

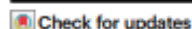


An optimized Nurrl agonist provides disease-modifying effects in Parkinson's disease models

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The nuclear receptor, Nurrl, is critical for both the development and maintenance of midbrain dopamine neurons, representing a promising molecular target for Parkinson's disease (PD). We previously identified three Nurrl agonists (amodiaquine, chloroquine and glafenine) that share an identical chemical scaffold, 4-amino-7-chloroquinoline (4A7C), suggesting a structure-activity relationship. Herein we report a systematic medicinal chemistry search in which over 570 4A7C-derivatives were generated and characterized. Multiple compounds enhance Nurrl's transcriptional activity, leading to identification of an optimized, brain-penetrant agonist, 4A7C-301, that exhibits robust neuroprotective effects in vitro. In addition, 4A7C-301 protects midbrain dopamine neurons in the MPTP-induced male mouse model of PD and improves both motor and non-motor olfactory deficits without dyskinesia-like behaviors. Furthermore, 4A7C-301 significantly ameliorates neuropathological abnormalities and improves motor and olfactory dysfunctions in AAV2-mediated α -synuclein-overexpressing male mouse models. These disease-modifying properties of 4A7C-301 may warrant clinical evaluation of this or analogous compounds for the treatment of patients with PD.

Parkinson's disease (PD), affecting 2–3% of the population over the age of 65, is the second most common neurodegenerative disorder, after Alzheimer's disease^{1–3}. Selective degeneration of midbrain dopamine neurons (mDANs) in the substantia nigra and neurotoxic α -synuclein (α Syn) accumulation and aggregation in Lewy bodies are hallmark pathological features of PD. Manifestation of PD is thought to be caused by the combined action of genetic and environmental factors via multiple interacting pathways including mitochondrial dysfunction, oxidative stress, neuroinflammation, and dysregulated protein

degradation/autophagy^{4–7}. Presently, dopamine (DA)-replacement therapy (e.g., L-DOPA) is the gold standard treatment. While it significantly improves PD patients' quality of life, the therapeutic window without unacceptable side effects, such as dyskinesia, and the degree of benefit both decrease over time^{8,9}, and there is no treatment that can halt or slow disease progression. Therefore, there is a great unmet need to develop novel disease-modifying treatment for PD^{10,11}.

During the last several decades, mDANs' transcriptional regulatory cascades have been comprehensively studied¹². Two major

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