Selective DDR1 over DDR2 inhibitors from efficient screening and structure-guided design

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Abstract

Discoidin Domain Receptor 1 (DDR1) is an attractive target against renal fibrosis and cancer. A lean strategy involving limited screening combined with structure-guided optimization was employed for lead identification. Two screens were applied: (1) a focused library constructed by various computational methods and (2) the Roche DNA encoded library technology (DELT). A number of classes with excellent selectivity against both the closely related DDR2 kinase as well as the full kinome were derived using this approach. In particular, representatives from a spiroindolinone series exhibited DDR1 selectivity together with promising in vitro safety and favorable physicochemical and pharmacokinetic properties. One compound prevents collagen-induced activation of renal epithelial cells producing DDR1 and reduces tissue damage in a preclinical mouse model of Alport syndrome, a hereditary rare kidney disease.