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Development of an Improved Guanidine-Based Rac1 Inhibitor with in vivo Activity against Non-Small Cell Lung Cancer

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Abstract

The Rho GTPase Rac1 is involved in the control of cytoskeleton reorganization and other fundamental cellular functions. Aberrant activity of Rac1 and its regulators is common in human cancer. In particular, deregulated expression/activity of Rac GEFs, responsible for Rac1 activation, has been associated to a metastatic phenotype and drug resistance. Thus, the development of novel Rac1-GEF

interaction inhibitors is a promising strategy for finding new preclinical candidates. Here, we studied structure-activity relationships within a new family of N,N'-disubstituted guanidine as Rac1 inhibitors. We found that compound 1D-142, presents superior antiproliferative activity in human cancer cell lines and higher potency as Rac1-GEF interaction inhibitor in vitro than parental compounds. In addition, 1D-142 reduces Rac1-mediated TNFα-induced NF-κB nuclear translocation during cell proliferation and migration in NSCLC. Notably, 1D-142 allowed us to show for the first time the application of a Rac1 inhibitor in a lung cancer animal model.

Keywords: N,N′-disubstituted guanidines; Rac1 inhibitors; lung cancer; protein-protein interaction inhibitors.

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