

# Targeting nuclear protein TDP-43 by cell division cycle kinase 7 inhibitors: A new therapeutic approach for amyotrophic lateral sclerosis

Rojas-Prats, E.  
Martinez-Gonzalez, L.  
Gonzalo-Consuegra, C.  
Liachko, N.F.  
Perez, C.  
Ramírez, D.  
Kraemer, B.C.  
Martin-Requero, Á.  
Perez, D.I.  
Gil, C.  
de Lago, E.  
Martinez, A.

## Abstract

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease with no known cure. Aggregates of the nuclear protein TDP-43 have been recognized as a hallmark of proteinopathy in both familial and sporadic cases of ALS. Post-translational modifications of this protein, include hyperphosphorylation, cause disruption of TDP-43 homeostasis and as a consequence, promotion of its neurotoxicity. Among the kinases involved in these changes, cell division cycle kinase 7 (CDC7) plays an important role by directly phosphorylating TDP-43. In the present manuscript the discovery, synthesis, and optimization of a new family of selective and ATP-competitive CDC7 inhibitors based on 6-mercaptapurine scaffold are described. Moreover, we demonstrate the ability of these inhibitors to reduce TDP-43 phosphorylation in both cell cultures and transgenic animal models such as *C. elegans* and Prp-hTDP43 (A315T) mice. Altogether, the compounds described here may be useful as versatile tools to explore the role of CDC7 in TDP-43 phosphorylation and also as new drug candidates for the future development of ALS therapies.

## Author keywords

ALS  
CDC7 inhibitors  
Drug discovery  
FTLD  
TDP-43