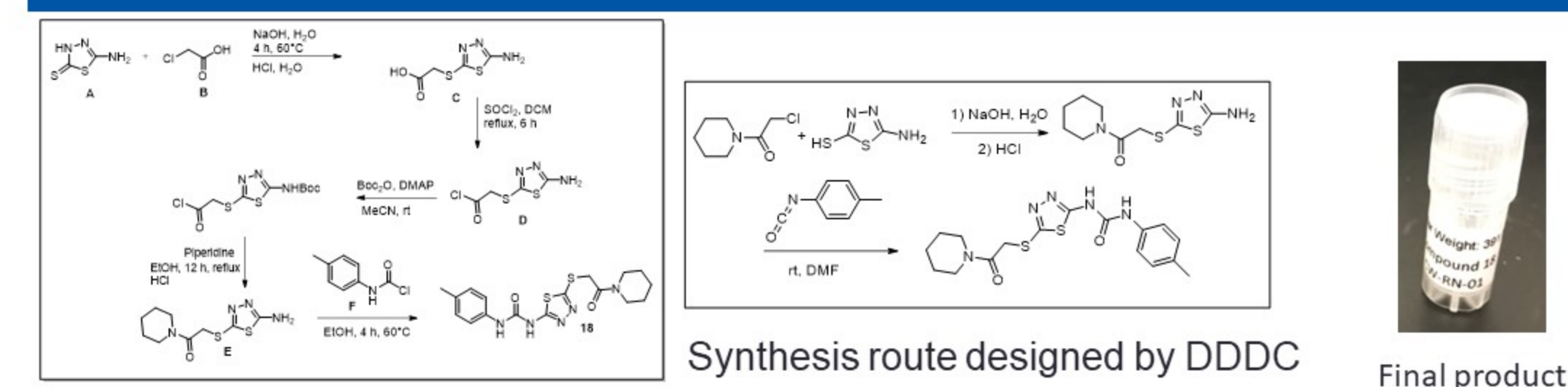
Solubility	Permeability	Metabolic Stability	Plasma Protein Binding	Cytotoxicity
<ul style="list-style-type: none">• Kinetic• Thermodynamic• pH 2, 6.4, 7.4	<ul style="list-style-type: none">• Parallel Artificial Membrane Permeability Assay (PAMPA)• Caco-2 cells	<ul style="list-style-type: none">• Liver microsomes• Human, mouse, rat• Liver S9 fraction• Human, mouse	<ul style="list-style-type: none">• Human• Rat• Mouse	<ul style="list-style-type: none">• MTT Colorimetric Assay• Amenable to various cell lines

SAR & CUSTOM LIBRARY SYNTHESIS



DDDC offers medicinal chemistry services for the discovery of small molecules.

