

Characterization of ERK Docking Domain Inhibitors that Induce Apoptosis by Targeting Rsk-1 and Caspase-9

Sarice R Boston, Rahul Deshmukh, Scott Strome,
U Deva Priyakumar, Alexander D MacKerell Jr, Paul Shapiro

1. *Correspondence: pshapiro@rx.umaryland.edu, Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland 20 N. Pine St. Baltimore, MD 21201 USA
2. Center for Computational Natural Sciences and Bioinformatics (CCNSB), International Institute of Information Technology (IIIT-H) Gachibowli, Hyderabad 500032, India,

Journal: *BMC Cancer* 2011, **7**

DOI: 10.1186/1471-2407-11-7, Publication Date : 10th January 2011

Cite this article as: Boston et al

Abstract:

Background: The extracellular signal-regulated kinase-1 and 2 (ERK1/2) proteins play an important role in cancer cell proliferation and survival. ERK1/2 proteins also are important for normal cell functions. Thus, anti-cancer therapies that block all ERK1/2 signaling may result in undesirable toxicity to normal cells. As an alternative, we have used computational and biological approaches to identify low-molecular weight compounds that have the potential to interact with unique ERK1/2 docking sites and selectively inhibit interactions with substrates involved in promoting cell proliferation.

Methods: Colony formation and water soluble tetrazolium salt (WST) assays were used to determine the effects of test compounds on cell proliferation. Changes in phosphorylation and protein expression in response to test compound treatment were examined by immunoblotting and in vitro kinase assays. Apoptosis was determined with immunoblotting and caspase activity assays.

Results: In silico modeling was used to identify compounds that were structurally similar to a previously identified parent compound, called 76. From this screen, several compounds, termed 76.2, 76.3, and 76.4 sharing a common thiazolidinedione core with an aminoethyl side group, inhibited proliferation and induced apoptosis of HeLa cells. However, the active compounds were less effective in inhibiting proliferation or inducing apoptosis in non-transformed epithelial cells. Induction of HeLa cell apoptosis appeared to be through intrinsic mechanisms involving caspase-9 activation and decreased phosphorylation of the pro-apoptotic Bad protein. Cell-based and in vitro kinase assays indicated that compounds 76.3 and 76.4 directly inhibited ERK-mediated phosphorylation of caspase-9 and the p90Rsk-1 kinase, which phosphorylates and inhibits Bad, more effectively than the parent compound 76. Further examination of the test compound's mechanism of action showed little effects on related MAP kinases or other cell survival proteins.

Conclusion: These findings support the identification of a class of ERK-targeted molecules that can induce apoptosis in transformed cells by inhibiting ERK-mediated phosphorylation and inactivation of pro-apoptotic proteins.