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Protein phosphatase-1 as a target for antiviral small molecules against HIV-1 infections

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HIV-1 transcription is activated by Tat protein that recruits CDK9/cyclin T1 to TAR RNA. We previously showed that Tat also binds to protein phosphatase-1 (PP1) through the Q35VCF38 sequence and translocates PP1 to the nucleus. PP1 dephosphorylates CDK9 and activates HIV-1 transcription. We recently identified PP1-targeting small molecule, 1H4, that prevented HIV-1 Tat interaction with PP1 and inhibited HIV-1 gene transcription. Using the model of 1H4-PP1 complex we iteratively designed and synthesized follow-up libraries that were analyzed for the inhibition of HIV-1 transcription and toxicity. We obtained a tetrahydroquinoline derivative, 1E7, which inhibited phosphatase activity of PP1 and also disrupted the interaction of Tat with PP1. We further optimized 1E7 and obtained compound 1E7-03 that inhibited HIV-1 with low IC50, showed no toxicity when administered in mice. The 1E7-03 was also active in HIV-1 transgenic mice preventing death from acute lung inflammation induced by LPS injection. The LPS administration led to neutrophil and macrophages recruitment to the lungs where HIV-1 expression in the lung macrophages prevented neutrophil clearance. Injection of 1E7-03 reduced both macrophages and neutrophil accumulation in the lungs likely due to the reduction of HIV-1 expression. We further analyzed stability of 1E7-03 compound and identified its major metabolites. We also developed 1E7-03 analogs that had improved stability and showed similar activity to the parental compound. Our study shows that PP1 can serve as a target for development of novel therapeutics against HIV-1 to target HIV-1 expression in lungs and potentially other organs.

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