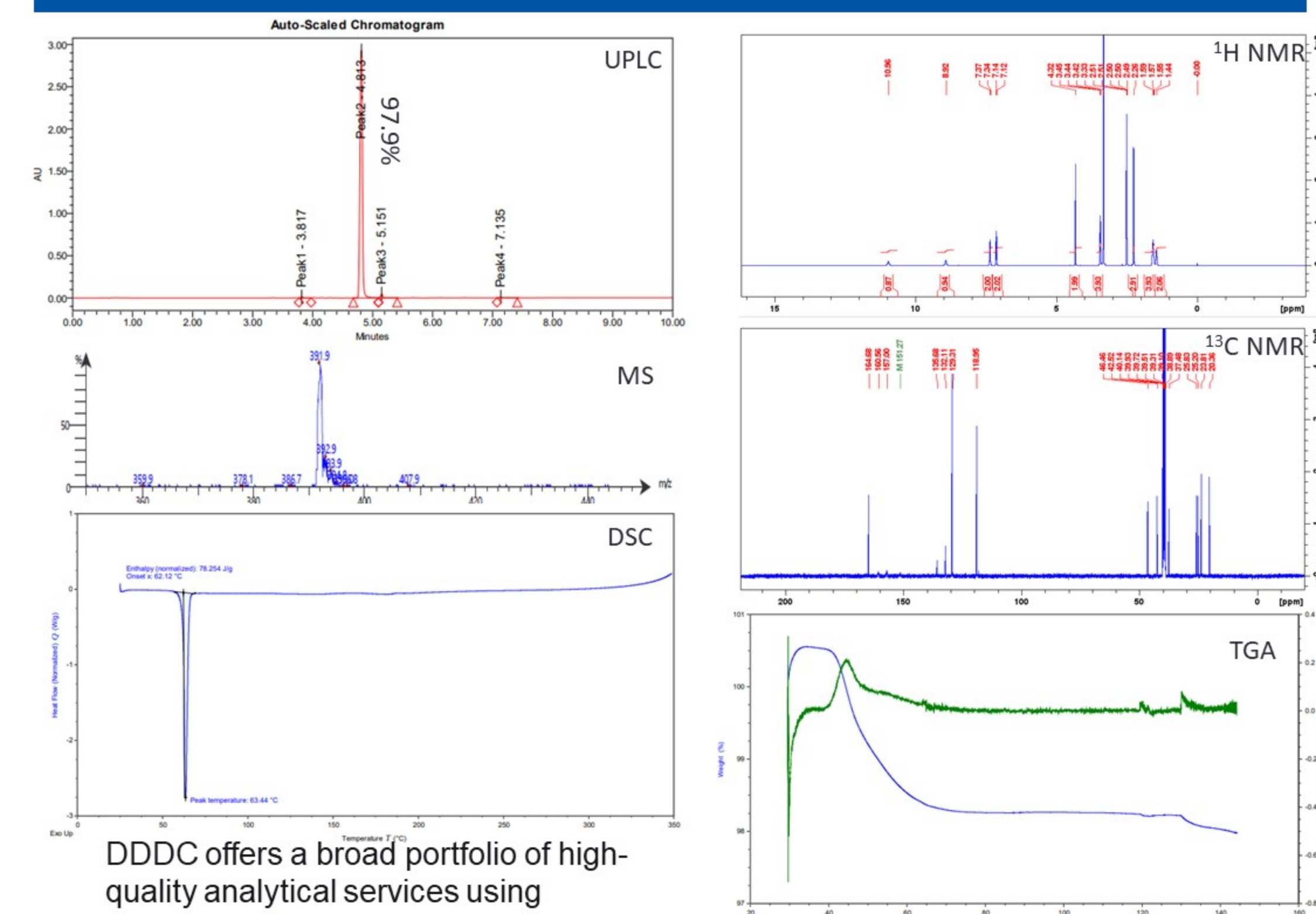
DESIGN SYNTHETIC ROUTE



Synthesis route provided by the customer

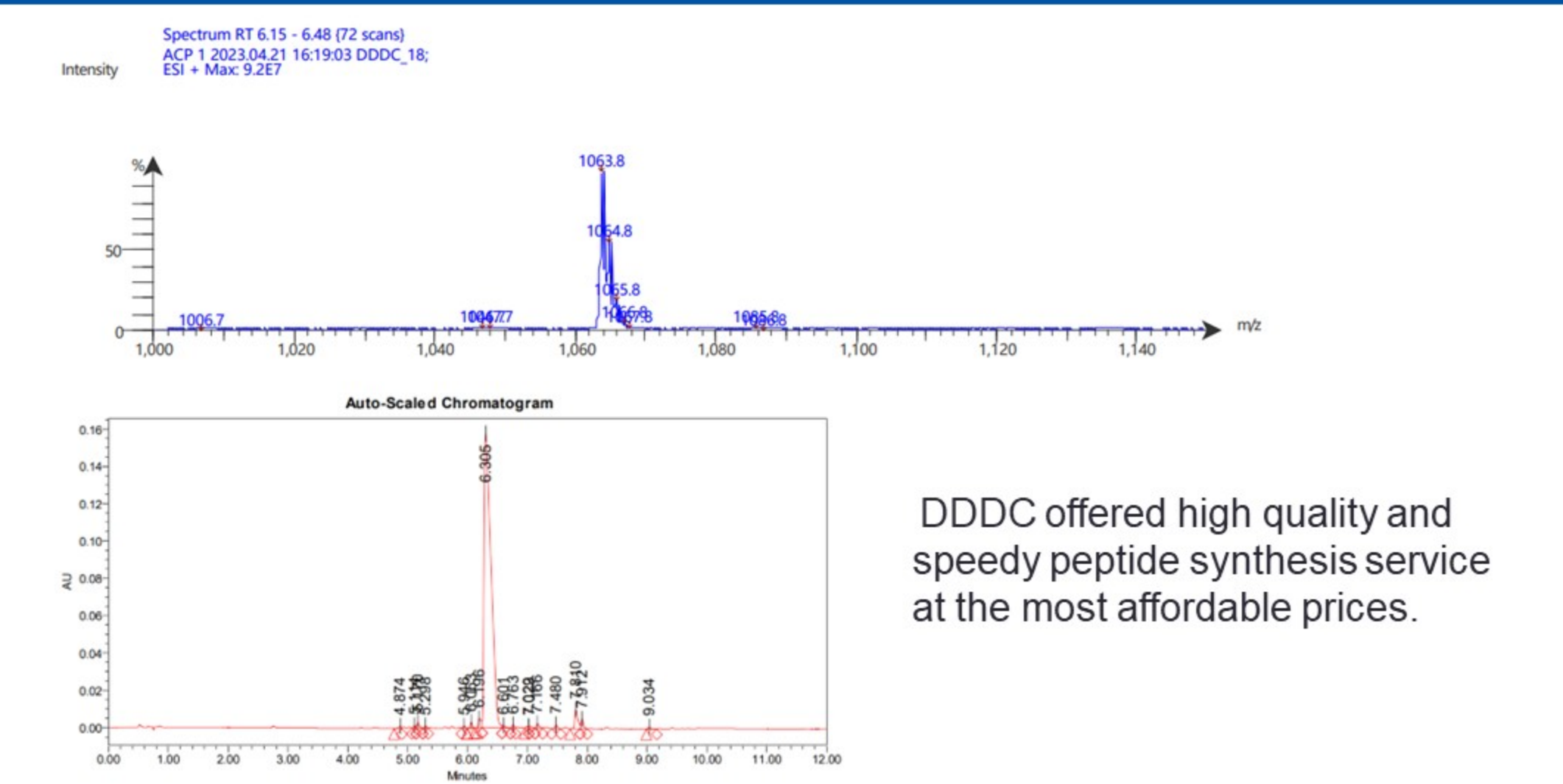
DDDC provides an optimized route in terms of time, amount of by-products, environmental