From Model to Molecule: Rapid Discovery of Potent CDK2 Inhibitors Using Boltz-2

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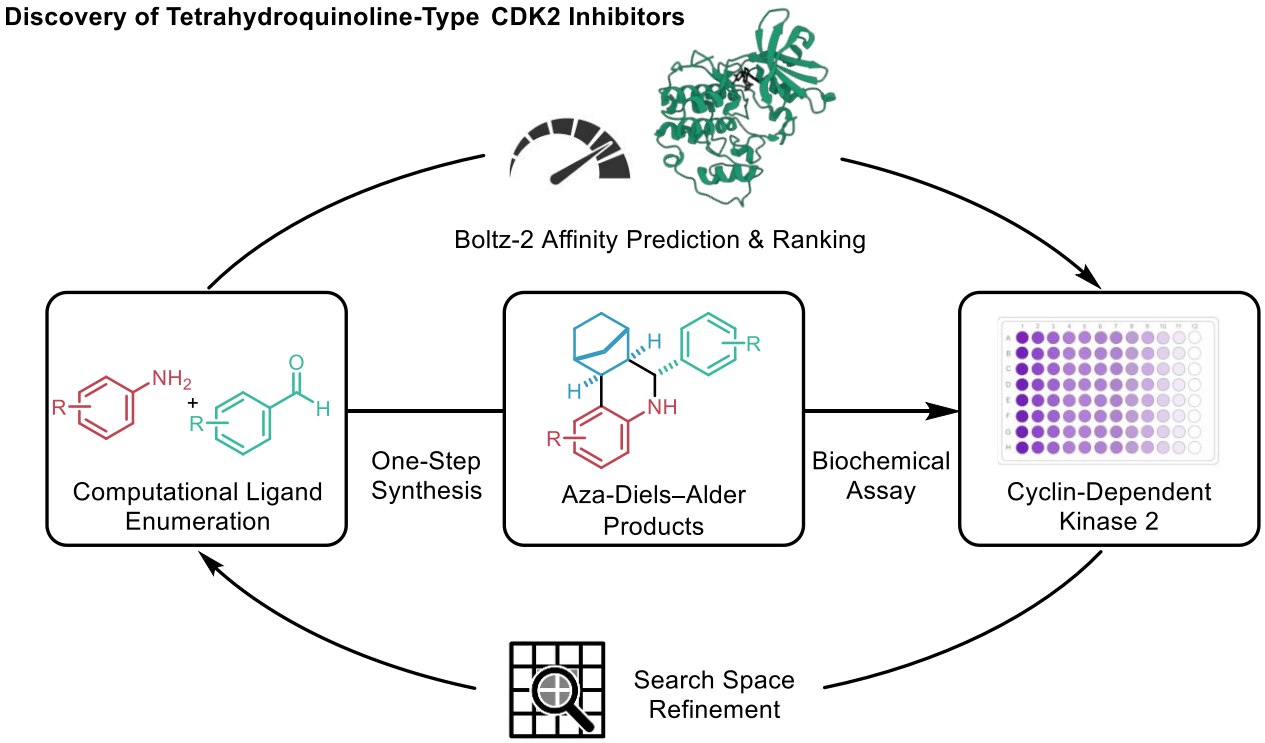

Abstract

Cyclin-dependent kinases (CDKs) are central regulators of cell-cycle progression and transcription, and their dysregulation is a hallmark of many human cancers.[1] Within this family, CDK2 has emerged as an attractive oncology target due to its distinct biological role and its potential to complement existing CDK4/6 therapies.[2] Despite sustained interest, the discovery of novel CDK2 chemotypes remains challenging, and only a limited number of inhibitors have progressed to the clinical stage, in part due to the time-consuming and highly iterative nature of conventional medicinal chemistry campaigns.

Recent advances in computer-aided drug discovery, particularly models capable of jointly predicting ligand–protein complex structures and binding affinities such as Boltz-2[3], promise to accelerate early discovery. However, their practical utility in real-world experimental campaigns remains insufficiently explored. Here, we present a fully integrated computational–experimental platform for the rapid identification of small-molecule kinase

inhibitors, with Boltz-2 serving as the primary prediction engine. We demonstrate the performance of this platform through the discovery of single-digit micromolar inhibitors of CDK2, and illustrate how model predictions can be leveraged to guide iterative ligand design.

Our workflow integrates virtual ligand enumeration, synthesis, and biochemical evaluation into a single standardized pipeline. A large virtual library (>10^6 compounds) is generated from simple, commercially available building blocks and filtered using common design principles for orally active molecules and compatibility with aqueous kinase assays. Promiscuous binders[4], potential covalent inhibitors, and low-solubility candidates are excluded prior to synthesis. Selected ligands are assembled via Aza-Diels–Alder multicomponent reactions to afford structurally diverse tetrahydroquinoline scaffolds in a single synthetic step. Under optimized conditions, many products precipitate upon aqueous workup, enabling straightforward isolation without chromatographic purification.

Ligand activity is quantified using miniaturized chemiluminescence-based kinase assays. Initial two-point inhibition measurements are followed by full IC_{50} determinations for prioritized candidates. Experimental inhibition data are compared with Boltz-2 affinity predictions and used to iteratively refine the computational search space.

Taken together, this platform establishes a rapid and scalable route from in silico prediction to biochemical validation, enabling efficient exploration of underexplored chemical space for CDK2 inhibition. Beyond CDK2, we anticipate that this approach will be broadly applicable to other kinases, aligning with larger community efforts such as Target 2035[5] to accelerate experimental ligand discovery.

Related Work

Pronounced antiproliferative effects on panels of cancer cell lines have previously been reported for structurally related tetrahydroquinolines.[6] Beyond these studies, more distantly related tetrahydroquinoline-type ligands have been proposed as potential allosteric binders of CDK2; however, these compounds have not been optimized into highly potent inhibitors, nor have they been evaluated within systematic structure–activity relationship campaigns.[7]

Boltz-2 has been benchmarked on selected experimental datasets, some of which are likely to overlap with its training data.[8] In contrast, independent validation in prospective experimental discovery campaigns, particularly on unseen ligand series, remains scarce for Boltz-2 and related ligand–protein affinity prediction models.

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