A bicyclic α-iminophosphonate improves cognitive decline in 5xFAD murine model of neurodegeneration

Bicyclic α-iminophosphonates as Imidazoline I_2 Receptor Ligands

C. Escolano[a], S. Abás,[a] S. Rodríguez-Arévalo,[a] A. Bagán,[a] C. Griñán-Ferré,[a] F. Vasilopoulou,[a] I. Brocos-Mosquera,[b] C. Muguruza,[b] L. F. Callado,[b] B. Pérez,[c] P. Pérez-Lozano,[d] J. Brea,[e] M. I. Loza,[e] E. Hernández-Hernández,[f] J. A. García-Sevilla,[f] M. J. García-Fuster,[f] M. Radan,[g] T. Djikic,[g] K. Nikolic,[g] C. Díaz,[h] J. Pérez,[h] C. Ramos,[h] F. Vicente,[h] E. Molins,[i] and M. Pallàs,[a]

[a] *Department of Pharmacology, Toxicology and Medicinal Chemistry, Faculty of Pharmacy and Food Sciences, and Institute of Biomedicine of the University of Barcelona (IBUB), Institut de Neurociències, University of Barcelona. Spain.*
[b] *Department of Pharmacology, University of the Basque Country, UPV/EHU, Leioa, Bizkaia, Spain.*
[c] *Department of Pharmacology, Therapeutic and Toxicology, Autonomous University of Barcelona, Barcelona, Spain.*
[d] *Department of Pharmacy and Pharmaceutical Technology, and Physical Chemistry, Faculty of Pharmacy and Food Sciences, University of Barcelona. Spain.*
[e] *Innopharma screening platform, BioFarma research group, Centro de Investigación en Medicina Molecular y Enfermedades Crónicas (CIMUS), Universidad de Santiago de Compostela, Santiago de Compostela, Spain.*
[f] *IUNICS University of the Balearic Islands (UIB), Health Research Institute of the Balearic Islands (IdISBa), P. Mallorca, Spain.*
[g] *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia*
[h] *Fundacion MEDINA, Health Sciences Technology Park, Granada, Spain.*
[l] *Institut de Ciència de Materials de Barcelona (CSIC), Cerdanyola, Spain.*

I_2 receptors (I_2-IR) are widely distributed in the central nervous system. I_2-IR ligands are associated with a neuroprotective effect but, as I_2-IR structure remains unknown, the discovery of better and more selective ligands is necessary to understand the pharmacological and molecular implications of I_2-IR.

Recently, we described a new imidazoline-structure family which showed high affinity and selectivity for I_2-IR. *In vivo* studies in mice indicated a neuroprotective role and revealed beneficial effects in behaviour and cognition with a murine model of neurodegeneration, senescence-accelerated prone mouse (SAMP8).

Herein, we report a novel non-imidazoline-structure of bicyclic α-iminophosphonates family with high affinities for I_2-IR. *In vivo* studies in 5X-FAD mice (a transgenic representative model of AD) and SAMP8 mice (a model of neurodegeneration linked to aging) showed an improvement in behaviour and cognition, a reduction of AD hallmarks and of neuroinflammation markers for the mice treated with the lead compound B06. After evaluating several pathways associated with neurodegeneration, we demonstrated that CaN pathway plays a critical role on the neuroprotective effects of I_2-IR ligands on SAMP8 mice model.

To rule out warnings of the novel family, we calculated DMPK and physicochemical properties for the novel bicyclic α-iminophosphonates. As well, we carried out drug metabolism, safety studies and in vivo pharmacokinetics for lead compound B06.

In summary, we present a novel family of I_2-IR ligands, its effectiveness in *in vivo* models and the possible neuroprotective molecular mechanism mediated by them. This highlights that the

modulation of I_2-IR by bicyclic α-iminophosphonates may open a new therapeutic venue for unmet neurodegenerative conditions.

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