De novo molecular design – From models to molecules

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Generative artificial intelligence (AI) is revolutionizing drug discovery by designing novel, synthetically accessible molecules with optimized pharmacological profiles [1]. These deep learning frameworks navigate vast chemical search spaces more efficiently than traditional methods like high-throughput screening, integrating molecular design, property prediction, and synthetic planning [2]. When coupled with high-throughput experimentation and late-stage functionalization, generative AI significantly compresses design-make-test cycles while minimizing material consumption (Figure 1) [3].

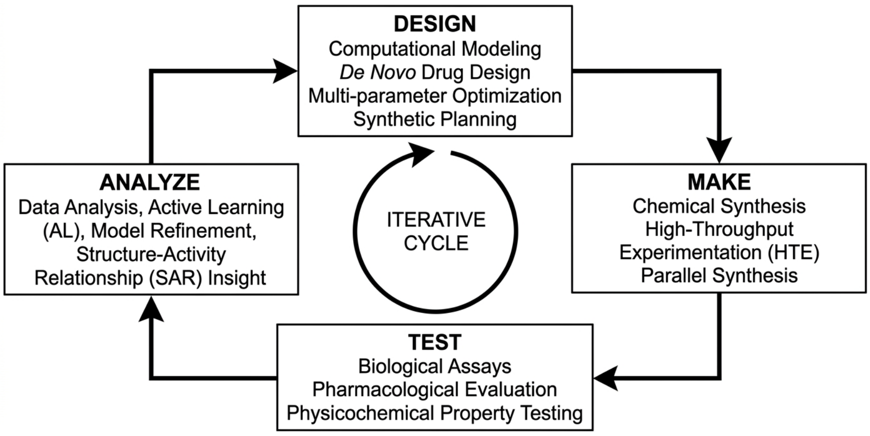

Figure 1. Schematic of the design-make-test-analyze (DMTA) cycle in drug discovery.

However, data scarcity remains a primary bottleneck for predictive accuracy. Active learning addresses this by enabling models to iteratively select the most informative experiments, maximizing the utility of limited experimental bandwidth and reducing the total number of cycles required to reach target performance [4].

Complementary advances in geometric deep learning further enhance model fidelity. By utilizing geometric graph neural networks that maintain translational and rotational equivariances, these models accurately predict reaction outcomes and molecular properties [5,6]. This predictive filtering ensures experimental efforts are focused on the most synthetically tractable candidates, streamlining hit-to-lead optimization and structure-activity relationship exploration.

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