impact, yield, purification, or other parameters.

ANALYTICAL SERVICES



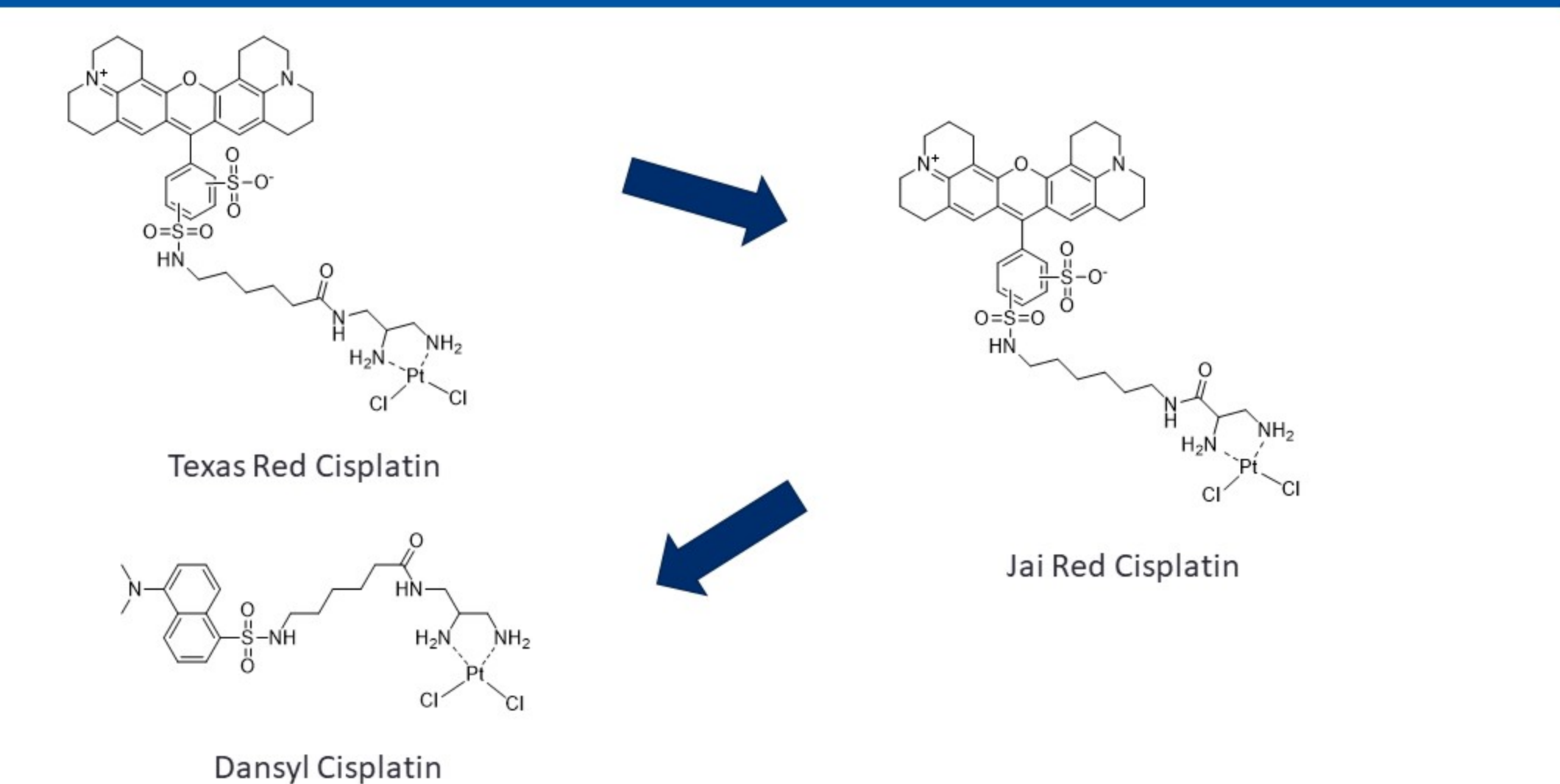
DDDC offers a broad portfolio of high-quality analytical services using advanced methods and instrumentation.

