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Sub-Theme: Neurodegenerative Disorders: Novel Therapeutic Strategies and Molecular Targets in Alzheimer's and Parkinson's Disease

Neuroprotective properties of arylpiperazine-sulphonamides in in vitro models of Parkinson's disease

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Introduction: Parkinson's disease (PD) is a neurodegenerative disease characterised by the degeneration of dopaminergic neurons in the substantia nigra. While incompletely understood, mitochondrial dysfunction, oxidative stress, neuroinflammation and α-synuclein accumulation through impaired protein clearance have been implicated in PD pathogenesis. Current treatments for symptom management do not target the underlying pathophysiology, thus provide no cure or prevent disease progression. Compounds with arylpiperazine moieties have been shown to possess neuroprotective properties and may provide a valuable treatment for PD. As such, this programme of work sought to investigate the neuroprotective potential of novel arylpiperazine-sulphonamides in an in vitro model of PD.

Methods: Retinoic acid differentiated SHSY5Y cells were incubated with neurotoxins that cause mitochondrial dysfunction (MPP+) and impaired protein clearance (lactacystin) to model PD in vitro. MTT assays were used to assess cell viability following 24 hours of co-incubation with neurotoxins at IC50 concentrations, and compounds 4206, 4207, 4298 and 4133 at concentrations ranging from 0-10µM.

Approach for statistical analysis: One-way ANOVAs with Dunnett's multiple comparisons were used to compare the effects of each compound at a range on concentrations with a toxin-treated control group.

Results and conclusions: Treatment with compounds 4206, 4207, 4298 and 4133 improved cell viability by 58.25% ($p<0.05$), 78.95% ($p<0.001$), 75.25% ($p<0.01$) and 82.55% ($p<0.001$), respectively, at the optimum doses, compared to MPP+ treated cells. Compounds 4207 and 4133 were also successful at improving cell viability by 99% ($p<0.01$) and 80% ($p<0.01$), respectively, compared to lactacystin treated cells. That these compounds display neuroprotective properties against multiple pathogenic mechanisms is extremely encouraging for their potential as treatments in neurodegenerative disease, since these mechanisms occur simultaneously and can act on one another. Additional work to further examine the neuroprotective properties and investigate the mechanisms of action of these compounds will be completed in due course.