Unlocking Macrocycles at Scale with ⁿGen: Integrated High-Throughput Synthesis and Generative AI

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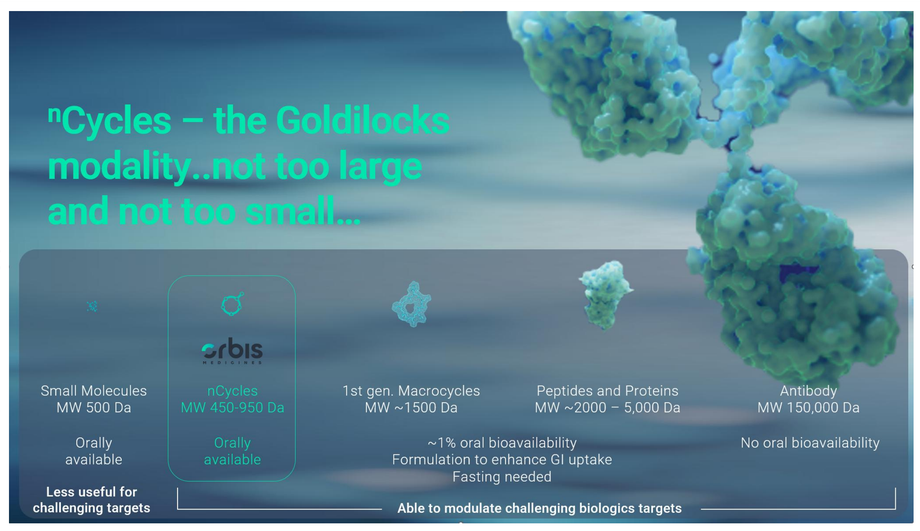
https://doi.org/10.17952/38EPS.2026.P333

Abstract

Small macrocycles represent a promising therapeutic modality against challenging proteins and protein-protein interactions (PPIs) often inaccessible to traditional small molecules, particularly in immunology, inflammatory- and cardiometabolic disease. However, their broader application has been hampered by synthetically complex, low-throughput production methods, limiting efficient exploration of chemical space, systematic SAR development, and the simultaneous optimization of key properties such as potency and permeability.

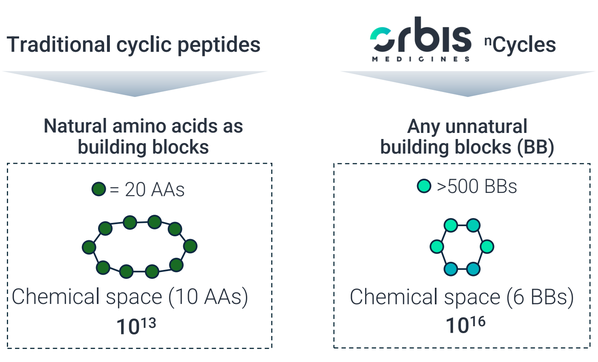
The ⁿGen platform developed by Orbis Medicines, based on seminal work at EPFL, addresses these limitations by enabling automated parallel synthesis of tens of thousands of drug-like macrocycles (ⁿCycles) within a few weeks. The platform supports large target-agnostic libraries, systematic chemical space exploration, and computationally *de novo*-designed target-focused libraries - all screened in parallel and high-throughput for activity and cellular function alongside biophysical characterization. The resulting proprietary datasets continuously fuel internally developed computational models that prioritize compounds for the next round of optimization.

Here, we illustrate the strength and versatility of the platform across three target classes: (1) an enzyme target, Thrombin, for which we computationally designed novel inhibitors from scratch [1]; (2) a PPI, where first-in-class, potent, orally active cytokine receptor antagonists were obtained within months; and (3) a GPCR relevant to obesity, for which - starting from a native linear ligand - we forged functionally active, low-nanomolar agonists with exquisite selectivity over closely related GPCRs and improved physicochemical properties while demonstrating in-vo permeability for key representatives. Together, these examples highlight the potential of Orbis Medicines' platform to unlock difficult target classes and enable the efficient discovery of novel, potent, selective, and orally available macrocyclic therapeutics.