CUSTOM PEPTIDE SYNTHESIS



DDDC offered high quality and speedy peptide synthesis service at the most affordable prices.

PROVIDE COST-EFFECTIVE SOLUTIONS

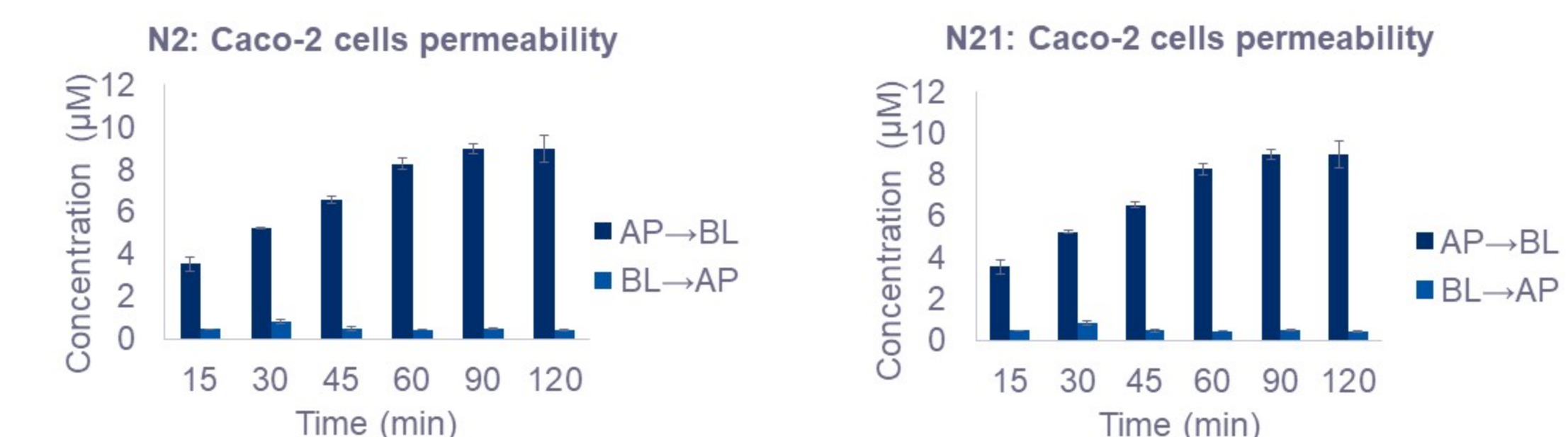


DDDC can develop quick, scalable, safe, and cost-effective processes for customer compounds.

