## Proposed EC/sub-subclass

Not specified in the provided data

## Accepted name

Cyclin-dependent kinase 7

## Synonyms

CDK7; catalytic subunit of CDK-activating kinase (CAK)

## Phylogeny

CDK7 is a member of the cyclin-dependent kinase (CDK) family within the CMGC group of protein kinases. Orthologues occur from yeast to mammals, indicating an ancient, conserved role (Hunter & Manning, 2015; Malumbres, 2014). Throughout evolution the enzyme retained dual functionality: (i) activation of other CDKs that drive cell-cycle transitions and (ii) regulation of RNA polymerase II transcription as part of the TFIIH complex (Hunter & Manning, 2015).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Alexander, 2008)

## Cofactor Requirements

Mg²⁺ is essential for coordinating ATP and enabling phosphoryl transfer (Alexander, 2008).

## Substrate Specificity

CDK7 phosphorylates:  
• Activation-loop threonine residues of CDK1, CDK2, CDK4 and CDK6, enabling their full activity (Johnson et al., 2023).  
• Ser⁵ (and other serines) within the Y₁S₂P₃T₄S₅P₆S₇ heptad repeats of the RNA polymerase II C-terminal domain, promoting transcription initiation (Al-Rawi et al., 2023).  
• Additional transcription/processing factors such as SPT5, SF1 and p53 (Johnson et al., 2023; Al-Rawi et al., 2023).  
High-throughput profiling shows preference for Ser-Pro motifs and local structural elements that favour kinase docking (Johnson et al., 2023).

## Structure

CDK7 contains the canonical bilobal protein-kinase fold with an N-terminal β-sheet lobe and a predominantly helical C-terminal lobe. The ATP-binding cleft lies between the lobes, and a conserved catalytic Asp in the catalytic loop acts as the base. Activity requires phosphorylation of the activation (T-) loop (Lolli et al., 2004). In cells, CDK7 forms a heterotrimeric CAK complex with cyclin H and MAT1; cyclin H realigns catalytic motifs, whereas MAT1 stabilises the active conformation and influences substrate orientation (Düster et al., 2024).

## Regulation

1. Complex assembly – Binding to cyclin H and MAT1 is mandatory for proper folding and catalytic activation (Fisher, 2005).
2. Activation-loop phosphorylation – Dual phosphorylation of the T-loop stabilises the active state (Düster et al., 2024).
3. Feedback from DNA-damage signalling – CDK7-mediated activation of p53 leads to p53-dependent inhibition of CDK7, integrating the DNA-damage response with cell-cycle control (Fisher, 2017).

## Function

• Cell-cycle control: As the CAK catalytic subunit, CDK7 activates CDK1/2/4/6, thereby governing G1-S and G2-M transitions (Al-Rawi et al., 2023).  
• Transcription initiation: Within TFIIH, CDK7 phosphorylates RNA polymerase II CTD Ser⁵, enabling promoter clearance and transition to productive elongation (Aquino, 2022).  
• DNA-damage response: Phosphorylation of p53 and other factors links transcriptional regulation to genome-integrity checkpoints (Fisher, 2017).

## Inhibitors

The covalent ATP-competitive inhibitor THZ1 and related compounds selectively target CDK7, blocking phosphorylation of downstream CDKs and the RNA polymerase II CTD (Ramani, 2020).

## Other Comments

Because CDK7 coordinates cell-cycle progression and transcription, it is an attractive anticancer target. Inhibition disrupts both CDK activation and transcriptional programs in tumour cells (Pellarin et al., 2025). No specific disease-linked CDK7 mutations are detailed, but dysregulated activity is implicated in oncogenesis (Ramani, 2020).

## References

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