

NOVEL BENZOXATHIINE-BASED PROTEASOME ACTIVATORS WITH ANTI-AGEING AND NEUROPROTECTIVE ACTIVITY

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Ageing is a natural, unavoidable process characterized by a progressive deterioration of physiological function occurring in almost all organisms. With age, cells accumulate damaged, misfolded, cross-linked, and aggregated proteins leading to an imbalance in proteostasis equilibrium. Proteasome is one of the main intracellular proteolytic machineries that plays a pivotal role in the maintenance of protein homeostasis (proteostasis). This multi-catalytic enzymatic complex participates in almost all cellular functions through the degradation of normal, damaged or non-functional proteins. Proteasome has been shown to malfunction during ageing and age-related diseases. Thus, its activation constitutes a promising strategy for the deceleration of organismal ageing and the progression of neurodegenerative diseases such as Alzheimer's and Huntington's¹.

Despite the pivotal role of the proteasome, the research towards the discovery of small molecules acting as structural proteasome activators is still at its infancy. Towards this aim, our group has developed a novel class of bio-inspired hybrid compounds possessing proteasome activating properties². In the context of the present study, novel benzoxathiine bioisosteres of Vitamin E bearing five-membered heterocyclic pharmacophores were designed and synthesized². The new analogues were evaluated for their ability to activate purified 20S proteasome *in vitro* through direct interaction. The most potent structural activator conferred amelioration of healthspan *in vitro* in human primary fibroblasts and *in vivo* in *C. elegans*. In addition, it resulted to the extension of lifespan in *C. elegans* thus, indicating a very promising anti-ageing agent. Finally, its neuroprotective properties were also evaluated with encouraging results.

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References

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- 2) EP3761950A1, "Bioinspired proteasome activators with antiageing activity". Applicant: Ioulia and Irene Tseti Pharmaceutical Laboratories SA. Inventors: Koufaki M., Calogeropoulou T., Chondrogianni N., Papahatjis D., Gonos E., Fotopoulou T., Prousis K., Chazapi E.