EFMC-YMCS
Young Medicinal Chemists' Symposium
Zagreb, Croatia
September 7-8, 2023

BOOK OF ABSTRACTS

Organised by

EFMC

HKD 1926

EFMC Young Scientists Network

Zagreb, Croatia
September 7-8, 2023
www.efmc-ymcs.org

HITTING A NEW COMBINATION OF BIOLOGICAL TARGETS TO COPE WITH ALZHEIMER'S DISEASE

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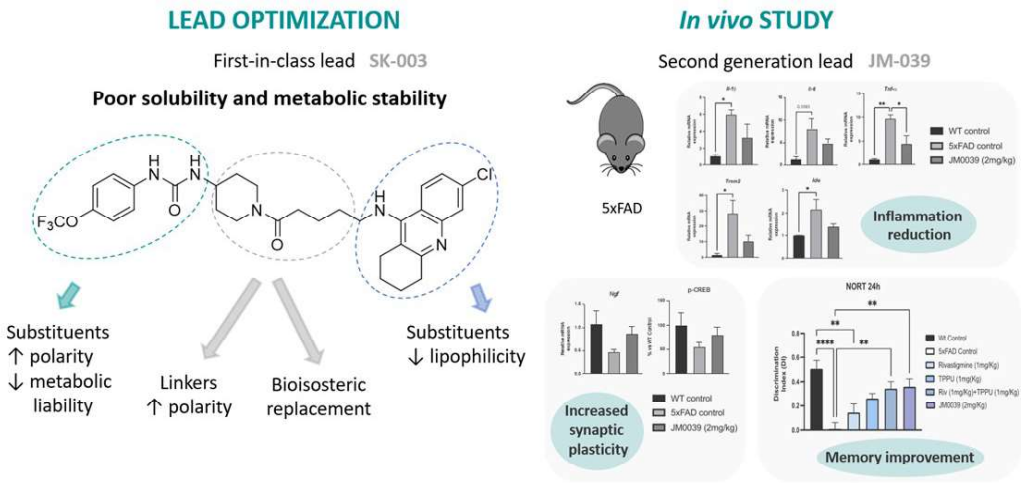
Alzheimer's disease (AD) is a dire unmet medical need, in part due to its multifactorial nature, which makes very challenging the development of efficacious drugs. Thus, new therapeutic approaches modulating multiple biological targets with a key pathogenic role are necessary. In this context, our group recently reported the discovery of a novel class of dual inhibitors of the enzymes soluble epoxide hydrolase (sEH) and acetylcholinesterase (AChE) [1], with a multitarget profile *in vitro* and beneficial *in vivo* effects against neuroinflammation and memory impairment. Although the lead compound showed well-balanced nanomolar potencies at both targets, good blood-brain barrier permeability and no cytotoxicity, its suboptimal solubility and metabolic stability might hamper its applicability for the treatment of AD. Here we report a lead optimization campaign, aiming to achieve more favourable DMPK properties, while retaining the high dual potencies and brain permeation of the initial lead. To this end, we have explored the effects of the introduction of different polar substituents in diverse positions of the molecule of the first-generation lead. Chronic oral administration of a low dose (2 mg/kg) of the optimized lead (JM-039) to a transgenic mouse model of AD leads to beneficial effects on cognition and biological markers of neuroinflammation and synaptic plasticity. Thus, JM-039 emerges as a promising anti-AD drug candidate, able to address the early disease mechanisms.



* Funding from Sociedad Española de Química Terapéutica (SEQT) with the "Ramon Madroñero" award from the "XXI Convocatoria de Premios para Investigadores Noveles de la SEQT" is gratefully acknowledged.

References

1) Codony, S.; Pont, C.; et al. Discovery and In Vivo Proof of Concept of a Highly Potent Dual Inhibitor of Soluble Epoxide Hydrolase and Acetylcholinesterase for the Treatment of Alzheimer's Disease. J. Med. Chem. 2022, 65, 4909–4925.