Antioxidants counterbalance the harmful effects of reactive oxygen species and therefore may be useful for treatment of oxidative stress-related pathologies including neurodegenerative diseases. 4-methylcoumarins preserve many biological activities of the coumarins and lack most of their side effects. The antioxidant activity of these compounds have recently been studied by many research groups and there are some reports on the antioxidant properties of 7,8-diacetoxy-4-methylcoumarins. In this study, we assessed the neuroprotective activity of several synthetic derivatives of 4-methylcoumarins containing 7,8-diacetoxy as well as 7-acetoxy and 6,5-diacetoxy moieties. We used a neuronal cell model in which, apoptosis is induced by hydrogen peroxide in cultured PC12 cells. This model uses conditions that are similar to the oxidative stress induced damage in neurodegenerative diseases. PC12 cells were preincubated with different concentrations of test compounds and then hydrogen peroxide was added to induce apoptosis. Cell viability and the capacity of the compound to prevent cell death was measured by the MTT assay. Antioxidant activity of test compounds was also measured by DPPH radical scavenging and ferric reducing antioxidant power (FRAP) assays. 7,8-Diacetoxy-4-methylcoumarins with different substitutions at C3 position (including ethoxycarbonylethyl and ethoxycarbonylmethyl moiety) showed moderate antioxidant activity in FRAP and DPPH assays but most of them significantly inhibited PC12 cell damage at low micromolar concentrations. 7-Acetoxy and 6,7-diacetoxy derivatives did not show activity in cell-free and cell-based models. In conclusion, these data show that ortho-diacetoxy derivatives of 4-methylcoumarins have a high potential for discovery of novel neuroprotective molecules for management of neurodegenerative disease.