

**Supplementary Figure 9.** *Comparison of pathway inhibitor action on intracellular ROS production between cell lines.* To be assured that the action of the pathway inhibitors on reducing the intracellular ROS response to serum deprivation in the CF10 cells was not due to the lack of PrP expression in these cells, two further PrP expressing cell lines were tested; Neuro2a (N2a, murine neuroblastoma) and OBL-21 (murine olfactory bulb). The cell lines were assayed for ROS production in response to serum deprivation with and without a selection of the pathway inhibitors used in the main text and the data is presented relative to viability. Two-way ANOVA with Bonferroni's secondary analysis of the cell lines and inhibitors showed that only DPI inhibition of the NADPH oxidase family of enzymes was significantly different in the CF10 cells compared with the N2a and OBL-21 cells ( $F = 3.264$ ,  $p = 0.043$ ,  $n = 4$ ). This might indicate an endogenous PrP effect on NADPH oxidase signalling that is not involved in the CF10 reaction to PrP23-89. The conditions found to most significantly reduce ROS production in response to serum deprivation (inhibition of trafficking and MEK1/2) were not significantly different between the cell lines.

