Structure-Kinetic Relationship Study of CDK8/CycC Specific Compounds and Beyond

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Target Information and Validation
Cyclin-dependent kinase 8 (CDK8) / cyclin C (CycC) complex

CDK module of the Mediator of transcription complex

Transcriptional regulator (targeting RNA Pol II CTD)

Potent oncogene
- involving β-catenin/wnt signaling in colon cancerogenesis
- linked to melanoma progression as histone kinase
- positive regulator of transcriptional activity (TGF-β/BMP pathway, Serum Response Pathway)

STAT1-phosphorylating kinase as means to regulate IFN response and control NK cell-mediated tumor surveillance
Target Information and Validation
Cyclin-dependent kinase 8 (CDK8) / cyclin C (CycC) complex

- First structure of human CDK8/CycC in complex with the deep-pocket binder sorafenib (BAY-43006, Bayer Pharma) solved in 2011

- Clinical success of sorafenib and imatinib (STI-571, Novartis Pharma AG) attributed to their deep pocket binding mode, slow binding kinetics and a long residence time to solve frequent problems of lead compounds such as
  - limited *in-vivo* efficacy
  - non-durable target inhibition

Goal: Rational engineering of compounds with long residence time similar to sorafenib. Still very challenging. In contrast to SAR, structure-kinetic-relationships (SKRs) are not well understood for most target families / binding modes.

Step 1: Library screen using the Proteros Reporter Displacement Assay for identification of fast and slow binders

Step 2: Kinetic profiling of hit and related compounds

Step 3: Combining kinetic with structural data via crystallization

Step 4: Summary of SKR

(1) Schneider, PNAS, 2013
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