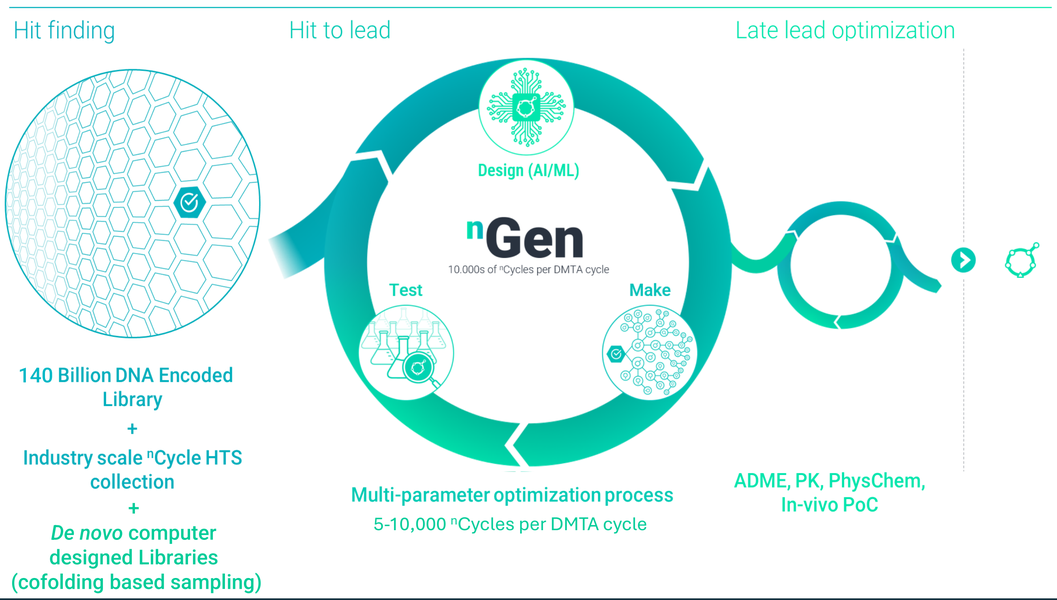


Orbis macrocycle "ⁿGen" platform

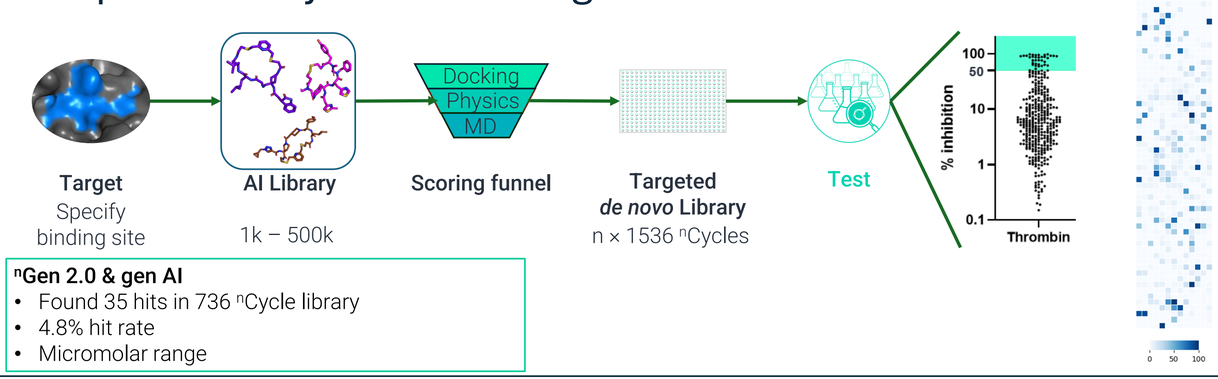
- Hits are identified by screening of either general (DEL and HTS) or target-specific *de novo* designed libraries (ligand-based and structure-based cofolding technologies)
- The Orbis ⁿGen platform – with its massive productivity of thousands of ⁿCycles (<1000 Da) monthly – is then applied for the rapid optimization of the macrocycle Hits



