

P011 Design and Characterisation of a Small Molecule Inhibitor Specific for PTEN

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Tensin homologue deleted on chromosome 10 (PTEN) is a major tumor suppressor protein that dephosphorylates membrane phosphatidylinositol lipids such as PtdIns(3)P, PtdIns(3,4)P₂ and PtdIns(3,4,5)P₃, thus, counteracting the action of PI3-kinases and its downstream targets. Therefore, PTEN is an important regulator of insulin dependent signaling and its loss or impairment results in an anti-diabetic impact, which led to the suggestion that PTEN could be an important target for drugs against type II diabetes. Here we report the design and validation of a small molecule inhibitor of PTEN, a vanadium complex that fits into the enzyme's wide catalytic site cleft. The compound was found to increase cellular PtdIns(3,4,5)P₃/ PtdIns(3,4)P₂ levels, phosphorylation of Akt and glucose uptake in adipocytes at nanomolar concentrations. *In vitro* phosphate release assays show that the compound is highly specific for PTEN when compared to other cysteine based phosphatases. The findings presented here demonstrate the applicability of a novel and specific chemical inhibitor against PTEN, in research and drug development.