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3-Hydroxypyridin-4-one based derivatives as promising neuroprotective agents for Parkinson's disease

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Abstract

Background: Parkinson's Disease (PD) is a multifactorial, complex and progressive neurodegenerative disease, characterized by the degeneration of dopaminergic neurons in the *substantia nigra pars compacta* [1,2]. Several pathophysiological mechanisms are involved in PD, namely Lewy bodies formation, mitochondrial dysfunction, neuroinflammation, oxidative stress and iron accumulation within the brain [3]. Iron triggers ferroptosis, a form of cell death characterized by uncontrolled lipid peroxidation, glutathione (GSH) depletion and decreased glutathione peroxidase 4 (GPx4) activity [4]. The drugs currently available to treat PD predominantly aim to relieve symptoms [5]. Therefore, there is an urgent demand for an effective treatment capable to stopping or slowing the disease progression. **Objective:** The main goal of this study was to evaluate, *in vitro*, the cytotoxicity and the neuroprotective effects of a small library of 3-hydroxypyridin-4-one based derivatives. **Methods:** Differentiated SH-SY5Y cells (dopaminergic phenotype) were used as *in vitro* model. The compounds' cytotoxicity was evaluated, 24h after exposure, by the neutral red uptake and resazurin reduction assays, to select the non-cytotoxic concentrations. To evaluate the potential neuroprotective effects of the compounds, cells were exposed for 24h to i) ferric nitrilotriacetate (FeNTA), a ferric (Fe^{3+}) iron aggressor, ii) *tert*-butyl hydroperoxide (*t*-BHP), an organic peroxide capable of inducing oxidative stress-mediated cell death, or iii) (1S,3R)-RSL3 (RSL3), a ferroptosis inducer that acts by inhibiting GPX4. The exposures were performed in the absence or presence of the test compounds. **Results:** In general, the compounds showed a safe cytotoxic profile for concentrations up to 5 μM. Noteworthy, several derivatives showed significant, concentration-dependent protective effects against *t*-BHP, FeNTA and RSL3, highlighting their promising neuroprotective effects. **Conclusions:** In conclusion, the 3-hydroxypyridin-4-one based derivatives demonstrated a multitarget mode of action, highlighting their potential as promising neuroprotective agents for PD treatment.

Keywords: Parkinson's disease; dopamine; ferroptosis; oxidative stress; hydroxypyridin-4-ones

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References

1. Simon, D.K.; Tanner, C.M.; Brundin, P. Parkinson's disease epidemiology, pathology, genetics, and pathophysiology. *Clin Geriatr Med* **2020**, 36, 1-12.
2. Raza C.; Anjum R.; Shakeel, N.U.A. Parkinson's disease: Mechanisms, translational models and management strategies. *Life Sciences* **2019**, 226, 77-90.
3. Kouli, A.; Torsney, K.M.; Kuan, W.L. Parkinson's disease: etiology, neuropathology, and pathogenesis. In *Parkinson's Disease: Pathogenesis and Clinical Aspects*, 2nd ed.; Stoker, T.B., Greenland, J.C., Eds.; Publisher: Brisbane, Australia, **2018**; Section 1.
4. Moreau, C.; Duce, A.J.; Rascol, O.; Devedjian, J.C.; Berg, D.; Dexter, D.; Cabantchik, Z.l.; Bush, A.I.; Devos, D. Iron as a therapeutic target for Parkinson's disease. *Mov Disord* **2018**, 33, 568-574.
5. Dong, J.; Yanhua, C.; Song, L.; Weidong, L. Current pharmaceutical treatments and alternative therapies of Parkinson's disease. *Curr Neuropharmacol* **2016**, 14, 339-355.