Discovering a potent NMDA receptor antagonist against Alzheimer’s Disease: from the initial design stage to *in vivo* testing.

A. L. Turcu1, 4, C. Griñán-Ferré2, R. Leiva1, J. Companys-Alemany2, L. León-García3, E. Gratacòs-Batlle4, J. Brea5, M. I. Loza5, F. X. Sureda3, M. Pallàs2, D. Soto4, S. Vázquez1

1 Laboratori de Química Farmacèutica (Unitat Associada al CSIC), Facultat de Farmàcia i Ciències de l’Alimentació and Institut de Biomedicina (IBUB), Universitat de Barcelona, Av. Joan XXIII, 27-31, Barcelona, E-08028, Spain. aturcu@ub.edu

2 Unitat de Farmacologia, Facultat de Farmàcia i Ciències de l’Alimentació and Institut de Neurociències, Universitat de Barcelona, Av. Joan XXIII, 27-31, Barcelona, E-08028, Spain.

3 Unitat de Farmacologia, Facultat de Medicina i Ciències de la Salut, Universitat Rovira i Virgili, C/St. Llorenç 21, Reus, 43201, Spain.

4 Laboratori de Neurofisiologia, Departament de Biomedicina, Facultat de Medicina, Universitat de Barcelona. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). Institut de

Neurociències, Barcelona, Spain.

5 Innopharma Screening Platform, Biofarma Research Group, Centro de Investigación en Medicina Molecular y Enfermedades Crónicas, Universidad de Santiago de Compostela, Av. Barcelona, S/N, E-15706, Santiago de Compostela, Spain.

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*N*-methyl-*D*-aspartate receptors (NMDAR) modulate the survival of the neurons. However, excessive NMDAR activity causes excitotoxicity and promotes cell death, underlying a potential mechanism of neurodegeneration that occurred in Alzheimer's Disease (AD). Despite years of intensive efforts by scientists to develop new safe and effective treatments for AD, memantine is the only NMDA uncompetitive receptor antagonist that has been approved for the treatment of this fatal disease.[1]

To address this challenge, our research group has designed, synthesized, and carried out the pharmacological and electrophysiological evaluation of a variety of new NMDAR antagonists bearing an amine polycyclic scaffold. All the compounds exhibited comparable potency and an electrophysiological profile similar to that of memantine.[2] Based on these studies, we determined the ideal candidate for further *in vitro* profiling. Compound **1** was selected as the best candidate for *in vivo* proof-of-concept in the SAMP8 mice model because of its excellent *in vitro* profile. The oral administration of compound **1** led to better cognitive performance and a neuroprotective effect through specific pathways.[3]

**References**

[1] a) Zhou, C., Tajima N. *Biochem Soc Trans*. **2023**; 51, 1713-1731. b) Ahmed, H., Haider, A., Ametamey, S. M. *Expert. Opin. Ther. Pat.* **2020**, 30, 743-767.

[2] R. Leiva, M. B. Phillips, A. L. Turcu, E. Gratacòs-Batlle, L. León-García, F. X. Sureda, D. Soto, J. W. Johnson, S. Vázquez. *ACS Chem. Neurosci*. **2018**, 21, 2722-2730.

[3] J. Companys-Alemany, A. L. Turcu, A. Bellver-Sanchis, M. I. Loza, J. M. Brea, A. M. Canudas, R. Leiva, S. Vázquez, M. Pallàs, C. Griñán-Ferré. *Pharmaceutics*. **2020**, 22, 284.