PREFORMULATION STUDIES^b

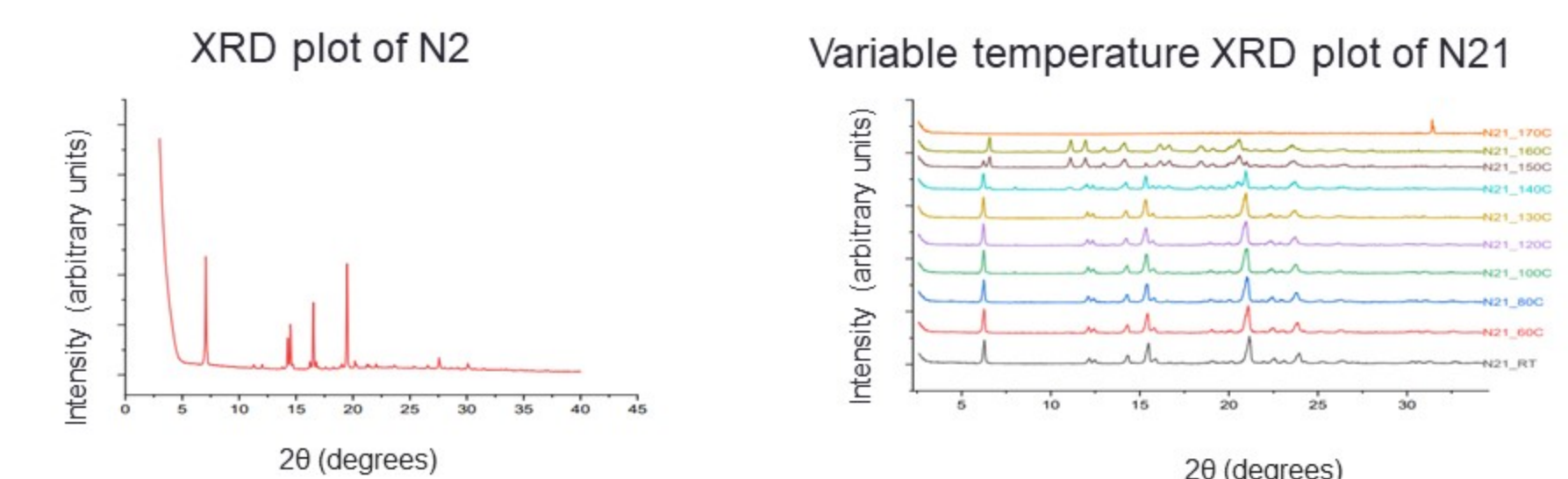
Applications of the UPLC methods

Parameter	N2	N21
Aqueous saturation solubility at 37° C	0.16 ±0.02 µg/mL	0.17 ±0.03 µg/mL
LogP value	4.88 ±0.02	5.76 ±0.07
Apparent permeability coefficient (Papp ×10 ⁻⁶ (cm/s)): Apical (AP)→Basolateral (BL) (3)	17.76 ±0.88	18.31 ±1.83



• The initial concentration in the donor compartment (N =9) was 69.9 ±0.2 µM for N2 and 58.1 ±0.7 µM for N21. AP→BL permeability was higher than BL→AP.

X-ray powder diffractometry



DISCUSSION

Identifying researchers with the necessary abilities to support large research investments is a major challenge for academia and industry worldwide. At the DDDC, we seek to ensure that the pipeline of graduate trainees understand the research problems in academia and industry. We see opportunities for both academic and for industry-academic engagement. We have established a track record of advancing drug discovery/synthesis and launching new research initiatives on time and within budget. We continue to expand our skillsets and to invest in a knowledge-based drug discovery core within a dedicated academic medical center.

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REFERENCE:

- Drug Discovery & Delivery Core (DDDC). <https://www.creighton.edu/medicine/departments/biomedical-sciences/translational-hearing-center/coBRE-translational-hearing-center/drug-discovery-delivery-core> accessed 4/17/24
- Satish G. Agrawal, E Jeffrey North, Alekha K. Dash. Preformulation studies on two novel indole-2-carboxamides highly potent against nontuberculous mycobacteria. AAPS 2022

DDDC website