- Access to much larger chemical space
- High affinity despite smaller size
- Rapid optimization process
- More resistant to proteolytic degradation
- Oral bioavailability and cell permeability

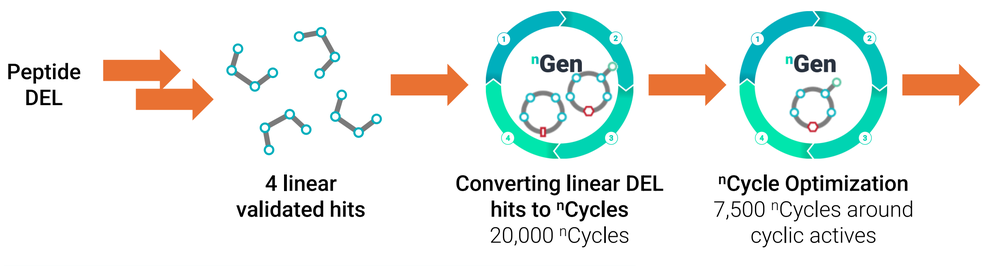


Computationally *de novo* designed Thrombin inhibitors



ⁿGen 2.0 & gen AI
- Found 35 hits in 736 ⁿCycle library
- 4.8% hit rate
- Micromolar range

Hit finding : First-in-class oral cytokine receptor antagonist



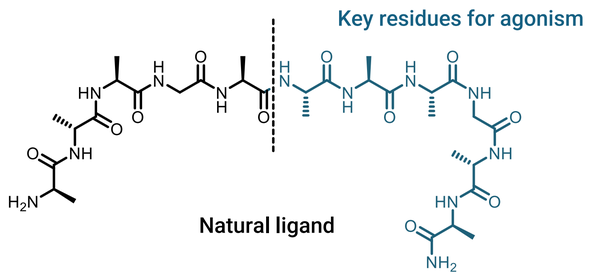
- Potent ⁿCycles with decent properties rapidly obtained
- A vast amount of SAR data generated for further optimization
- Numerous D-M-T-A cycles completed in 6 months

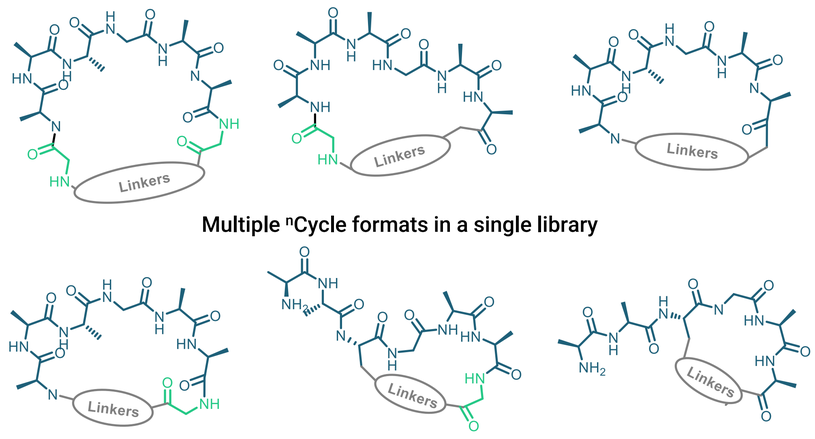
Case study: discovery of novel macrocyclic GPCR agonists (undisclosed target)

- We are targeting a GPCR relevant in treatment of obesity
- No orally available candidates in development

- A cyclic library was designed around the natural linear ligand
  - Cut down to **key residues** required for agonism
  - Introduce **unnatural amino acids**
  - Cyclize with **diverse linkers**

⇨ 10,680 ⁿCycles synthesized in the first library





Library 1 - 11,000 ⁿCycles
From linear to cyclic
ⁿGen
Potent (3 nM)
Selective (~20x)
Partial agonism

