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Investigating the multi-target potential for complex diseases of the alkaloid-containing pyrrolo[2,1-*a*]isoquinoline scaffold

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Neurodegenerative disorders and cancer constitute a public health concern due to the growing incidence and lack in effective therapies. For these multifactorial diseases, the multitarget approach appears as promising strategy for the search of new drug candidates. Diverse isoquinoline alkaloids showed a variety of pharmacological activities, including anticancer and antiviral activities, as well as inhibition of efflux pumps responsible for multidrug resistance (MDR) [1, 2].

In recent years, we synthesized and investigated the medicinal chemistry of several derivatives of 1-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (1-Ph-DHPIQ), that is the scaffold of the alkaloid lamellarins I, which carry out in the C2 position the aldehyde group and related imino adducts, as well as carboxylate groups (COOH, COOEt), nitrile (CN) and Mannich bases (i.e., morpholinomethyl derivatives). Some fifty newly synthesized compounds were assayed for their cytotoxic/antiproliferative activity against diverse cancer cell lines, including some MDR tumors, and against targets related to Alzheimer disease (AD), such as cholinesterases (ChEs), monoamine oxidases (MAOs) and amyloid-β (Aβ) aggregation [3] (Fig. 1). The results from our SAR, in-silico docking and hit-to-lead optimization studies will be presented and discussed.

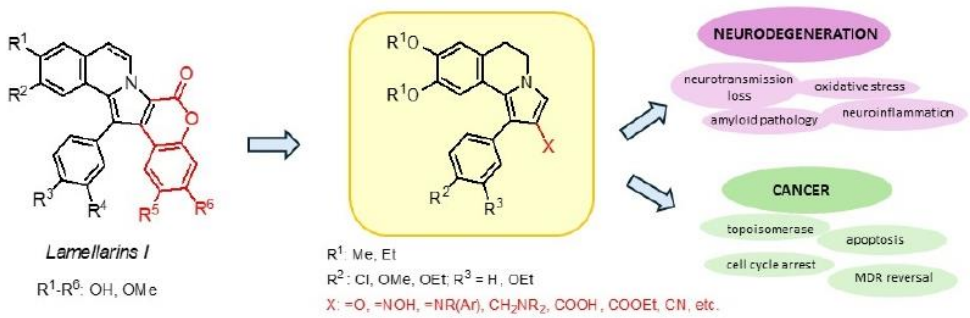

Figure 1. Main targets and biological activities of lamellarins I and synthetic 1Ph-DHPIQ derivatives.

[1] M.D. Matveeva, R. Purgatorio, L.G Voskressensky, C.D Altomare, *Future Med. Chem.,* **2019**, 11(20), 2735–2755.
[2] A.A. Nevskaya, R. Purgatorio, T.N. Borisova, A. V. Varlamov, *et al*. *Pharmaceuticals* **2024**, *17*, 539.
[3] A.A. Nevskaya, L.V. Anikina, R. Purgatorio, M. Catto, *et al*., *Molecules* **2021**, *26*, 359.