INTRODUCTION

G1 phase of the cell cycle is critical for the regulation of transcriptional events. CDK9 (Cyclin T1) is a key regulator of transcription in eukaryotic cells and has been implicated in the control of cell cycle progression and cell transformation. CDK9 interacts with RNA polymerase II (RNAP II) to phosphorylate the C-terminal domain (CTD) of RNAP II, which is essential for transcription initiation and elongation. CDK9 is activated by cyclin T1, and its activity is regulated by phosphorylation at several distinct sites. CDK9 inhibitors (CDK9i) have shown promise in preclinical models and have been explored as potential antitumor agents.

RESULTS

We have developed a focused library of potent and selective CDK9 inhibitors (CDK9i-1) that are highly efficacious in vitro and in vivo. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation resulting in decreases in MYC, MCL-1 and Cyclin E protein levels. The lead CDK9i-1 is a potent and selective CDK9 inhibitor with high potency and selectivity for CDK9.

CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53. CDK9i-1 inhibits cell proliferation independent of CDK4/6. CDK9i-1 inhibits RNAP II CTD Ser2 phosphorylation in palbociclib-resistant MCF7 cells resulting in a decrease of pRNAP II and its downstream target p53.

SUMMARY

Our results suggest that CDK9 is a potential new target for the treatment of tumor types that have intrinsic or acquired resistance to CDK9 inhibitors.