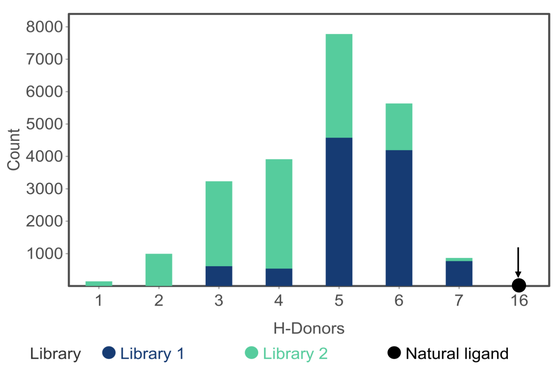
Library 2 - 12,000 ⁿCycles
Optimize potency & properties
ⁿGen
Potent (<1 nM)
Selective (~80x)
Full agonism

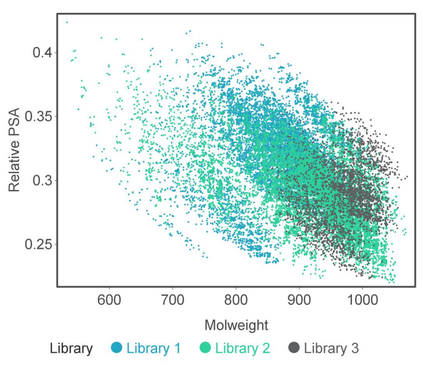
Library 3 - 3,000 ⁿCycles
Optimize stability
ⁿGen
Fine-tuning activity, permeability, selectivity
Addressing metabolic liabilities

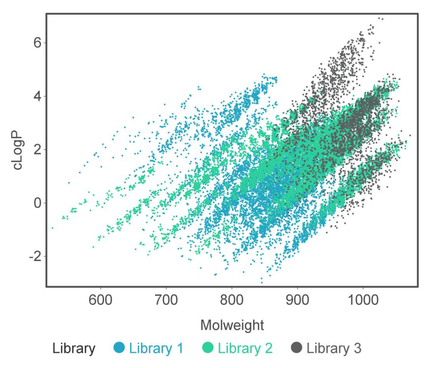
ⁿCycle	Target GPCR EC_{50} (nM)	x selective over GPCR 1	x selective over GPCR 2
ORB-xxxxx102	13	33	402
ORB-xxxxx291	3	83	1549
ORB-xxxxx023	93	271	583

Some key-representative ⁿCycles

- Several potent and selective ⁿCycles were identified. Minimal permeability was observed from library 1 hits in PAMPA and MDCK assays
- N-methylated and non-methylated amino acids were used in a combinatorial fashion to determine the optimal N-methylation pattern for activity, selectivity, and permeability
- Following libraries were constructed to improve potency, stability and physicochemical properties: reduction of polar surface area and number of hydrogen bond donors







Properties of focused libraries. They show vast improvements compared to the natural ligand with stepwise improvement in PSA/MW – a key metric for developing membrane permeable bRo5 compounds. 8,400 of 11,900 macrocycles have values between 0.2 and 0.3 A^2/Da and are thus in an optimal space ("Rule of 1/5": Möbitz H. , ChemMedChem. 2024 Mar 1;19(5): Design Principles for Balancing Lipophilicity and Permeability in beyond Rule of 5 Space).

In less than 6 months, we identified potent and selective GPCR agonists. This program is now available for partnering. Next steps focus on improving further permeability and advancing in vivo characterization. In parallel, the vast amount of proprietary data generated throughout the project feeds and strengthens our Data Science platforms and algorithms, accelerating future DMTA cycles and supporting every discovery programs at all stages (from Hit Finding up to Lead Optimization).

Acknowledgements

We would like to thank the entire Orbis Medicines team for their contributions to the projects depicted in this poster and to the macrocycle synthesis & screening platform. Physicochemical properties were calculated and plotted using DataWarrior. [1] : Manuscript in preparation.