Scientific Letters

Poster Communication 20

Evaluation of novel xanthene derivatives as potential neuroprotective agents for Alzheimer's disease

Inês Costa [1,2,3,*], Tiago Gonçalves [1,2,4], Diana Resende [3,4,5], Daniel José Barbosa [6,7], Maria Emília Sousa [3,5] and Renata Silva [1,2]

[1] i4HB Associated Laboratory - Institute of Health and Bioeconomy, Faculty of Pharmacy, University of Porto (FFUP), Porto, Portugal
[2] UCIBIO - Applied Molecular Biosciences Unit, Toxicology Laboratory, FFUP, Porto, Portugal
[3] CIIMAR - Interdisciplinary Centre for Marine and Environmental Research, Leixões Cruise Terminal, Matosinhos, Portugal
[4] ICBAS - Abel Salazar Institute of Biomedical Sciences, University of Porto, Porto, Portugal
[5] Laboratory of Organic and Pharmaceutical Chemistry, Department of Chemical Sciences, FFUP, Porto, Portugal
[6] Associate Laboratory i4HB - Institute for Health and Bioeconomy, University Institute of Health Sciences - CESPU, Gandra, Portugal
[7] UCIBIO - Applied Molecular Biosciences Unit, Translational Toxicology Research Laboratory, University Institute of Health Sciences (1H-TOXRUN, IUCS-CESPU), Gandra, Portugal

* Correspondence: inessilvacosta@hotmail.com

Abstract

Background: Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder characterized by the accumulation of amyloid-beta (Aβ) plaques, hyperphosphorylated Tau tangles, and increased oxidative stress, among other pathological features. Despite being the leading cause of dementia, AD remains inadequately treated, as current therapies offer limited efficacy [1, 2]. With global cases projected to more than triple by mid-century, there is a pressing need for next-generation disease-modifying therapies targeting these fundamental pathological mechanisms. Xanthenes, oxygen-containing tricyclic heterocycles with a dibenzo[b,e]pyran scaffold, have emerged as promising neuroprotective agents. Their ability to modulate neurodegenerative processes highlights their therapeutic potential in AD [2, 3]. **Objective:** This study aimed to synthesize xanthene derivatives incorporating dopamine and levodopa moieties (Figure 1), containing the catechol group, a pharmacophoric feature associated with neuroprotection [4], and to evaluate their cytotoxicity and neuroprotective effects. **Methods:** Eight xanthene derivatives incorporating dopamine and levodopa moieties were synthesized via condensation reactions with carboxylic acids (structures confirmed by nuclear magnetic resonance spectroscopy). Their cytotoxicity (0–25 μM) was evaluated in SH-SY5Y cells differentiated into a cholinergic phenotype, using the neutral red (NR) uptake and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction assays. Neuroprotective potential was assessed against *tert*-butyl hydroperoxide (*t*-BHP)-induced oxidative stress, using a reactive oxygen/nitrogen species (ROS/RNS)-sensitive fluorescent probe and the NR uptake assay. **Results:** All synthesized xanthene derivatives were successfully obtained, structurally characterized, and were non-cytotoxic at concentrations up to 10 μM. All compounds markedly attenuated *t*-BHP-induced oxidative stress (reduced ROS/RNS generation and/or significant decrease in *t*-BHP-induced cell death), and their protective effects were not reversed by the Nrf2 inhibitor ML385, indicating an Nrf2-independent mechanism. **Conclusions:** These findings establish xanthene derivatives as potent oxidative stress modulators, although additional studies are needed to evaluate their efficacy against other AD hallmarks. Elucidating these broader mechanistic targets will be essential to validate their potential as multitarget drug candidates for AD therapy.

Keywords: Alzheimer's disease; xanthene derivatives; neuroprotection

Acknowledgments/Funding

This work was supported by national funds from FCT-Fundação para a Ciência e a Tecnologia, I.P., in the scope of the Research Unit on Applied Molecular Biosciences–UCIBIO (projects UIDP/04378/2025 and UIDB/ 04378/2025), the Associate Laboratory Institute for Health and Bioeconomy–i4HB (project LA/P/0140/2025), and the project UID/50006/2025 (DOI 10.54499/UID/50006/2025 - Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos). Inês Costa is supported by a PhD fellowship from FCT (2023.04980.BD).

References

1. Monteiro, A. R. et al. Alzheimer's disease: Insights and new prospects in disease pathophysiology, biomarkers and disease-modifying drugs. *Biochem Pharmacol* **2023**, *211*, 115522, doi:10.1016/j.bcp.2023.115522.
2. Maia, M. et al. Xanthenes in medicinal chemistry - Synthetic strategies and biological activities. *Eur J Med Chem* **2021**, *210*, 113085, doi:10.1016/j.ejmech.2020.113085.
3. Ghahsare, A.G. et al. Structure-bioactivity relationship study of xanthene derivatives: A brief review. *Curr Org Synth* **2019**, *16*, 1071–1077, doi:10.2174/1570179416666191017094908.
4. Velander, P. et al. Catechol-containing compounds are a broad class of protein aggregation inhibitors: Redox state is a key determinant of the inhibitory activities. *Pharmacol Res* **2022**, *184*, 106409, doi:10.1016/j.phrs.2022.106409.